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Computer simulating a clinical trial of a load-bearing implant: example of an intramedullary prosthesis.

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Abstract

Computational modelling is becoming ever more important for obtaining regulatory approval for new medical devices. An accepted approach is to infer performance in a population from an analysis conducted in an idealized or 'average' patient; we present here a method for predicting the performance of an orthopaedic implant when released into a population – effectively simulating a clinical trial. Specifically we hypothesise an analysis based on a method for predicting the performance in a population will lead to different conclusions than an analysis based on an idealised or 'average' patient. To test this hypothesis we use a finite element model of an intramedullary implant in a bone whose size and remodelling activity is different for each individual in the population. We compare the performance of a low Young's modulus implant (E = 20 GPa) to one with a higher Young's modulus (200 GPa). Cyclic loading is applied and failure is assumed when the migration of the implant relative to the bone exceeds a threshold magnitude. The analysis in an idealized of 'average' patient predicts that the lower modulus device survives longer whereas the analysis simulating a clinical trial predicts no statistically-significant tendency (p=0.77) for the low modulus device to perform better. It is concluded that population-based simulations of implant performance — simulating a clinical trial — presents a very valuable opportunity for more realistic computational pre-clinical testing of medical devices.

Keywords

Simulated clinical trials, intramedullary fixation, stochastic model, finite element analysis, mechanobiology

1 Introduction

Computational analysis of biomechanical implants has been performed ever since finite element modelling emerged as a practical tool for analysing complex shapes. In the early days the clinical utility was limited because of the lack of computational power; often simple two-dimensional geometries were used (Huiskes and Chao, 1983; Prendergast, 1997). As computational power increased models did improve as patient-specific geometries derived from medical images could be modelled more easily. With patient-specific geometric modelling, limitations of loading and material properties could be addressed; daily loading datasets were developed (Bergmann et al., 2001; Heller et al., 2005) and models incorporating more advanced patient-specific material properties were advanced (see for example Helgason et al., 2008). Current technologies now allow for accurate modelling, corroborated against experimental or other data for many types of medical device, e.g. for orthopaedic implants (Verdonschot and Huiskes, 1997; Taylor and Barrett, 2003; Stolk et al., 2007; Lennon et al., 2007). While these analyses give accurate predictions of how an implant will perform in a representative case, they may not give good predictions of how an implant will perform when released into a population because a medical device may perform superbly in an average individual but will perform poorly in individuals whose anatomy or pathology differ from average. The variable performance in a population has been shown by, for example, the Swedish hip register where the probability of a Müller hip prostheses lasting for 10 years is 81.7% ±4.1% (Malchau et al., 1993) whereas for a Lubinus it is 96.3% ± 0.3% (Kärrholm et al., 2007). Awareness of the need to account for such differences in the range of performance of different implants has led to a new wave of modelling approaches that attempt to include aspects of population variability when simulating implant behaviour, e.g. Laz et al., 2006; Viceconti et al., 2006; Knight et al., 2007; Dopico-Gonzalez et al., 2009.

There are several factors that may cause variation in the outcome; these may be classified as either environmental factors or genetic factors. Environment factors include:

- surgical variation in implant positioning, as some implant designs may be more sensitive to being inserted in non-optimal positions than others,
- loading, as each patient will subject the device to different loads (Bergmann et al., 2001; Morlock et al., 2001; Heller et al., 2001)., and
- bone geometry, as no bones are identical (Noble et al., 1988; Fitzpatrick et al., 2008) and implants may be sensitive to bone size and shape.

The genetic differences between patients that are particularly relevant to the performance of a load-bearing implant include genetic variation in tissue mechanoresponsiveness. As Frost (1987) speculated, each individual's bone tissue has a somewhat different response to mechanical stress — and this mechanosensitivity will also vary with age; some patients' bone tissue will be indifferent to the change in stress whereas other bone tissue will be mechanosensitive to a considerable degree leading to different amounts of bone resorption around the implant, or different patterns of bone ingrowth. Many follow-up studies have shown this; recently for example Panisello et al (2009) showed that an anatomic non-cemented stem had bone loss which ranged from 12% to 27% after 1 post-operative year.

In this paper we test the hypothesis that, if two devices are to be compared an analysis based on an idealised or average patient will lead to different conclusions than one that models the variability inherent in human populations. To test this hypothesis a finite element model of an intramedullary implant is used, with variability included in bone geometry and mechanosensitivity of the bone tissue. An intramedullary implant is chosen as intramedullary fixation is frequently used for many orthopaedic implants (Prendergast, 2001); furthermore, Huiskes et al. (1987) used an axi-symmetric finite element model of an intramedullary implant in the first computational studies of peri-prosthetic bone remodelling. Later Prendergast and Taylor (1992) simulated remodelling around an intramedullary implant using damage-adaptive remodelling. Because Young's modulus is critical to the success of implant fixation (Weinans et al., 1992; Scannell and Prendergast, 2009), it is varied in this study. If the hypothesis is corroborated – for even this simplified intramedullary geometry – then this has implications for how computational simulation of medical device performance is conducted in the future.

2 Methods

The simplified intramedullary implant consisted of a hollow tube of homogeneous cortical bone containing a tapered straight stem (Fig. 1). A force was applied to the stem at nodes at the centre of its top surface while all nodes at the distal end of the bone were restrained from movement. Total applied force to the stem was calculated by estimating the equivalent force on the bone annulus to produce a pressure that could induce an axial strain of 1,500 με in the bone tube. This strain magnitude was chosen as representative of a maximum strain in a long bone diaphysis under normal conditions (Fritton and Rubin, 2001). Debonded contact was assumed between the stem and bone with a friction coefficient of 0.3. A region of elements near the restraints was excluded from the bone adaptation simulation due to unphysiological strains arising from the restraints in this region.

The bone remodelling algorithm used in this study was presented in Mulvhill and Prendergast (2008). Briefly, the algorithm follows the proposal of Frost (1983, 1987, 1990) that bone mechanoresponsiveness is categorised into four 'windows': a disuse window where strain is below a minimum effective strain, denoted here as ε_{min}, an adapted window where no net change occurs between ε_{min} and ε_{max}, a window where modelling occurs to create new bone mass on surfaces above ε_{max}, and a pathologic region where matrix damage causes bone loss — in our remodelling algorithm we denote this occurring above ω_{crit}. (In this study ω_{crit} = 4.67x10^{-5} calculated assuming critical damage corresponds to the damage occurring during one cycle of 4,000 με. It is calculated based on a linear damage rule (i.e. $\omega = N/N_f$ where N = number of cycles and N_f = cycles to failure at a given stress) and an empirical equation for cycles to failure proposed by Carter et al. (1976) is used, i.e., $\log N_f = H\log \sigma + J\theta + K\rho + M$ where σ, θ, ρ are stress (MPa), temperature (^{o}C), and density (g/cm^3) respectively and H = -7.789, J = -0.0206, K = -2.364, M = 15.47 are empirical constants. Density is assumed to be 1.65 g/cm and is used to calculate stress based on the density-modulus relationship noted below. Temperature is assumed to be 37 ^{o}C.)

During resorptive activity osteoclasts are assumed to resorb bone causing a local rate of apparent density reduction of $-C$ g/cm^3 per day while during formation osteoblast deposition is assumed to be a fraction, *n*, of osteoclast resorption, giving a local rate of apparent density increase of nC g/cm^3 per day; the resorption rate C was calculated based on an assumption that a BMU is capable of resorbing 1.4 μm/day (Eriksen et al., 1984a) and that the ratio of formation to resorption is n=0.31 (Eriksen et al., 1984b). The following algorithm describes the four remodelling states:

If $\omega < \omega_{crit}$ then

  If $\varepsilon < \varepsilon_{min}$: $\dot{\rho} = -C$ — Strain-based resorption (disuse)

  Else if $\varepsilon > \varepsilon_{max}$: $\dot{\rho} = nC$ — Strain-based formation (overuse)

  Else: $\dot{\rho} = 0$ — Remodelling equilibrium (stasis)

Else $\dot{\rho} = -C$ — Damage-induced resorption (pathology)

The algorithm for bone remodelling is illustrated in Fig. 2. This algorithm is used with a finite element analysis to simulate changes in bone density over time due to stress-shielding arising from introduction of the intramedullary stem.

Proceeding as illustrated in Fig. 2, the simulation is initiated by calculating the strain field within the bone using a finite element analysis. Each bone element is checked for remodelling status, and its rate of change of density is calculated according to the algorithm above. Next the apparent density change is calculated using the time step and element status as $\Delta\rho = \dot{\rho}\Delta t$. Stiffness of the element is then adapted according to a relationship between apparent density and Young's modulus, E, proposed by Carter and Hayes (1977) and as used by Weinans et al (1992):

$$E = 3790\,\rho^3 \qquad \text{Eq. 1}$$

Upon reloading, the change in bone Young's modulus causes a change in the resistance to stem displacement, leading to a different final position under peak load relative to the previous step, and a new strain distribution, which is used to drive the bone adaptation algorithm and update the material properties for the next time step. Iterative execution of the algorithm over a series of time steps thus simulates adaptation of the bone. As the stiffness of the bone tissue changes, the motion of the implant relative to the bone changes, which results in prosthesis migration over time. The simulation is terminated when the migration exceeds 3 mm.

Variability was introduced into the simulations by varying bone size and mechanosensitivity. First, a scaling transformation was used to warp the extra-cortical surface of the bone so that *every* case in the trial would have a different diameter bone reflecting the variability that exists in the human population. A uniform distribution for bone diameter was assumed in the population, and a random number was generated within a range of 20 mm to 25 mm for the bone diameter, taken from Noble et al (1988). Secondly, the strain-based resorption (ε_{min}) and formation (ε_{max}) thresholds were also randomly generated in order to represent variable mechanosensitivity, again assuming a uniform distribution, with a range of 1,000±500 με for ε_{min} and 2,000±500 με for ε_{max}. Therefore the 'width' of the zone of equilibrium strains in the reference case is 1,000 με, with variability in the strain-based resorption (ε_{min}) and formation (ε_{max}) thresholds set, following Frost (2003) as ±500 με. Therefore the reference case representing idealized or 'average' bone has the following variables: bone external diameter = 22.5 mm, ε_{min} = 1,000 με, and ε_{max} = 2,000 με.

In order to test the concept of a clinical trial for two intramedullary stems, two sets of simulations were performed: one for a low stiffness implant (Young's modulus = 20 GPa representing a lower bound for the Young's modulus of implant materials; see Katti, 2004) and one for a stiff implant (Young's modulus = 200 GPa representing steel). The simulated clinical trial consisted of 100 simulations per implant, i.e. 200 simulations in total.

3 Results

For the reference ideal case, the change in bone strain during the simulation takes on a different pattern depending on implant material. Among the differences are:

a) For the stiff implant a large region of strain-induced resorption occurs due to a greater degree of immediate post-operative bulk bone stress reduction whereas for the low stiffness implant damage-induced interfacial resorption occurs in a small proximal region due to proximal interfacial damage, refer to Fig. 3, time = 0 weeks, for evidence of this.

b) As the simulations progressed, interfacial damage-induced resorption appeared around both stems but differed in spatial distribution; in the low stiffness stem it progressed from proximal to distal whereas in the high stiffness stem it initiated distally and progressed proximally. Refer to Fig. 3, time = 10 weeks and time = 20 weeks.

c) Initially damaging of the *proximal* bone/implant interface occurs for the low stiffness stem causes strain-induced proximal bone loss to occur whereas for the high stiffness stem initial damaging of the *distal* bone/implant interface

interface occurs disconnecting the implant from the distal bone and placing further load on the proximal bone thereby halting resorption, see Fig. 3, time = 30 weeks. In other words complete opposite consequences of interfacial damage-induced resorption occur vis-à-vis bulk bone remodelling for high stiffness compared to low stiffness stems.

These aspects of the effect of materials selection on peri-prosthetic bone adaptations has not been observed previously either because the remodelling algorithms were simpler (Huiskes et al, 1987) or because the more complex anatomical geometries mask the general nature of the biomechanics of bone/implant systems (Scannell and Prendergast, 2009).

Referring to Fig. 4, quantitative analysis of the damage accumulation and associated density changes in the bone tissue shows proximal (GZ1) damage is initially greatest with the low stiffness stem but the damage obtained with the high stiffness stem eventually exceeds it (Fig. 4a). On the other hand, the low stiffness stem always induces a higher damage at the interface (Fig. 4a). Density changes in the bone due to both strain and damage are shown in Fig 4b.

Reductions in bone density cause increased migration of the implant under a cyclic load. In the reference case the mechanism causes a notable difference in the migration rate of the two implants, with the stiffer 200 GPa implant migrating more rapidly and thus failing more rapidly, than the low stiffness 20 GPa implant (Fig. 5).

However, when the simulation is run on the whole population very significant variation can be seen (Fig. 6) showing that the outcome is very variable in a population. Analysis of time-to-failure data shows that there is no statistical difference in the performance of the two implants in the population, despite the differences in the performance of the reference case (Table 1).

4 Discussion

This study set out to test the hypothesis that an analysis based on a method for predicting the performance in a population will lead to different conclusions than an analysis based on an idealised average patient. Using an intramedullary implant as an example, we found that the differences reported in an average idealised case are not found in an analysis that simulates the behaviour of the implant when used in a population. Deterministic analyses predicted that an intramedullary implant made of low stiffness material would migrate less than a high stiffness implant and should therefore have greater longevity; however our results show that if the variability in a population is modelled this result no longer holds –the data shows no statistical difference when variability of the kind that occurs in a population was included. Therefore the factors causing a variable outcome in a population are such that there is a significant overlap in the performance of two designs of intramedullary-fixated implants is corroborated.

The limitations of this study are that the analysis pertains only to a simplified intramedullary implant. A real anatomic bone shape and implant design could have been used where, we might expect, the variability would be even greater — in this respect it is more stringent to test the hypothesis in a simplified geometry compared to a complex anatomical geometry where the variability would be even greater. Similarly we could have varied other parameters such as the loading whereas in these simulations the loading is proportional to bone crosssectional area so that each bone is assumed to have an identical pre-surgical homeostatic strain level of 1500 με; again variation of loading or the homeostatic strain assumption would be likely to further increase variability. A limitation of the finite element analysis is that the bone properties used are isotropic and homogeneous whereas it is known that bone stiffness is anisotropic and spatially heterogeneous.

The bone remodelling algorithm used has been presented previously (Mulvihill and Prendergast, 2008; Mulvihill and Prendergast, 2010) and is based on the experimental work of (Lee et al., 2002) which associated microcracking with bone adaptation and the earlier theoretical work of McNamara and Prendergast (2007). The algorithm has been partly corroborated previously against simulations in 3D around noncemented total hip replacements (Scannell and Prendergast, 2009). Finally in this study no consideration was given to the possible repair of the interface when the resorbed tissue is replaced by soft tissue and then bone in a process of osseointegration (Prendergast, 2007).

The results presented here have implications for the conduct of preclinical testing using finite element modelling (Stolk et al., 2007). It suggests that simulations of implants in population-averaged or “ideal” anatomies may lead to conclusions that one implant is superior to another would not be borne out in a clinical trial. Since computational power is now sufficient to do simulations of clinical trials of the kind presented here then there is a case that these should be included in pre-clinical testing platforms used in seeking regulatory approval for devices. Such pre-clinical analyses could be aided by making available reference libraries of models of skeletal and other relevant anatomical structures, perhaps even different libraries for different ethnic groups reflecting differences in anatomy. Results of this study also suggest the importance of mechanoregulation parameters, which will also be variable in the population due to genetic differences and age variability in patients (Frost, 1987; Khayyeri et al., 2011).

In this study we have simulated a clinical trial on a simplified intramedullary implant. We have shown that, despite discernable differences in implants when analyses are performed on standard cases, there is no statistically significant difference when the implants are subjected to a simulated clinical trial.

A further aspect to be considered is that it is not the average performance that is important, but rather the proclivity to perform below par in a percentage of cases. Computational simulations of clinical trials have the potential to analyse this aspect of the behaviour of an implant design

In conclusion this study has identified that it is possible to perform a simulation of a clinical trial, and that such simulations have a value over and above analyses performed in idealised population-averaged reference cases since simulated clinical trials lead to different conclusions. It is proposed that these kinds of simulations be carried out taking account of the differences in the response of tissues to mechanical stress, as well as variations in anatomy. Furthermore an advantage of this kind of work is that the results are, in principle, validatable against the results of the clinical trial. If this proved to be true then it would overcome one of the most often made criticisms of computer modelling in implant analysis: the lack of falsifiability of the models.

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Figure 1: A 3D finite element mesh of an intramedullary implant of the reference dimension of 22.5 mm external bone diameter. Note that the loading applied to the implant is that which would give a 1,500 με in the longitudinal direction were it applied directly to the bone surface.

Figure 2: An illustration of the bone remodelling algorithm. A finite element model is used to compute the stress and strain in the bone tissue. If damage (denoted ω) is above a critical value then the tissue is pathologically injured and it resorbs, otherwise strain-adaptive remodelling occurs as follows: if strain (denoted ε) is above a threshold then addition of bone tissue occurs otherwise if it is below a threshold then resorption occurs, otherwise it is in homeostasis and neither resorption or deposition occurs. When the changes computed are very low the structure is converged and the algorithm 'exits'.

Figure 3: Contour plots of strain and damage activity at different time points during the simulation for the reference ideal 'average' cases for each stem. Note that the reference case is with a bone external diameter of 22.5 mm, ε_{min} = 1000 με and ε_{max} = 2000 με.

Figure 4: A detailed analysis of (a) the damage accumulation and (b) associated density changes in the bone tissue. Note that GZ stands for Gruen Zone, i.e. a region of the bone surrounding the implant.

Figure 5: In the reference case there is a difference in the subsidence rate of the two implants, with the 20 GPa implant migrating more rapidly and this failing more rapidly, than the 200 GPa implant.

Figure 6: When all analyses are run (100 per implant, therefore 200 in total) very significant variation is in subsidence is predicted. Statistical analysis shows that there is no statistical difference between the performance of the implants (refer to Table 1).

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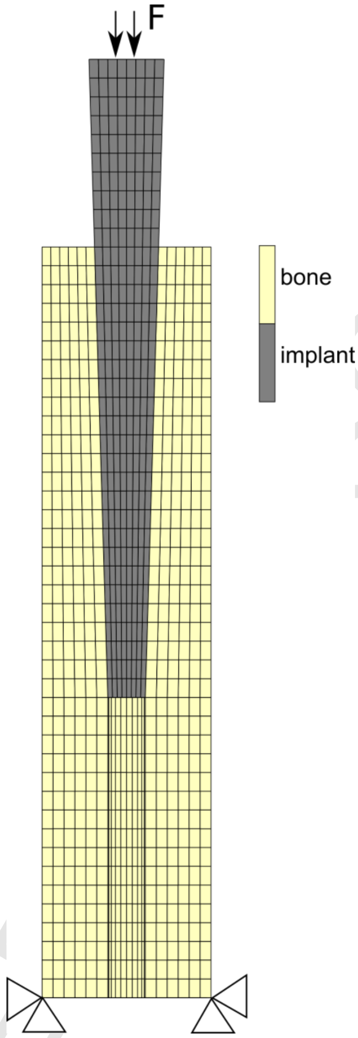
Table 1: Analysis of time-to-failure data shows that there is no statistical difference in the performance of the two implants in the population, despite the apparent differences in the performance of the reference models.

Table 1: Analysis of time-to-failure data shows that there is no statistical difference in the performance of the two implants in the population, despite the apparent differences in the performance of the reference models.

	E=20 GPa	**E=200 GPa**
Mean	45.58	45.91
Median	44.75	45.83
Standard Deviation	35	44
Sample Variance	8.14	7.62
Kurtosis	66.33	58.10
Skewness	-0.85	-0.64
Range	30	30
Minimum	34	32
Maximum	64	62
Confidence Interval (95.0%)	1.51	1.62
p (t-test)	0.77	



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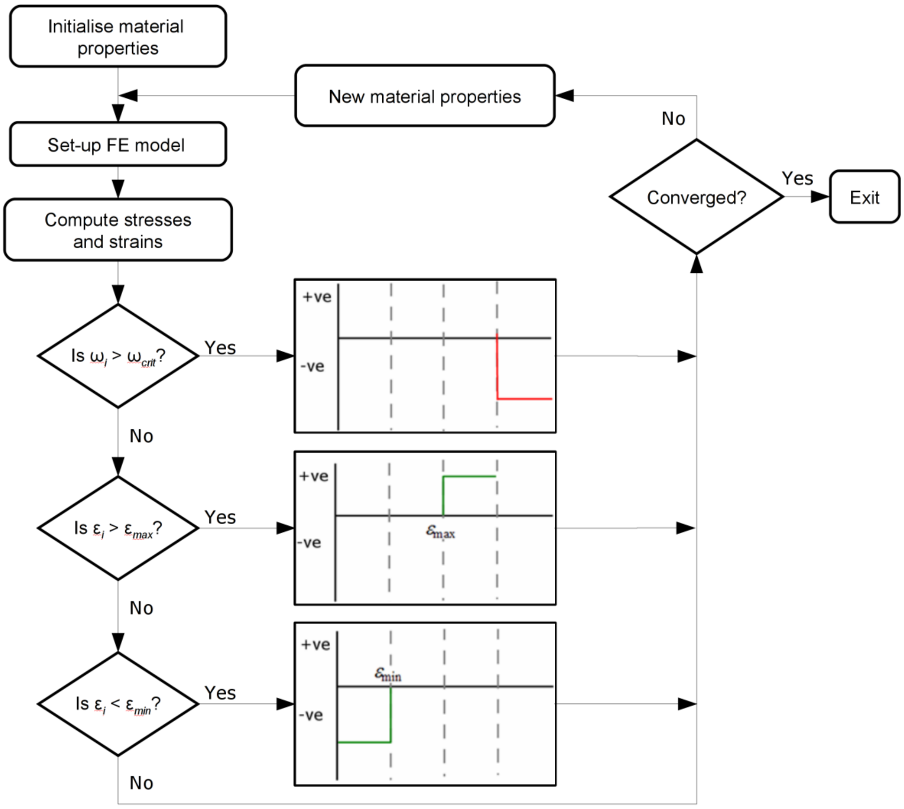


Figure 2: An illustration of the bone remodelling algorithm. A finite element model is used to compute the stress and strain in the bone tissue. If damage (denoted ω) is above a critical value then the tissue is pathologically injured by microcracking and it resorbs, otherwise strain-adaptive remodelling occurs as follows: if strain (denoted ε) is above a threshold then addition of bone tissue occurs otherwise if it is below a threshold then resorption occurs, otherwise it is in homeostasis and neither resorption or deposition occurs. When the changes computed are very low the structure is converged and the algorithm 'exits'.

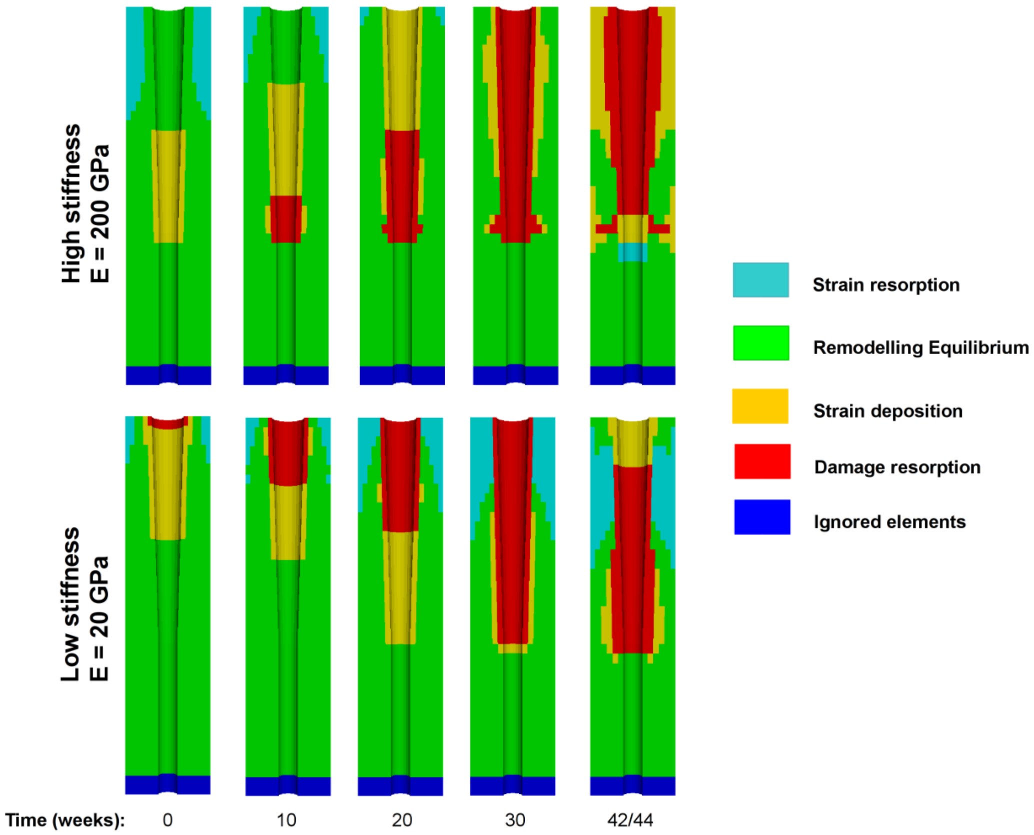
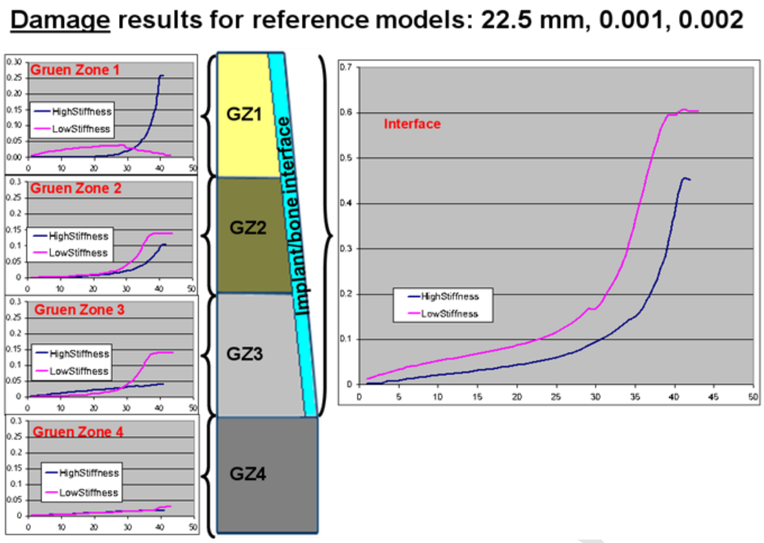
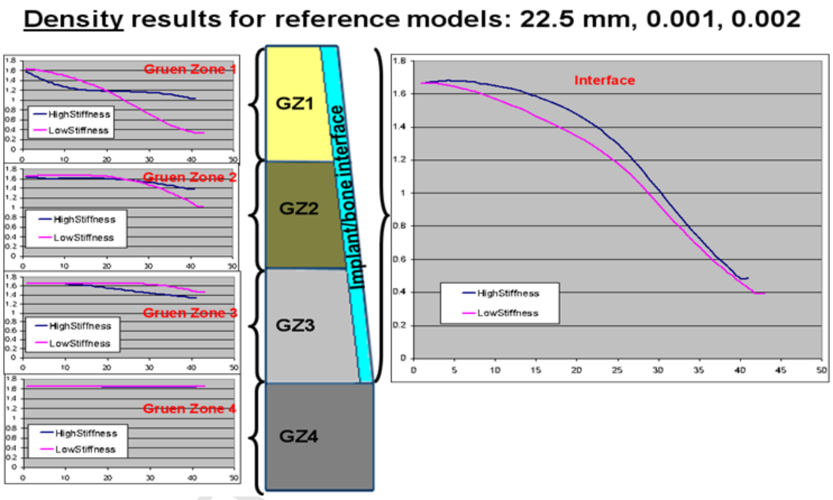


Figure 3: Contour plots of strain and damage activity at different time points during the simulation for the reference ideal 'average' cases for each stem. Note that the reference case is with a bone external diameter of 22.5 mm, ε_{min} = 1000 με and ε_{max} = 2000 με.



(a)



(b)

Figure 4: A detailed analysis of (a) the damage accumulation and (b) associated density changes in the bone tissue. Note that GZ stands for Gruen Zone, i.e. a region of the bone surrounding the implant.

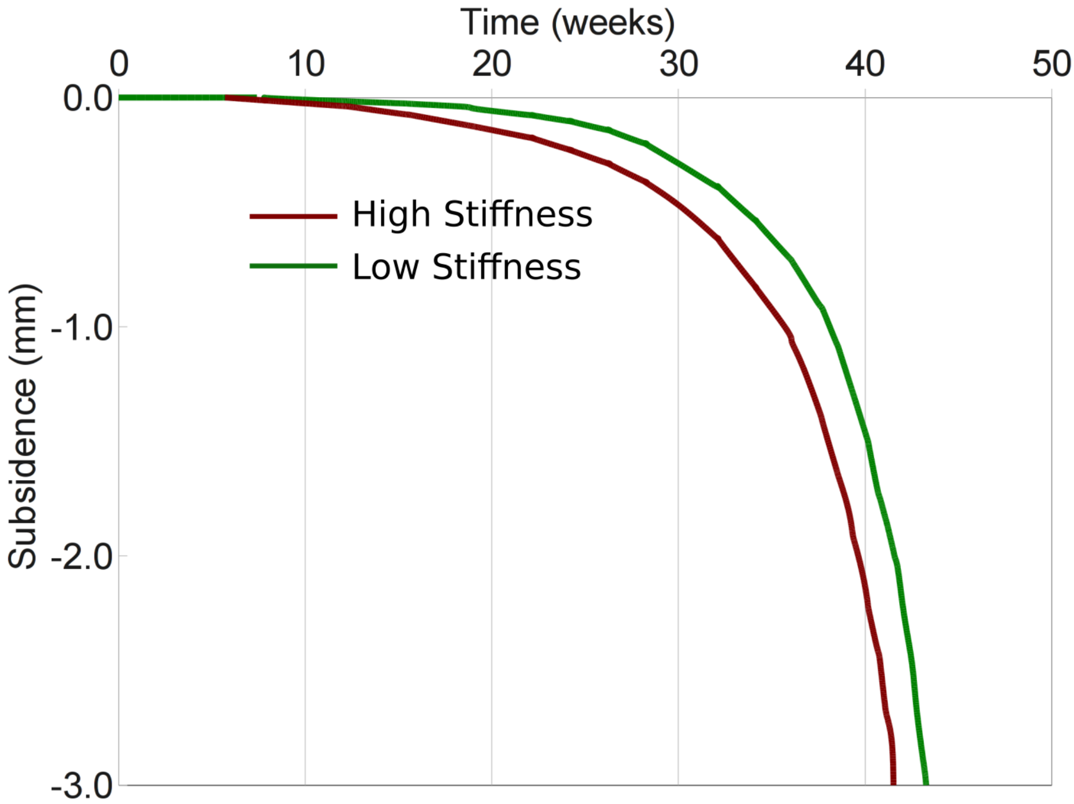


Figure 5: In the reference case there is a difference in the subsidence rate of the two implants, with the 20 GPa implant migrating more rapidly and this failing more rapidly, than the 200 GPa implant.

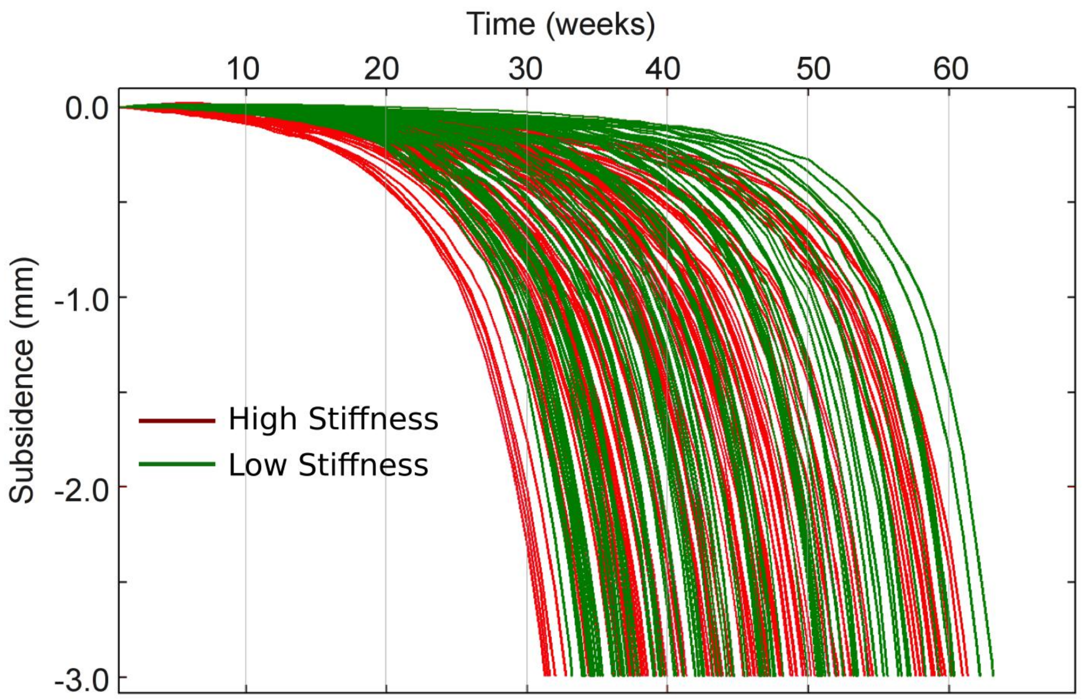


Figure 6: When all analyses are run (100 per implant, therefore 200 in total) very significant variation is in subsidence is predicted. Statistical analysis shows that there is no statistical difference between the performance of the implants (refer to Table 1).