Computational analysis of primary implant stability in trabecular bone

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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.

1 INTRODUCTION

1.1 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 (Huiskes, 2000). 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 (Kelly, 1998). 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 (Kelly, 1998). 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 (Huiskes, 1995). 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. 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.

1.2 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 (Kanis et al., 2013, 2010, 1992) the prevalence of osteoporotic fractures is still increasing because the proportion of the elderly in our population is constantly growing (Johnell and Kanis, 2006; Kanis et al., 2004). It has been estimated that in the year 2000, a total 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 (Johnell and Kanis, 2006). 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 (Kanis et al., 2004). 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 (Burton and Watters, 2006; Perren, 2002). 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 (Burton and Watters, 2006). 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 (Schenk and Buser, 1998).

Despite the fact that local bone properties are known to play a major role in the fixation capacity of fracture fixation implants (Basler et al., 2013; Schiuma et al., 2013), 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 even more 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 (Giannoudis and Schneider, 2006; Schneider et al., 2005). 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 (Bonnaire et al., 2005; Seebeck et al., 2005, 2004; Thiele et al., 2007). These findings have been supported by several clinical studies, where a low cortical and cancellous bone mass resulted in decreased implant stability (Goldhahn et al., 2008; Kim et al., 2001). 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 (Bindl et al., 2013; Kubo et al., 1999; Nikolaou et al., 2009). 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:

1. bone possesses a highly heterogeneous structure and thus anisotropic mechanical properties (Keaveny et al., 2001) not only differing between individuals (Eckstein et al., 2002) but also among different sites of the same individual (Eckstein et al., 2002) and even within the same bone of a specific individual (Tingart et al., 2003; Wirth et al., 2011) (Fig. 1);
2. implants are very variable in terms of design depending on their function (e.g. fracture fixation, joint replacement, etc.) and anatomical 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;
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 *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 vitro model?) (Huiskes and Chao, 1983). In a recent review paper, the following modeling parameters have been claimed to be crucial for valid FE models of bone-implant constructs (Wirth et al., 2010). The FE models should include:

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;
4. an accurate representation of bone-implant interaction; and
5. an appropriate representation of the failure behavior in bone-implant constructs.

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. 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: 100nm - 1 µm]: fibrillar collagen and embedded mineral; (5) Sub-nano-scale (length scale: < 100 nm): minerals, molecular structure of collagen and non-collagenous organic proteins (Podshivalov and Fischer, 2012; Rho et al., 1998). 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 (Müller, 2009; Stauber et al., 2006). 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 (Rho et al., 1998). Furthermore, it can also vary across different locations within the same bone (Keaveny et al., 2001). 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 (Huiskes et al., 2000) 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. Osseonintegration is highly dependent on the choice of material, requiring bioinert or bio-active material and surface configurations (Schenk and Buser, 1998) which in turn influence the degree of micromotion in the peri-implant region. Moderate micromotion has been shown to enhance bone remodelling (Duyck et al., 2006; Szmukler-Moncler et al., 1998; Wazen et al., 2013; Willie et al., 2010). However, excessive micromotion leads to the development of fibrous tissues and therefor hampers effective osseointegration and hampers secondary implant stability (Gao et al., 2012). 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.

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.

3.1 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 behavior (Huang et al., 2008; Karunratanakul et al., 2013; MacLeod et al., 2012; Natali et al., 2008).

The mechanical behavior of fracture fixation screws in synthetic bone have 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 ($R^2 > 0.96$) (Hou et al., 2004). 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 ($R^2 > 0.72$) (Hou et al., 2004). 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 (Rho et al., 1998). These local density variations are associated with variations in the local mechanical competence (Bevill et al., 2009; Morgan et al., 2003), 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 (Rho et al., 1995). This technique has been developed (Taddei et al., 2004; Taylor et al., 2002; Zannoni et al., 1998) and experimentally validated (Gupta et al., 2004; Taddei et al., 2007) for various bone types demonstrating that different relationships exist for different anatomical locations (Helgason et al., 2008; Morgan et al., 2003). 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 hemipelvis (Kluess et al., 2009).

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 (Karunratanakul et al., 2013). 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 0.6 mm 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.

3.2 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 obtain a sufficiently representative volume of interest in which the apparent mechanical properties of such a cellular solid can modeled as a continuum (Diamant et al., 2005; Gordon et al., 1998; Harrigan et al., 1988). 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 (Müller and Rüeggsegger, 1994). 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 (van Lenthe et al., 2006; Vanderoost et al., 2011). Such models would have the potential to analyze the mechanical behavior of bone-implant systems as well. Yet, this has not been presented in literature.

More recently, a purely computational strut-model has contributed to a better understanding of the mechanics underlying implant stability (Ruffoni et al., 2012). For this purpose, a three-dimensional beam lattice model was developed that modeled the trabecular bone structure (Fig. 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 (Adams and Taylor, 2000; van Rietbergen et al., 1995).This *in silico* approach has been proven to be a robust and reliable method to quantify the mechanical behavior of trabecular bone (Chevalier et al., 2007; van Lenthe et al., 2006). Parallel computing methods with dedicated FE solver have allowed increasing the bone model size beyond 100 Mio. elements (Adams et al., 2004; Arbenz et al., 2008; Flaig, 2012). To the best of the authors' knowledge, the largest linear-elastic μFE model so far has been run on the Jaguar at Oak Ridge National Laboratory (Cray XT5) with $388*10^9$ 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) (Flaig, 2012).

Furthermore, non-linear μFE models of trabecular bone have been introduced to simulate bone strength (Bevill and Keaveny, 2009; Christen et al., 2010; Hambli, 2013). 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 $1.5*10^9$ DoF (Fields et al., 2012; Nawathe et al., 2014).

Voxel-based μFE models with a detailed representation of the peri-implant structure have revealed obvious differences between continuum FE and discrete FE models (Fig. 3, (Wirth et al., 2012)) and have contributed to a better understanding of the mechanics underlying implant stability (Wirth et al., 2011). In the latter study, the bone microstructure of twelve humeral heads was assessed using μCT 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.

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 (Wirth et al., 2009). 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 (Pistoia et al., 2002) 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 bone having substantially different microstructure.

Voxel-based µFE models typically assume bonded bone-implant interfaces. In case of well-osseointegrated implants (Gabet et al., 2010; Stadelmann et al., 2012), 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, µFE 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.

4. EXPERIMENTAL EVALUATION OF PERI-IMPLANT BONE MECHANICS

An insightful technique to evaluate peri-implant bone mechanics 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 μCT. 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 (Schiuma et al., 2013, 2011). Ideas exist to implement this technique into a clinical setting (Edwards et al., 2012).

In a more sophisticated approach, imaging and mechanical testing are being combined in one single experimental set-up. Digital Image Correlation (DIC) has been used to quantify the micro-motion of the cement-bone interface in arthroplasty (Mann et al., 2008). 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 *in vitro* prepared cemented total hip replacements subjected to nondestructive mechanical loading. It was shown that most of the compliant response due to mechanical loading occurs at the bone-cement interface indicating highly non-linear 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 μCT is being used as the imaging technique. The combination of step-wise micro-compression in combination with time-lapsed μCT 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 (Basler et al., 2013; Gabet et al., 2010; Mueller et al., 2013). 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) (Mueller et al., 2013). 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 (Basler et al., 2013). 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 (Basler et al., 2011; Gabet et al., 2010).

5. 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 μFE study (Basler et al., 2011). The calculated displacement fields were in good agreement with the experimentally measured displacements fields (R^2 =0.67 - 0.92); yet, the displacements in the peri-implant region were overestimated up to a factor 4 (Fig. 4). Hence, a mismatch is present between the local displacements as calculated from the micro-FE model and measured in the *in vitro* experiments.

The μFE 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 approach. Specifically, in a recent study, synchrotron radiation micro-computed tomography (SRμCT) based micromechanical finite element models of trabecular 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 (Gross et al., 2012). Furthermore, successful validation for μCT based FE models of trabecular bone, in which bone trabeculae had been modeled consisting of homogenous material properties only (Chevalier et al., 2007; van Lenthe et al., 2006), 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 (Bartold et al., 2011; Lee and Baek, 2010; Wawrzinek et al., 2008). In a recent study (Torcasio et al., 2012) 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 was measured using strain gauges. Furthermore, specimen-specific μFE models were created. For each limb four models were created: one in which the bone was assumed to be fully osseo-integrated, and three additional models in which a weak peri-implant bone layer of 40 µm, 80 µm, and 160 µm was simulated (Fig. 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.

Another modeling feature that may explain the mismatch between measured and calculated mechanical properties is micromotion between implant and bone. This finding is supported by DIC experiments of bone-cement constructs (Mann et al., 2008). 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 µFE study has questioned the importance of friction regarding its effect on micromotion between implant and bone (Limbert et al., 2010). In their study, a µCT-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 arthoplasty), 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 *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 µFE 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 *in silico* and to validate *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.

6. 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 the Introduction.

Class of models	**Bone+Implant geometry**	**Material properties**	**Boundary conditions**	**Bone-implant interaction**	**Failure behavior**
Continuum model	+	+	+++	+	+
Microstructural models					
- Beam	++	+	++	+	+
- Voxel	+++	++	++	+	+
- Smooth-surface	**+++**	**++**	**++**	**++**	**++**

Table 1: + poor, ++ moderate, +++ good modeling features

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, *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, *in silico* methods, such as FE modeling, do not suffer from this limitation. However, it is important to note that any *in silico* method requires a rigorous validation with corresponding *in vitro* models as well as verification of its accuracy and robustness (Huiskes and Chao, 1983). Whereas continuum FE models can provide reasonable estimates of bone-implant interaction, they cannot be used for the detailed analysis of bone-implant interface 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 µFE models to further improve the accuracy of patient specific µFE models of bone-implant constructs.

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Reference List

Adams, M., Taylor, R.., 2000. Parallel multigrid solvers for 3D-unstructured large deformation elasticity and plasticity finite element problems. Finite Elem. Anal. Des. 36, 197–214.

Adams, M.F., Bayraktar, H.H., Keaveny, T.M., Papadopoulos, P., 2004. Ultrascalable implicit finite element analysis in solid mechanics with over half a billion degrees of freedom. In ACM/IEEE Proceedings of Supercomputing 2004: High Performance Networking and Computing 00, 1–15.

Arbenz, P., van Lenthe, G.H., Mennel, U., Muller, R., Sala, M., 2008. A scalable multi-level preconditioner for matrix-free mu-finite element analysis of human bone structures. Int. J. Numer. Methods Eng. 73, 927–947.

Bartold, P.M., Kuliwaba, J.S., Lee, V., Shah, S., Marino, V., Fazzalari, N.L., 2011. Influence of surface roughness and shape on microdamage of the osseous surface adjacent to titanium dental implants. Clin. Oral Implants Res. 22, 613–8.

Basler, S.E., Mueller, T.L., Christen, D., Wirth, a J., Muller, R., van Lenthe, G.H., 2011. Towards validation of computational analyses of peri-implant displacements by means of experimentally obtained displacement maps. Comput. Methods Biomech. Biomed. Engin. 14, 165–74.

Basler, S.E., Traxler, J., Müller, R., van Lenthe, G.H., 2013. Peri-implant bone microstructure determines dynamic implant cut-out. Med. Eng. Phys. 35, 1442–9.

Bevill, G., Farhamand, F., Keaveny, T.M., 2009. Heterogeneity of yield strain in low-density versus high-density human trabecular bone. J. Biomech. 42, 2165–70.

Bevill, G., Keaveny, T.M., 2009. Trabecular bone strength predictions using finite element analysis of micro-scale images at limited spatial resolution. Bone 44, 579–84.

Bindl, R., Oheim, R., Pogoda, P., Beil, F.T., Gruchenberg, K., Reitmaier, S., Wehner, T., Calcia, E., Radermacher, P., Claes, L., Amling, M., Ignatius, A., 2013. Metaphyseal fracture healing in a sheep model of low turnover osteoporosis induced by hypothalamic-pituitary disconnection (HPD). J. Orthop. Res. 31, 1851–7.

Bonnaire, F., Zenker, H., Lill, C., Weber, A.T., Linke, B., 2005. Treatment strategies for proximal femur fractures in osteoporotic patients. Osteoporos. Int. 16 Suppl 2, S93–S102.

Burton, D.J.C., Watters, a. T., 2006. Management of proximal humeral fractures. Curr. Orthop. 20, 222–233.

Chevalier, Y., Pahr, D., Allmer, H., Charlebois, M., Zysset, P., 2007. Validation of a voxel-based FE method for prediction of the uniaxial apparent modulus of human trabecular bone using macroscopic mechanical tests and nanoindentation. J. Biomech. 40, 3333–40.

Christen, D., Webster, D.J., Müller, R., 2010. Multiscale modelling and nonlinear finite element analysis as clinical tools for the assessment of fracture risk. Philos. Trans. A. Math. Phys. Eng. Sci. 368, 2653–68.

Diamant, I., Shahar, R., Gefen, A., 2005. How to select the elastic modulus for cancellous bone in patient-specific continuum models of the spine. Med. Biol. Eng. … 2.

Duyck, J., Vandamme, K., Geris, L., Van Oosterwyck, H., De Cooman, M., Vander Sloten, J., Puers, R., Naert, I., 2006. The influence of micro-motion on the tissue differentiation around immediately loaded cylindrical turned titanium implants. Arch. Oral Biol. 51, 1–9.

Eckstein, F., Lochmüller, E.-M., Lill, C.A., Kuhn, V., Schneider, E., Delling, G., Müller, R., 2002. Bone strength at clinically relevant sites displays substantial heterogeneity and is best predicted from site-specific bone densitometry. J. Bone Miner. Res. 17, 162–71.

Edwards, J., Hoffmann, P.F., Keaveny, T.M., Kopperdahl, D.L., 2012. Patent: Automated patient-specific bone-implant biomechanical analysis; http://www.google.com/patents/US8126234.

Fields, A.J., Nawathe, S., Eswaran, S.K., Jekir, M.G., Adams, M.F., Papadopoulos, P., Keaveny, T.M., 2012. Vertebral fragility and structural redundancy. J. Bone Miner. Res. 27, 2152–8.

Flaig, C., 2012. PhD Thesis: A highly scalable memory efficient multigrid solver for µ-finite element analyses; http://e-collection.library.ethz.ch/view/eth:6562. ETH.

Gabet, Y., Kohavi, D., Voide, R., Mueller, T.L., Müller, R., Bab, I., 2010. Endosseous implant anchorage is critically dependent on mechanostructural determinants of peri-implant bone trabeculae. J. Bone Miner. Res. 25, 575–83.

Gao, S.-S., Zhang, Y.-R., Zhu, Z.-L., Yu, H.-Y., 2012. Micromotions and combined damages at the dental implant/bone interface. Int. J. Oral Sci. 4, 182–8.

Giannoudis, P. V, Schneider, E., 2006. Principles of fixation of osteoporotic fractures. J. Bone Joint Surg. Br. 88, 1272–8.

Goldhahn, J., Suhm, N., Goldhahn, S., Blauth, M., Hanson, B., 2008. Influence of osteoporosis on fracture fixation--a systematic literature review. Osteoporos. Int. 19, 761–72.

Gordon, C.L., Lang, T.F., Augat, P., Genant, H.K., 1998. Image-Based Assessment of Spinal Trabecular Bone Structure from High-Resolution CT Images. Osteoporos. Int. 8, 317–325.

Gross, T., Pahr, D.H., Peyrin, F., Zysset, P.K., 2012. Mineral heterogeneity has a minor influence on the apparent elastic properties of human cancellous bone: a SRµCT-based finite element study. Comput. Methods Biomech. Biomed. Engin. 15, 1137–44.

Gupta, S., van der Helm, F.C.T., Sterk, J.C., van Keulen, F., Kaptein, B.L., 2004. Development and experimental validation of a three-dimensional finite element model of the human scapula. Proc. Inst. Mech. Eng. Part H J. Eng. Med. 218, 127–142.

Hambli, R., 2013. Micro-CT finite element model and experimental validation of trabecular bone damage and fracture. Bone 56, 363–74.

Harrigan, T.P., Murali Jasty, Manna, R.W., Harris, W.H., 1988. Limitations of the continuum assumption in cancellous bone. J. Biomech. 21, 269–275.

Helgason, B., Perilli, E., Schileo, E., Taddei, F., Brynjólfsson, S., Viceconti, M., 2008. Mathematical relationships between bone density and mechanical properties: a literature review. Clin. Biomech. (Bristol, Avon) 23, 135–46.

Hou, S.-M., Hsu, C.-C., Wang, J.-L., Chao, C.-K., Lin, J., 2004. Mechanical tests and finite element models for bone holding power of tibial locking screws. Clin. Biomech. (Bristol, Avon) 19, 738–45.

Huang, H.-L., Hsu, J.-T., Fuh, L.-J., Tu, M.-G., Ko, C.-C., Shen, Y.-W., 2008. Bone stress and interfacial sliding analysis of implant designs on an immediately loaded maxillary implant: a non-linear finite element study. J. Dent. 36, 409–17.

Huiskes, H.W.J., 1995. The law of adaptive bone remodeling : a case for crying Newton? In: Odgaard A., W.H. (Ed.), Bone Structure and Remodeling. World Scientific, Singapore, pp. 15–23.

Huiskes, R., 2000. If bone is the answer, then what is the question? J. Anat. 197, 145–56.

Huiskes, R., Chao, E.Y., 1983. A survey of finite element analysis in orthopedic biomechanics: the first decade. J. Biomech. 16, 385–409.

Huiskes, R., Ruimerman, R., van Lenthe, G.H., Janssen, J.D., 2000. Effects of mechanical forces on maintenance and adaptation of form in trabecular bone. Nature 405, 704–6.

Johnell, O., Kanis, J. a, 2006. An estimate of the worldwide prevalence and disability associated with osteoporotic fractures. Osteoporos. Int. 17, 1726–33.

Kanis, J. a, Johnell, O., Gullberg, B., Allander, E., Dilşen, G., Gennari, C., Lopes Vaz, a a, Lyritis, G.P., Mazzuoli, G., Miravet, L., 1992. Evidence for efficacy of drugs affecting bone metabolism in preventing hip fracture. BMJ 305, 1124–8.

Kanis, J. a, Johnell, O., Oden, a, De Laet, C., Mellstrom, D., 2004. Epidemiology of osteoporosis and fracture in men. Calcif. Tissue Int. 75, 90–9.

Kanis, J. a, McCloskey, E. V, Johansson, H., Cooper, C., Rizzoli, R., Reginster, J.-Y., 2013. European guidance for the diagnosis and management of osteoporosis in postmenopausal women. Osteoporos. Int. 24, 23–57.

Kanis, J. a, McCloskey, E. V, Johansson, H., Oden, a, Ström, O., Borgström, F., 2010. Development and use of FRAX in osteoporosis. Osteoporos. Int. 21 Suppl 2, S407–13.

Karunratanakul, K., Kerckhofs, G., Lammens, J., Vanlauwe, J., Schrooten, J., Van Oosterwyck, H., 2013. Validation of a finite element model of a unilateral external fixator in a rabbit tibia defect model. Med. Eng. Phys. 35, 1037–43.

Keaveny, T.M., Morgan, E.F., Niebur, G.L., Yeh, O.C., 2001. Biomechanics of trabecular bone. Annu. Rev. Biomed. Eng. 3, 307–33.

Kelly, K., 1998. ESSAYS ON SCIENCE AND SOCIETY:The Third Culture. Science (80-.). 279, 992–993.

Kim, W.-Y., Han, C.-H., Park, J.-I., Kim, J.-Y., 2001. Failure of intertrochanteric fracture fixation with a dynamic hip screw in relation to pre-operative fracture stability and osteoporosis. Int. Orthop. 25, 360–362.

Kluess, D., Souffrant, R., Mittelmeier, W., Wree, A., Schmitz, K.-P., Bader, R., 2009. A convenient approach for finite-element-analyses of orthopaedic implants in bone contact: modeling and experimental validation. Comput. Methods Programs Biomed. 95, 23–30.

Kubo, T., Shiga, T., Hashimoto, J., Yoshioka, M., Honjo, H., Urabe, M., Kitajima, I., Semba, I., Hirasawa, Y., 1999. Osteoporosis influences the late period of fracture healing in a rat model prepared by ovariectomy and low calcium diet. J. Steroid Biochem. Mol. Biol. 68, 197–202.

Lee, N.-K., Baek, S.-H., 2010. Effects of the diameter and shape of orthodontic mini-implants on microdamage to the cortical bone. Am. J. Orthod. Dentofac. Orthop. 138, 8.e1–8.e8.

Limbert, G., van Lierde, C., Muraru, O.L., Walboomers, X.F., Frank, M., Hansson, S., Middleton, J., Jaecques, S., 2010. Trabecular bone strains around a dental implant and associated micromotions--a micro-CT-based three-dimensional finite element study. J. Biomech. 43, 1251–61.

MacLeod, A.R., Pankaj, P., Simpson, a H.R.W., 2012. Does screw-bone interface modelling matter in finite element analyses? J. Biomech. 45, 1712–6.

Mann, K. a, Miller, M. a, Cleary, R.J., Janssen, D., Verdonschot, N., 2008. Experimental micromechanics of the cement-bone interface. J. Orthop. Res. 26, 872–9.

Morgan, E.F., Bayraktar, H.H., Keaveny, T.M., 2003. Trabecular bone modulus–density relationships depend on anatomic site. J. Biomech. 36, 897–904.

Mueller, T.L., Basler, S.E., Müller, R., van Lenthe, G.H., 2013. Time-lapsed imaging of implant fixation failure in human femoral heads. Med. Eng. Phys. 35, 636–43.

Müller, R., 2009. Hierarchical microimaging of bone structure and function. Nat. Rev. Rheumatol. 5, 373–81.

Müller, R., Rüeggsegger, P., 1994. Three-dimensional finite element modelling of non-invasively assessed trabecular bone structures. Med. Eng. Phys. 17, 126–133.

Natali, A.N., Carniel, E.L., Pavan, P.G., 2008. Investigation of bone inelastic response in interaction phenomena with dental implants. Dent. Mater. 24, 561–9.

Nawathe, S., Akhlaghpour, H., Bouxsein, M.L., Keaveny, T.M., 2014. Microstructural failure mechanisms in the human proximal femur for sideways fall loading. J. Bone Miner. Res. 29, 507–15.

Nikolaou, V.S., Efstathopoulos, N., Kontakis, G., Kanakaris, N.K., Giannoudis, P. V, 2009. The influence of osteoporosis in femoral fracture healing time. Injury 40, 663–8.

Perren, S.M., 2002. Evolution of the internal fixation of long bone fractures: The scientific basis of biological internal fixation: choosing a new balance between stability and biology. J. Bone Jt. Surg. 84, 1093–1110.

Pistoia, W., van Rietbergen, B., Lochmüller, E.-M., Lill, C. a, Eckstein, F., Rüegsegger, P., 2002. Estimation of distal radius failure load with micro-finite element analysis models based on three-dimensional peripheral quantitative computed tomography images. Bone 30, 842–8.

Podshivalov, L., Fischer, A., 2012. Patient-Specific Diagnosis and Visualization of Bone. In: Gefen, A. (Ed.), Patient-Specific Modeling in Tomorrow's Medicine. Springer-Verlag Berlin Heidelberg 2011, pp. 27–52.

Rho, J.Y., Hobatho, M.C., Ashman, R.B., 1995. Relations of mechanical properties to density and CT numbers in human bone. Med. Eng. Phys. 17, 347–355.

Rho, J.Y., Kuhn-Spearing, L., Zioupos, P., 1998. Mechanical properties and the hierarchical structure of bone. Med. Eng. Phys. 20, 92–102.

Ruffoni, D., Müller, R., van Lenthe, G.H., 2012. Mechanisms of reduced implant stability in osteoporotic bone. Biomech. Model. Mechanobiol. 11, 313–23.

Schenk, R.K., Buser, D., 1998. Osseointegration: a reality. Periodontol. 2000 17, 22–35.

Schiuma, D., Brianza, S., Tami, a E., 2011. Development of a novel method for surgical implant design optimization through noninvasive assessment of local bone properties. Med. Eng. Phys. 33, 256–62.

Schiuma, D., Plecko, M., Kloub, M., Rothstock, S., Windolf, M., Gueorguiev, B., 2013. Influence of peri-implant bone quality on implant stability. Med. Eng. Phys. 35, 82–7.

Schneider, E., Goldhahn, J., Burckhardt, P., 2005. The challenge: fracture treatment in osteoporotic bone. Osteoporos. Int. 16 Suppl 2, S1–2.

Seebeck, J., Goldhahn, J., Morlock, M.M., Schneider, E., 2005. Mechanical behavior of screws in normal and osteoporotic bone. Osteoporos. Int. 16 Suppl 2, S107–11.

Seebeck, J., Goldhahn, J., Städele, H., Messmer, P., Morlock, M.M., Schneider, E., 2004. Effect of cortical thickness and cancellous bone density on the holding strength of internal fixator screws. J. Orthop. Res. 22, 1237–42.

Stadelmann, V. a, Conway, C.M., Boyd, S.K., 2012. In vivo monitoring of bone-implant bond strength by microCT and finite element modelling. Comput. Methods Biomech. Biomed. Engin. 37–41.

Stauber, M., Rapillard, L., van Lenthe, G.H., Zysset, P., Müller, R., 2006. Importance of individual rods and plates in the assessment of bone quality and their contribution to bone stiffness. J. Bone Miner. Res. 21, 586–95.

Szmukler-Moncler, S., Salama, H., Reingewirtz, Y., Dubruille, J.H., 1998. Timing of loading and effect of micromotion on bone-dental implant interface: review of experimental literature. J. Biomed. Mater. Res. 43, 192–203.

Taddei, F., Pancanti, A., Viceconti, M., 2004. An improved method for the automatic mapping of computed tomography numbers onto finite element models. Med. Eng. Phys. 26, 61–69.

Taddei, F., Schileo, E., Helgason, B., Cristofolini, L., Viceconti, M., 2007. The material mapping strategy influences the accuracy of CT-based finite element models of bones: an evaluation against experimental measurements. Med. Eng. Phys. 29, 973–9.

Taylor, W.R., Roland, E., Ploeg, H., Hertig, D., Klabunde, R., Warner, M.D., Hobatho, M.C., Rakotomanana, L., Clift, S.E., 2002. Determination of orthotropic bone elastic constants using FEA and modal analysis. J. Biomech. 35, 767–73.

Thiele, O.C., Eckhardt, C., Linke, B., Schneider, E., Lill, C. a, 2007. Factors affecting the stability of screws in human cortical osteoporotic bone: a cadaver study. J. Bone Joint Surg. Br. 89, 701–5.

Tingart, M.J., Bouxsein, M.L., Zurakowski, D., Warner, J.P., Apreleva, M., 2003. Three-dimensional distribution of bone density in the proximal humerus. Calcif. Tissue Int. 73, 531–6.

Torcasio, A., Zhang, X., Van Oosterwyck, H., Duyck, J., van Lenthe, G.H., 2012. Use of micro-CT-based finite element analysis to accurately quantify peri-implant bone strains: a validation in rat tibiae. Biomech. Model. Mechanobiol. 11, 743–50.

Van Lenthe, G.H., Stauber, M., Müller, R., 2006. Specimen-specific beam models for fast and accurate prediction of human trabecular bone mechanical properties. Bone 39, 1182–9.

Van Rietbergen, B., Weinans, H., Huiskes, R., Odgaard, a, 1995. A new method to determine trabecular bone elastic properties and loading using micromechanical finite-element models. J. Biomech. 28, 69–81.

Vanderoost, J., Jaecques, S.V.N., Van der Perre, G., Boonen, S., D'hooge, J., Lauriks, W., van Lenthe, G.H., 2011. Fast and accurate specimen-specific simulation of trabecular bone elastic modulus using novel beam-shell finite element models. J. Biomech. 44, 1566–72.

Wawrzinek, C., Sommer, T., Fischer-Brandies, H., 2008. Microdamage in cortical bone due to the overtightening of orthodontic microscrews. J. Orofac. Orthop. 69, 121–34.

Wazen, R.M., Currey, J. a, Guo, H., Brunski, J.B., Helms, J. a, Nanci, A., 2013. Micromotion-induced strain fields influence early stages of repair at bone-implant interfaces. Acta Biomater. 9, 6663–74.

Willie, B., Yang, X., Kelly, N., 2010. Cancellous bone osseointegration is enhanced by in vivo loading. … Eng. Part C … 16.

Wirth, A.J., Goldhahn, J., Flaig, C., Arbenz, P., Müller, R., van Lenthe, G.H., 2011. Implant stability is affected by local bone microstructural quality. Bone 49, 473–8.

Wirth, A.J., Mueller, T.L., Vereecken, W., Flaig, C., Arbenz, P., Müller, R., Lenthe, G.H., 2009. Mechanical competence of bone-implant systems can accurately be determined by image-based micro-finite element analyses. Arch. Appl. Mech. 80, 513–525.

Wirth, A.J., Müller, R., van Lenthe, G.H., 2010. Computational analyses of small endosseous implants in osteoporotic bone. Eur. Cell. Mater. 20, 58–71.

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.

Zannoni, C., Mantovani, R., Viceconti, M., 1998. Material properties assignment to finite element models of bone structures: a new method. Med. Eng. Phys. 20, 735–40.

Figure legends:

Fig. 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. Reproduced 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.

Fig. 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.

Fig. 3: Direct comparison of continuum and discrete micro-CT 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 no 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.

Fig. 4: a) Visualisations of displacement fields obtained by strain mapping and b) micro-finite element analysis . Please note the different scale bars. Reproduced from Basler, S.E., Mueller, T.L., Christen, D., Wirth, a J., Muller, R., van Lenthe, G.H., 2011. Towards validation of computational analyses of peri-implant displacements by means of experimentally obtained displacement maps. *Comput. Methods Biomech. Biomed. Engin.* 14, 165–74.

Fig. 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) model, reduced mechanical competence was modeled by assigning a Young 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 micro-CT-based finite element analysis to accurately quantify peri-implant bone strains: a validation in rat tibiae. *Biomech. Model. Mechanobiol.* 11, 743–50.

Figure 1

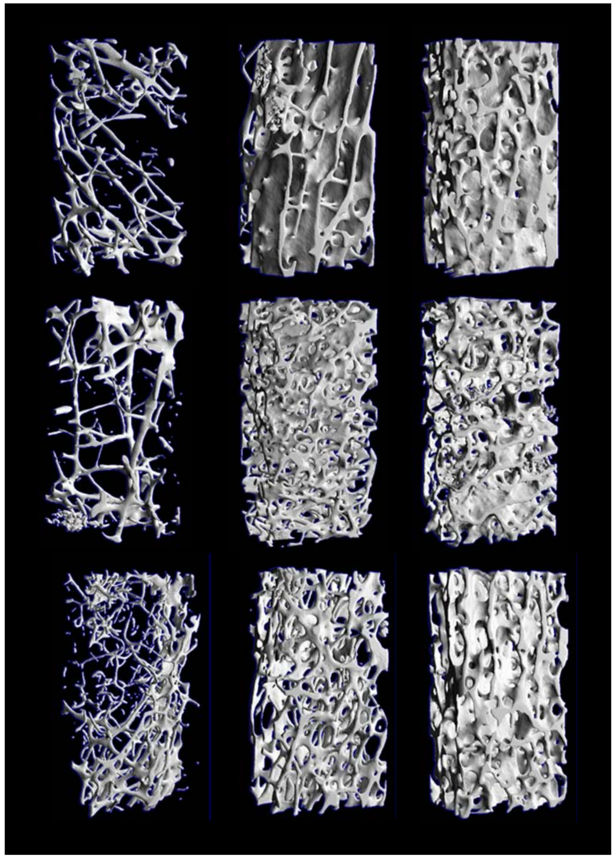
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Figure 2

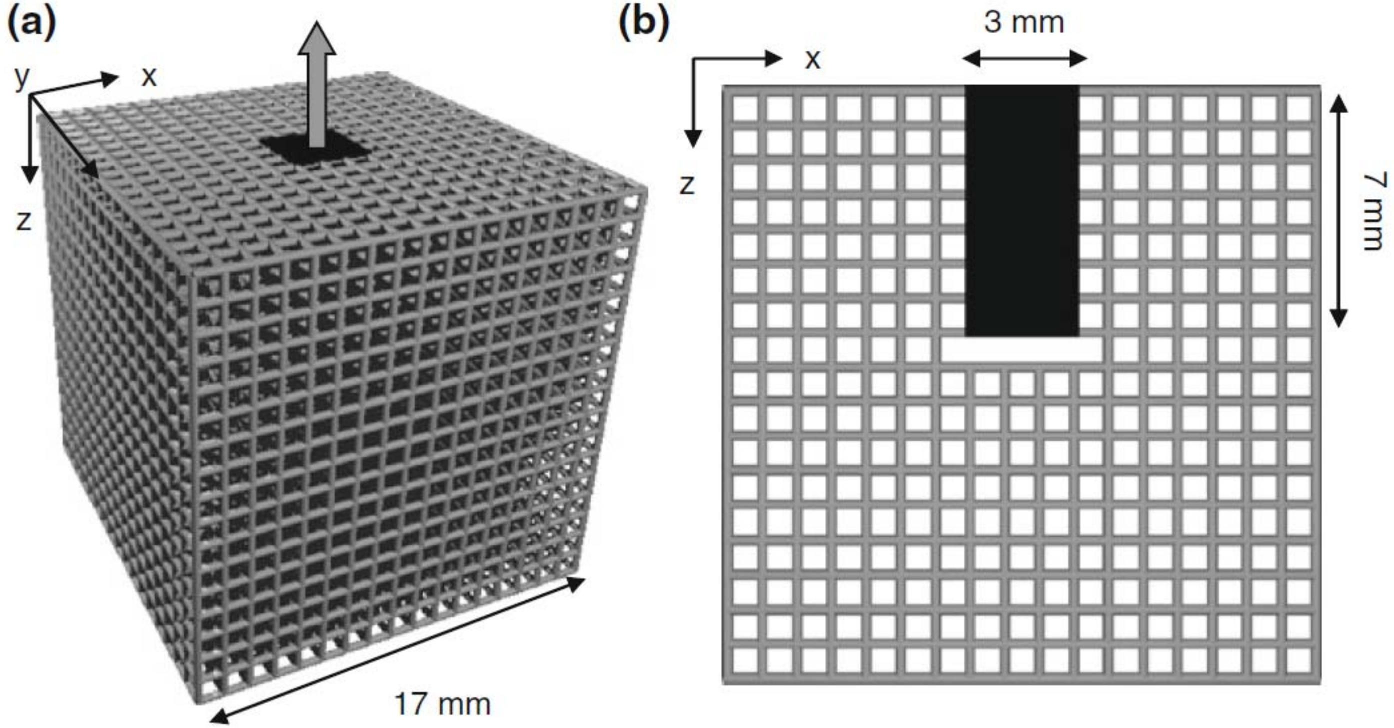

Figure 3

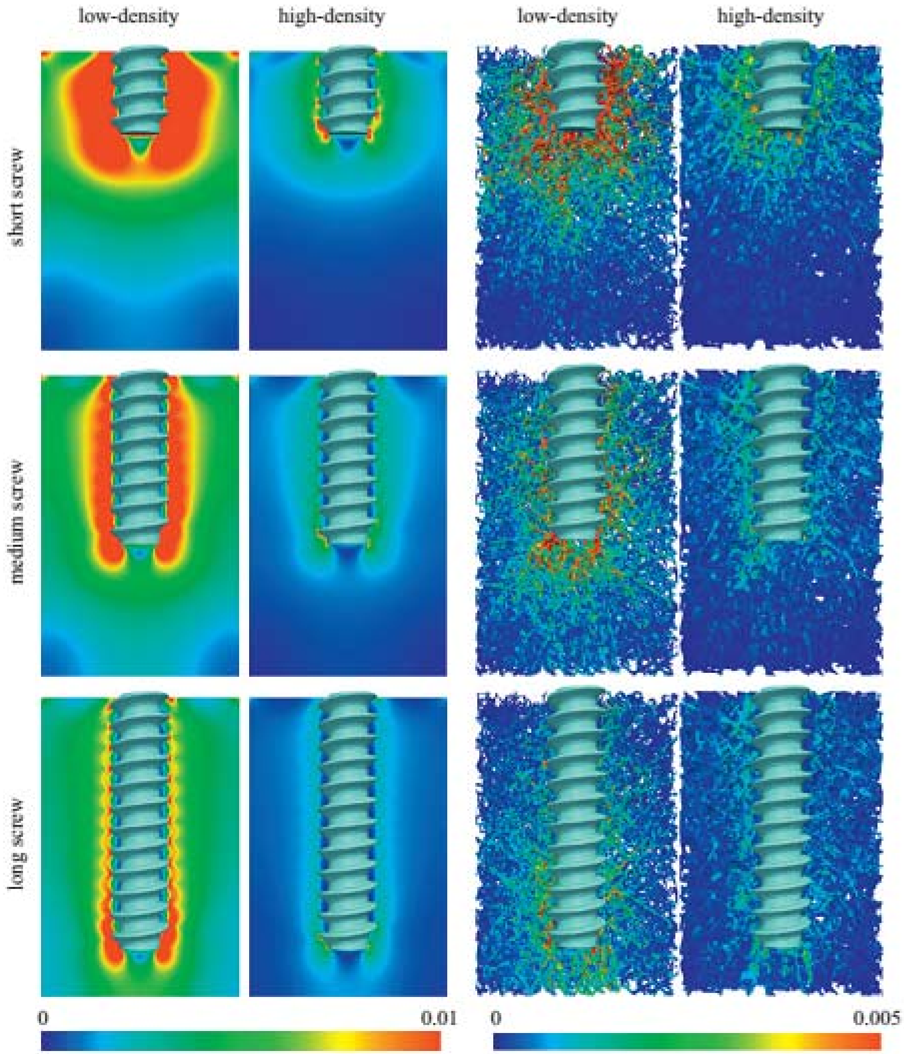
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Figure 4

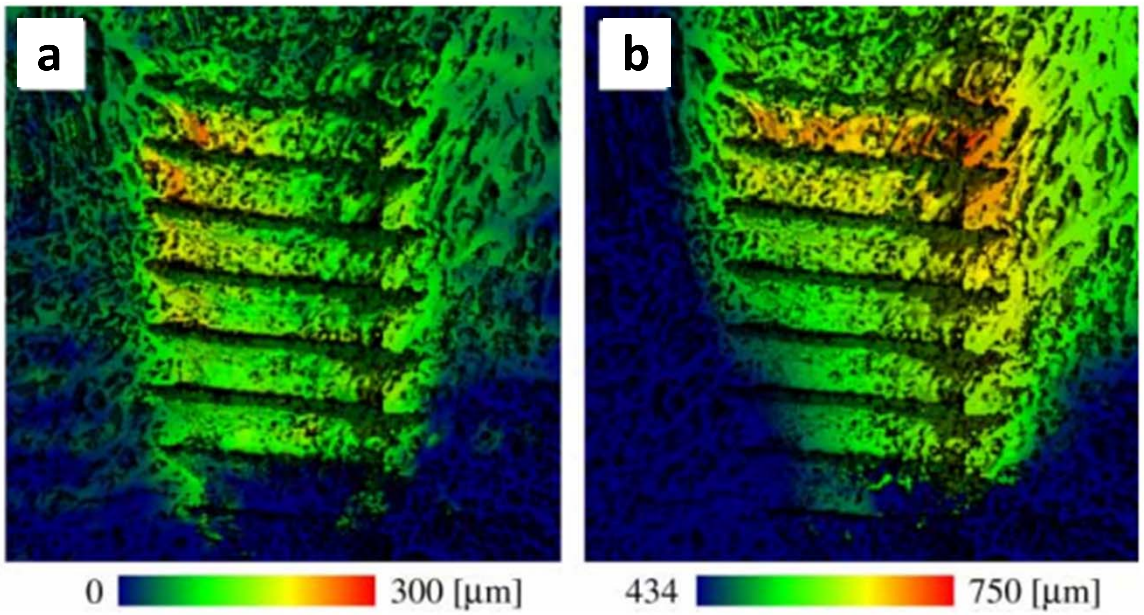

Figure 5