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REVIEW ARTICLE

# Computational modelling of bone augmentation in the spine

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**Summary** Computational models are gaining importance not only for basic science, but also for the analysis of clinical interventions and to support clinicians prior to intervention. Vertebroplasty has been used to stabilise compression fractures in the spine for years, yet there are still diverging ideas on the ideal deposition location, volume, and augmentation material. In particular, little is known about the long-term effects of the intervention on the surrounding biological tissue. This review aims to investigate computational efforts made in the field of vertebroplasty, from the augmentation procedure to strength prediction and long-term *in silico* bone biology in augmented human vertebrae. While there is ample work on simulating the augmentation procedure and strength prediction, simulations predicting long-term effects are lacking. Recent developments in bone remodelling simulations have the potential to show adaptation to cement augmentation and, thus, close this gap.


## Introduction

Demographic changes are among the most important challenges for our society in the 21st century. Advancements in modern medicine have reduced mortality rates and many members of our society are expected to reach old age. While there are about 810 million persons aged $\geq$ 60 years today, by 2050 this number is expected to surpass 2 billion [1]. As a consequence, the number of workers available to support one elderly person will decrease from eight to four in only 40 years [1]. If we want to ensure access to effective health care for the elderly population, we will be forced to control and reduce emerging costs. A key element will be the focus on the management of age-related diseases.

A particularly widespread disease among the elderly is osteoporosis—an illness that is characterised by a reduced bone mass and a concomitant increased fracture risk [2]. The morbidity of all osteoporotic bone fractures is

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substantial and severe cases in the spine and hip are also coupled with elevated mortality [3]. Osteoporosis is a major problem for health care systems because these fractures are frequent and often need extensive treatment. Recent estimates show that osteoporotic fractures cost the European Union €36 billion every year, and these costs are expected to more than double by 2050 [4].

A significant share of the financial burden is due to vertebral fractures. Estimates of clinically diagnosed vertebral fractures show that the lifetime risk of vertebral fractures at the age of 50 years can be $>$ 15% in women [5]. Worldwide, $>$ 1.4 million vertebral fractures are estimated to occur every year [6]—that is one fracture every 23 seconds. The yearly cost for osteoporotic fractures in the spine sum up to a total of €719 million in Europe alone [4]. Research in novel treatment options for spine fractures might therefore not only help reducing pain and impairments for patients, but also support controlling rising costs in general health care.

Vertebral compression fractures, mostly occurring in weak osteoporotic bone, are painful [7]. It is assumed that, in particular, the deterioration of the trabecular microstructure in the course of the disease leads to an increased fracture risk [8,9]. Patients typically need bed rest and are treated with medication [10]. However, advances in biomedical engineering give hope for a more widespread use of new intervention approaches that will help to reduce the period of bed rest, pain, and the need for pharmacologic treatment or even ideally prevent fractures. A particular potential lays in bone augmentation procedures such as vertebroplasty, because of the minimally invasive nature of these approaches. Vertebroplasty is an intervention where bone cement is injected percutaneously through a cannula into the fractured vertebral body to restore its mechanical stability [11]. With advancements in fracture risk assessment [12] potentially weak vertebrae can be detected and targeted prior to fracture. Thus, we hope in the future to use vertebroplasty to also prevent fractures by augmenting vertebral bodies that were previously defined as fragile.

Despite vertebroplasty being a straight-forward intervention, the close location of the vertebral bodies to vital organs and the spinal cord demands the reduction of side effects to an absolute minimum. Bone augmentation stabilises the spine and leads to functional improvements [13,14]. In addition, pain relief is reported in most cases [13–17], although some studies could not confirm greater pain relief compared with conservative treatments [18,19]. The immediate complications reported with vertebroplasty are mainly connected to cement leakage [14], but it remains unclear what the long-term impact of the intervention is. A strong but controversial concern with bone augmentation in the long-term is the occurrence of fractures in adjacent vertebrae due to the increased stiffness of the augmented vertebra [20,21].

Like in many other biomedical branches, the increased capability of computational tools opens new doors for the investigation of bone augmentation. Such tools allow not only studying the mechanisms of disorders, but also surgical treatments. Initially, computational models in musculoskeletal applications were based on idealised, simplified structures. Today, these models are typically based on image-derived geometries from computed tomography (CT) or magnetic resonance imaging and can thus be individualised to the specific patient [22]. In recent years, finite element (FE) analysis in particular has become a frequently used versatile, general purpose simulation tool. Not only does it allow a detailed description of the mechanical load transfer in the spine before and after vertebroplasty, but such simulations have the potential to predict optimal augmentation patterns and cement distribution for individual treatment planning. Advanced *in silico* experiments, modelling the biology of the bone, can help to better understand the long-term risks and outcomes of augmentation interventions. This review aims to describe the efforts made in computational modelling of bone augmentation in the spine, focusing on the clinical intervention itself, the biomechanical situation after the treatment, and predictions of the long-term outcome.

## Computational modelling of the bone augmentation procedure

Vertebroplasty is a minimally invasive intervention to restore and stabilise fractured vertebrae by augmenting the bone with cement, typically polymethylmethacrylate. The bone cement is injected under local anaesthesia percutaneously through the back of the patient by means of a large-bore needle or cannula, directly into the vertebral body. The injection is monitored in real time with fluoroscopic guidance in order to assure deposition in the proper location, as well as to avoid cement leakage. It is important to keep the patient resting during the subsequent cement hardening period of about 1 hour [11,23].

More advanced imaging techniques could allow not only a more precise deposition of the cement, but combined with computational methods they have the potential to help the surgeon in the planning of the intervention for each patient by predicting the best position of the needle for the cement placement and by defining the optimal filling volume. Moreover, such simulations would also help to select or develop cements optimised for a specific intervention.

A simple approach on the organ scale to define the incision point and angle for the injection needle is described by Kobayashi et al [24]. Although it does not directly require computational tools, the method follows an algorithm and aims to target the middle of the cement deposition area and thus the needle position. On a horizontal CT scan at the level of the pedicles, the target is determined as the anterior one-third point along the median line. The incision point and angle are then derived by simulating the needle passing through the pedicle. The method assists treatment planning and allows a single incision for the bone augmentation.

A computational model of vertebroplasty including the needle incision and the cement injection is presented by Chui et al [25]. The model is designed for a virtual training setup and includes visual as well as haptic feedback. In order to be rendered in real-time, it is kept relatively simple, but still considers structures at tissue level. The resistance for the needle insertion is calculated in two phases; the cortical bone as a linear elastic material, the cancellous bone with the highly computationally efficient

discrete element method, where trabeculae are simplified as single beams. The cement injection procedure [26] is based on a rheological model simulating bone cement flow through a branching-pipe network mimicking the trabecular network. The pressure drop in cement during injection is modelled with an improved version of the Hagen-Poiseuille law supplemented with a time and shear-rate dependent power law. It allows an accurate and fast estimation of the injection pressure during the virtual intervention training.

A few years earlier, Baroud and Yahia [27] established an FE rheological model to characterise the behaviour of cement flow. A modified power law was implemented, capable of modelling not only the pseudoplastic (shear rate dependent viscosity), but also the rheopectic (time dependent viscosity) behaviour of bone cements. The FE model was simulated as flow through an axi-symmetric tube and showed good agreement when compared with an analytical solution; however, the simulation was limited to predicting the extravertebral flow, i.e., the cement flow through the cannula only.

The potential for patient-specific simulation of vertebroplasty was demonstrated in preliminary work by Teo et al [28], in which clinical CT scan data was used to define the overall vertebral geometry and isotropic permeability of the trabecular bone. Permeability, assumed to vary proportionally with bone porosity, is a principal determinant of cement spreading velocity in a porous bone bed.

More elaborate models of the bone augmentation procedure have been described by Widmer and Ferguson [29—31]. The cement injection is simulated with a model taking into account both the cement flow and the displacement of the bone marrow in the porous trabecular network [29]. The cement dispersion is approximated with the "volume of fluid" method, a numerical method moving the object surface on a mesh by conserving both mass and volume. The fluid dynamics is governed by Darcy's equation, relating cement flow rate to applied pressure differential through the permeability proportionality constant. The model was verified on spherical domains and was able to reproduce flow patterns with a known analytical solution. In follow-up work [30] the relationship between the permeability and structural parameters of trabecular bone was investigated. With a sufficiently high imaging resolution, permeability maps can be derived directly from the morphometrical parameters of the bone structure [31] and the cement injection can be simulated with the previously mentioned methods (Figure 1). When upscaling the pore-scale solution to continuum-scale, via a regression model built on morhpometrical parameters available in clinical images, the validity of Widmer et al's [32] method for the prediction of the cement deposition pattern was shown. With his multi-scale approach, it was possible to set up and validate a framework for the accurate simulation of cement spreading during bone augmentation, in a patient-specific fashion (Figure 2).

## Computational modelling for strength prediction

### Modelling the spine

The determination of mechanical strength of the spine after cement augmentation is a main focus both in *ex vivo* as well as in *in silico* experiments. During the intervention, the porous structure of cancellous bone is filled with a material differing in many ways from the extruded bone marrow. The load transfer will be changed not only within the augmented vertebra, but also throughout the whole spine. Although the reconstitution of strength or stiffness is unlikely the only determinant of a successful intervention, it gives a good idea on the degree of the increased stability as well as an indication about possible threads of overloading the adjacent vertebrae.

Also, here FE is typically used to predict the model sizes ranging from single vertebral slices, to larger volumes such

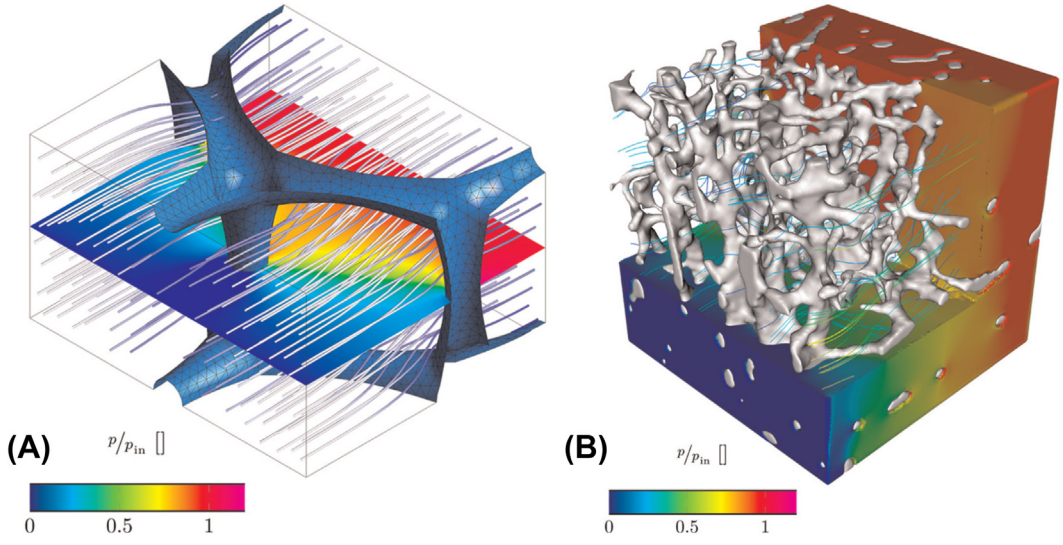


**Figure 1** (A) Streamlines of the fluid virtually flowing through the unit cell; and (B) a representative trabecular bone sample. *Note*. From "A comparison and verification of computational methods to determine the permeability of vertebral trabecular bone," by R.P. Widmer and S.J. Ferguson, 2013, *Proceedings of the Institution of Mechanical Engineers. Part H, Journal of Engineering in Medicine*, *227*, p. 617—28. Copyright 2013, SAGE. Reprinted with permission.

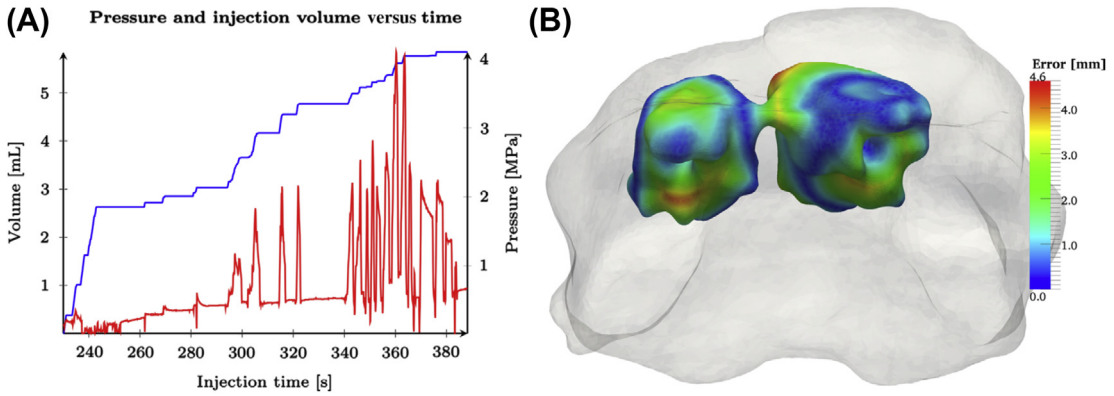


**Figure 2** (A) Demonstrates typical pressure and injection volume curves of a paramethoxyamphetamine-based bone cement injection using the motor-driven delivery device. The recorded cement volume profile was subsequently used to drive the continuum-scale model. During the progress of the injection, the cement hardens and a higher injection pressure is needed to force the cement into the vertebral body; (B) segmented experimental cement cloud coloured by the prediction error of the continuum-scale model. The principal source of error is uncertainty in the location of the cannula during the *in-vitro* experiments. *Note*. From "Numerical description and experimental validation of a rheology model for non-Newtonian fluid flow in cancellous bone," by R.P. Widmer, A. Lopez, C. Persson, L. Cristofolini, S.J. Ferguson, 2013, *Journal of the Mechanical Behavior of Biomedical Materials*, *27*, p. 43—53. Copyright 2013, Elsevier. Reprinted with permission.

as whole vertebrae with and without endplates or even multiple vertebral segments of the spine [33,34] (Figure 3). Although performing tests only on the level of a vertebral body may oversimplify the complex load transfer in the spine, it is difficult to accurately mimic the forces acting on multiple segments [33]. FE models are typically separated into either continuum models, where the microstructure is approximated by integrating the mechanical behaviour into large continuum elements, or micro FE models, where the mesh is fine enough to represent the bone micro-architecture, becoming more and more the state of the art in strength prediction [12].

The increased accuracy of computational tools developed in the past decades, from increased imaging resolution to more detailed modelling of mechanics, leads to considerable advantages over classical mechanical testing, especially in the spine. Not only is the availability of testing material expensive and limited; the potential degradation of *ex vivo* samples raises questions about their relevance. The preparation phase and inadequate conservation may change the mechanical properties [33]. In addition, *in silico* experiments allow the use of a single sample to investigate several augmentation volumes, patterns, and properties of the augmentation material without having to deal with variation from multiple samples [34]—a particular advantage when assessing the success of the intervention against untreated cases.

The geometry for the FE models is typically generated from CT images. Classical CT imaging is normally sufficient for the generation of the relatively rough mesh of

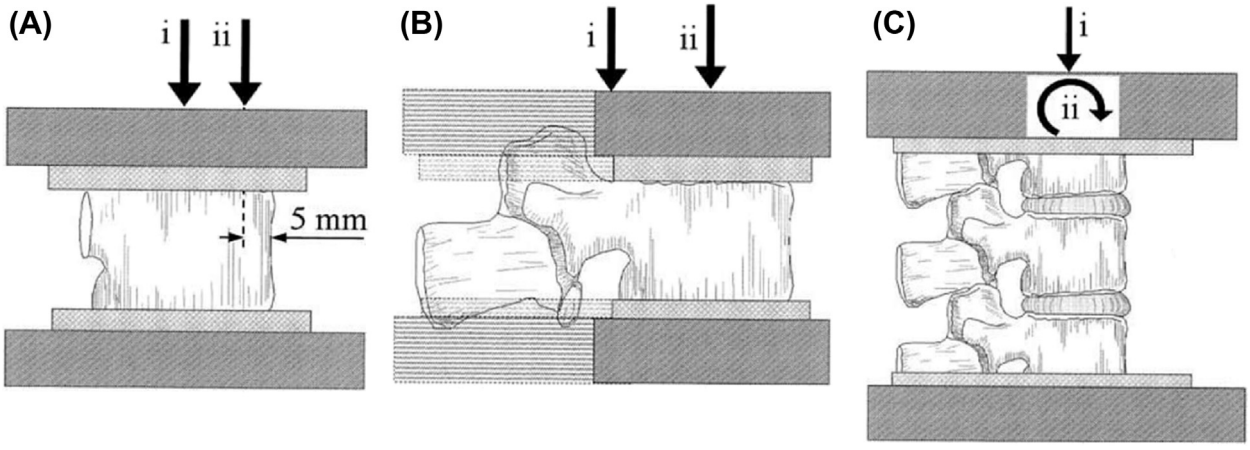


**Figure 3** Methods of specimen test-up showing: (A) a single vertebral body with (i) central and (ii) off set loading; (B) a single vertebra with loading applied to (i) the whole upper surface or (ii) only the vertebral endplate; and (C) a multisegment unit under (i) compression and (ii) bending. *Note*. From "The biomechanics of vertebroplasty: a review," by R.K. Wilcox, 2004, *Proceedings of the Institution of Mechanical Engineers. Part H, Journal of Engineering in Medicine*, *218*, p. 1—10. Copyright 2004, SAGE. Reprinted with permission.

continuum-scale FE. Some of the used material models however require structural information that is gathered from a sub-mesh resolution. Micro FE models have a mesh enough fine to represent the trabecular structure. In order to generate models from real bone, high resolution imaging techniques are needed. Where currently micro FE models of human bone are typically generated from *ex vivo* micro-CT measurements, the development of high-resolution peripheral quantitative CT allows *in vivo* imaging of the trabecular structure of human bone and the subsequent generation of micro FE meshes [35].

## Continuum models

Continuum FE models vary in the complexity of the used material models. Liebschner et al [36] used models where the geometry of vertebral bodies was derived from CT scans and converted to 20-noded brick elements. Different material models were used for cortical and cancellous bone. The cortical shell was modelled as an isotropic material with a constant modulus derived from experiments. The cancellous bone was modelled with changing moduli in the axial direction, in a linear relation to the mineral content. Baroud et al [37] proposed a model of a whole spinal unit including two vertebrae and the enclosed intervertebral disk. Similar to the previous model, the endplates and cortical shell were simulated as linear-elastic materials, whereas the cancellous bone was simplified to be isotropic linear elastic, with different moduli for the nonaugmented bone and for the bone cement composite. Eight linear elastic layers represented the annulus while the nucleus was modelled as a nonlinear incompressible solid. The whole spinal unit model was extended by Polikeit et al [38] in a model including not only two vertebral bodies and the endplates but also the facets and ligaments. The mesh was finer than that of the previous models, and the bone and cartilage elements were chosen as linear, homogeneous, and isotropic, whereas the fibres where modelled as tension-only truss elements. The facet joints were modelled as nonbonded elements with friction. Baroud et al [37] and Polikeit et al [38] were able to show with these multi-segment models that augmentation not only alters the properties of the treated vertebra, but through stiffening of this structure, an altered load transfer through the flexible intervertebral disc to the adjacent vertebra results. A similar model using linear elastic tetrahedral elements was presented by Zhang et al [39], again including two vertebrae with pedicles, ligaments, and friction facet joints as well as the endplates. With this model, Zhang et al [39] highlighted also that the load is shared between the vertebral bodies (85%) and the posterior processes (15%), and that this load sharing can be altered through augmentation, which was previously reported in an experimental study [40]. A model allowing damage accumulation was presented by Kinzl et al [41]. The elements of the homogenised bone are considered as a damageable spring and allow the model of both the elastic and nonlinear phase of the augmented vertebrae under load. Similarly, Tarsuslugil et al [42] considers both intact and damaged model elements. In this work, however, the damaged elements are defined in a previously performed mechanical test. Yet another aspect of bone augmentation is considered in the presented model of a whole augmented vertebra by Purcell et al [43]. Some augmentation procedures push the trabecular structures out of the augmentation volume leading to a region of more compact trabecular bone at the edge. In this model, the element nodes adjacent to the augmentation cement are thus considered as compacted bone elements with an increased modulus.

While still a continuum FE model, the model of Wijayathunga et al [44] represents a step towards a micro-FE model. Although relatively fine, the mesh does not entirely resolve the microstructure. This structure is, however, represented by directly integrating and converting the greyscale values to material properties within the elements. In addition, a nonlinear elastic perfectly plastic material model was chosen. The complexity of the material model was further increased in a study by Chevalier et al [45], where trabecular bone elasticity was represented in the continuum elements with a stiffness tensor taking into account the anisotropy of the axial and transverse directions and the local bone volume fraction.

## Microstructural models

Continuum FE models were developed to overcome the simplification of the geometry of the simulated tissue, but require complex material models. Today, both high-resolution imaging techniques as well as the improvements of computational power and algorithms allow the direct representation of the microstructure in micro-FE models. Because the real bone geometry is used, isotropic material properties are normally sufficient to adequately model the mechanical behaviour. Keller and colleagues [46] present a two-dimensional micro-FE model to investigate different augmentation patterns. The geometry was derived from a micro-CT cross-section of a vertebral body at 146 μm resolution. For simplicity reasons, sagittal symmetry was assumed and only half the vertebra was modelled. The geometry was mirrored on top to create two adjacent vertebrae with an enclosed intervertebral disc. Bone, marrow, cartilage, and bone cement elements were modelled with corresponding material properties. Later, the model was extended [47] to account for the intervertebral disc degeneration in the process of the degeneration of the whole motion segment and included several augmentation patterns for vertebroplasty (Figure 4). The reduced disc mobility was simulated by increasing the stiffness of the nucleus to the value of the surrounding annulus. In another, earlier project [48], the resolution was increased to 83 μm and a whole section of a vertebra was used without mirroring.

## Augmentation volumes

While the procedure for the geometry generation is generally standardised, simulations of augmented bone have been performed with a variety of different approaches. Several simulations include a prior simulation of bone fracture [36,46—49]. Models including fracture simulation are performed in two or more loading cycles [36,46—48]. In the adaptation cycles, the vertebrae are loaded and the moduli of bone elements exceeding a

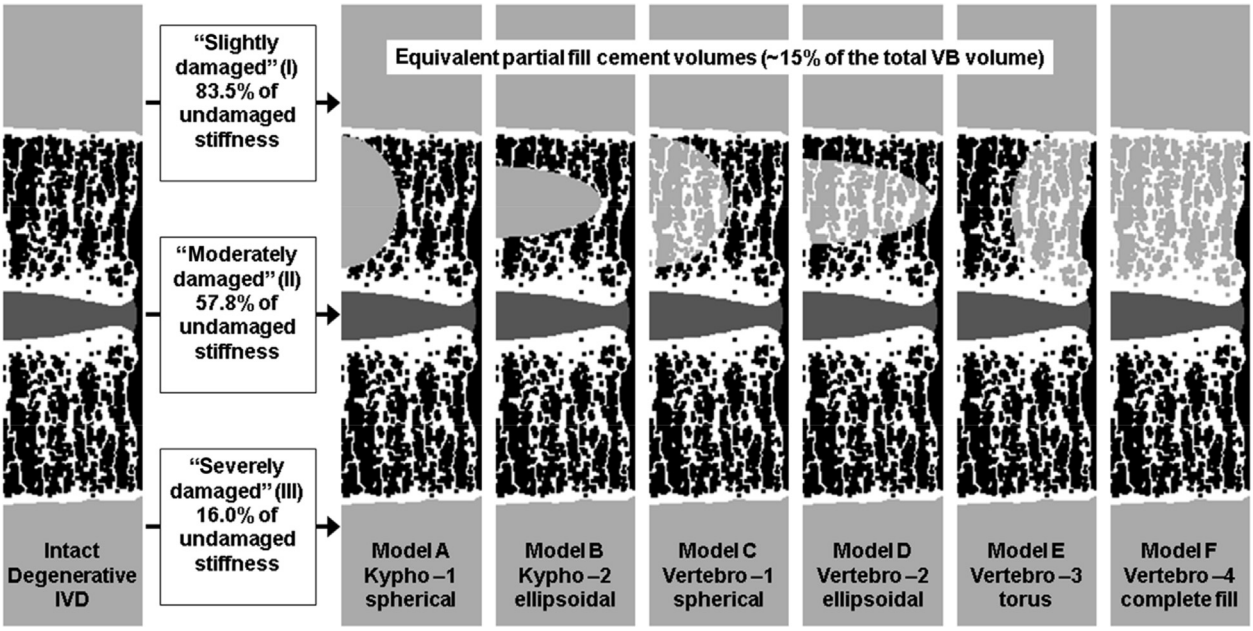


**Figure 4** An intact axi-symmetric degenerative intervertebral disk microstructural finite element motion segment model (left) is evaluated at three bone damage levels (I, II, and III) to determine the effectiveness of each of the six cement augmentation strategies (Models A—F). Paramethoxyamphetamine cement in regions above and below the superior and inferior vertebral bodies was added to mimic *in vitro* experimental validation test conditions. *Note*. From "Early stage disc degeneration does not have an appreciable affect on stiffness and load transfer following vertebroplasty and kyphoplasty," by V. Kosmopoulos, T.S. Keller, C. Schizas, 2009, *European Spine Journal*, *18*, p. 59—68. Copyright 2009, Springer. Reprinted with permission. IVD = intervertebral disk; VB = vertebral body.

compressive load threshold are reduced to represent microdamage of the trabecular structure. The deterioration levels vary from single [36] to multiple [46—48] stages of degradation. Instead of fracture, osteoporosis was also modelled by reducing the elastic moduli of the entire cancellous bone by 66% and the cortical shell by 33% [38].

In order to predict strength after augmentation, the geometry and material properties of the augmented cement volume have to be defined. The augmentation volume is often created artificially in order to test different augmentation shapes and levels of augmentation [38,39,43,46—49] as shown in Figure 5. Purcell et al [43] used a horizontally oriented barrel model to represent the augmentation volume. Similarly, Polikeit et al [38] modelled the cement as vertically oriented barrels to simulate bi- and unipedicular augmentation. The partial augmentation filled up about one-third of the vertebral body. In addition, full augmentation was modelled by replacing the cancellous bone elements with polymethylmethacrylate. As a whole spinal unit was modelled, effects of augmentation on the superior and inferior endplate could be investigated. The approach of complete filling was also used by Zhang et al [39] but extended to change the properties of the augmentation material and therefore allowing optimisation of the augmentation cement. Additionally, different augmentation patterns were modelled in the studies by Keller et al [46] and Kosmopoulos et al [47]. For this, the augmentation volume was kept constant at 15% of the total vertebral body volume. Augmentation patterns included elliptic filling with and without contact to the endplates, a model with a torus geometry connecting the superior and inferior endplate as well as complete filling. Augmentation was modelled by replacing bone marrow within the augmentation volume with cement but keeping the trabecular structures. In addition, the model was used to investigate the effects of cement stiffness on the stiffness of the whole augmented vertebra. In a similar study, Kosmopoulos and Keller [48] simulated six different degrees of augmentation filling with a spherical shape ranging from 12% to 100% filling of the interior vertebral body. In addition, real augmentation volumes derived from μCT data directly were also used [41,42,45].

Both *ex vivo* as well as *in silico* strength is typically predicted using axial compression loading. Fractures of osteoporotic bone, however, often occur because of non-characteristic loading due to unexpected impacts. Zhang et al [39] simulated different combined loading scenarios including pure axial loading, axial loading, and forward moment as well as axial loading and backward moment.

## Model validation

Typically, the validation of the predictive models is a very difficult task. In the work of Kinzl et al [41], each of the 41 models was validated with mechanical testing of the real underlying augmented specimens showing small deviations in strength and apparent stiffness. Also, the FE results were comparable to the pressure measurements on sensitive

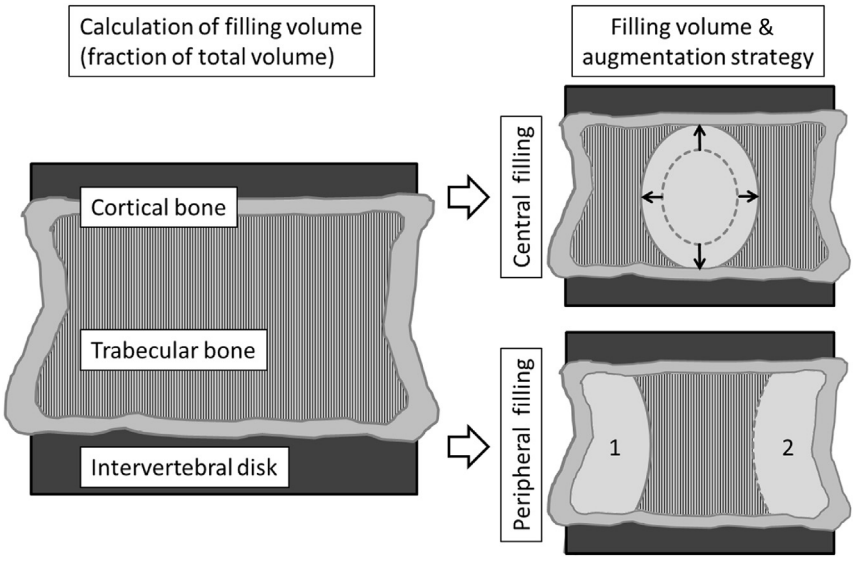


**Figure 5** Typical procedure for the definition of the simulated augmentation volumes: first, the filling volume is defined as a fraction of the total vertebral body volume. Then, the shape of the augmentation volume is defined depending on the augmentation strategy.

films. Wijayathunga et al [44] created 11 models directly from human samples and validated the results by comparison with mechanical tests of the real samples under loading to failure up to 25% reduction of initial height. The model parameters were fitted to three samples and the predictive power was determined for four nonaugmented and four augmented models. Validation of the simulations showed good agreement with experimental test for the nonaugmented bones, but models overestimated stiffness and strength in the augmented case. Chevalier et al [45] used 12 vertebral bodies that were scanned prior to axial compression to fracture. After fracture, the vertebrae were augmented and rescanned. FE models were developed for both nonaugmented and augmented samples and the stiffness compared. In addition, cements of different stiffness were tested *in silico*. They concluded that optimal augmentation was achieved with a compliant cement, completely bridging from superior to inferior endplate.

While continuum models suggest that already a small fill volume is enough to restore the stability of the vertebral body to the prefracture state [36], increasing the mesh resolution reveals that significant stiffening was observed only for vertebrae where cement was deposited through the whole height of the body [45]. Full augmentation increases the stiffness to more than in the prefracture state [37]. The cement deposition pattern appears to be of great importance for the fracture stabilisation. The models suggest that symmetric placement of small amounts of cement might be more appropriate [36]. The most effective strategy to repair stiffness with a partial augmentation seemed to be using a torus shaped geometry connecting superior and inferior endplates [46].

Cement augmentation changes the load transfer in the spine by reducing the bulge of the endplates and increasing the pressure in the intervertebral disk [37,38], which increases the stress under load in cancellous and cortical bone [38] as well as increasing stresses in the endplates [39,45] of the adjacent vertebra, potentially provoking subsequent fractures. However, the augmentation of the vertebral body successfully reduces the number of highly stressed trabeculae in the cancellous bone in both damaged and undamaged bone, if the degree of filling is high enough [48]. The facet joints were less loaded after augmentation which led to a load shift towards the anterior column [38]. Osteoporosis and augmentation had little effect on the internal pressure of the disk [39] and the cement modulus had almost no influence on the apparent stiffness unless the vertebral body was completely filled. Where available, validation showed good agreement with models, but cement stiffness was overestimated [44].

While the proposed models greatly simplify the system, the benefits of all approaches are the multitude of simulations that can be performed. However, no three-dimensional micro-FE models of augmented cancellous bone have been published so far. The two-dimensional structure analysis is not equally representative for the load transmission. Most models simplify the microstructure mechanics in complex material models. A particular difficulty lies in the bone and cement composite region of the continuum models.

## Computational modelling for *in silico* prediction of bone biology in augmented spines

### Bone adaptation

We know that the bone microstructure does not represent random orientations of the rod- and plate-like trabeculae, but that their alignment is very well oriented to withstand the forces of daily loading [50]. While the principle geometry of the bones is mostly genetically determined, the mechanics at the organ and tissue level regulate the microstructural adaptation [51]. The trabecular orientation is a result of the remodelling cycle, where different bone cells are involved in the renewal of the bone tissue: bone forming

osteoblasts and bone resorbing osteoclasts constantly rebuild the bone matrix and may be motivated by osteocytes embedded within the bone matrix sensing a mechanical signal [52]. While bone remodelling simply leads to bone turnover, mechanically driven remodelling leads to bone adaptation. Possible triggers for bone adaptation are electromagnetic fields, bone deformation or strain, fluid flow, vibration, damage, or any combinations of these [51]. While the complexity and the large number of involved cells and signalling pathways makes it difficult to describe bone remodelling on the cellular level, simplified models for tissue adaptation are available. Most importantly, the mechanostat principle [53] linking mechanical strains to bone formation and resorption has been widely accepted. According to the theory, bone will be formed in regions with high mechanical strains and removed from unloaded bone structures, hence guiding the tissue structure towards an optimal form that ensures a homogeneous stress distribution. Because of its simplicity and the predictive power, this model is ideally suited for *in silico* bone adaptation.

Bone formation and resorption is well balanced in healthy bones maintaining their net volume. In osteoporosis, the balance is disturbed towards an overall loss of bone mass and a concomitant increase in fracture risk [2]. Vertebroplasty is typically used for osteoporotic patients, and changes in bone density have to be taken into account for a long-term prediction of the treatment success. Bone is dynamic and constantly adapting to the changing needs in load transfer. While assessing the mechanical strength of augmented bone might give a good insight into the immediate postoperative stability, it is questionable, whether the strength of the cement and bone composite remains the same in the long-term. Augmentation changes the load transfer and will inevitably lead to under- and overloaded bone sites, as is also known from metal implants. *In silico* biology has the potential to significantly increase the success in the prediction of the intervention. In combination with accurate fracture risk assessment [12,54], it could give a better insight into the micromechanical changes of augmented bone and lead to a better understanding of the augmentation approach as a whole.

A variety of approaches to simulate bone remodelling have been proposed, ranging from organ-level to tissue-level to cell-level [55,56]. Organ-level approaches do not resolve the trabecular microstructure and are not suited for the assessment of long-term stiffness and stability. Cell-level bone adaptation simulations model the action of single cells and typically do not look at structural influences of the whole bone stability. The focus for *in silico* bone adaptation in augmented bones lies, thus, on tissue-level models.

## Nontargeted bone remodelling

A microstructural bone remodelling model was introduced by Mueller [57]. The algorithm sequentially applies Gaussian filtration and thresholding and models long-term architectural changes due to osteoporotic bone loss. It could potentially be used for a generic analysis of the long-term fracture risk in augmented bone; however, the lack of a mechanical feedback would not take into account the biological response to bone augmentation. Because the trabeculae are primarily oriented along a single principal loading direction, Gerhard et al [55] suggested the compression of the filter in the principal loading direction, and hence considering some of the adaptation of the bone to the loading. Nevertheless, the model cannot account for the changes of loading in the local microarchitecture around and within the augmentation material.

## Bone remodelling with mechanical signal

Microstructural remodelling simulations of whole bones are challenging because of the computational cost and few cases have been reported so far. Wang et al [58] presented a remodelling simulation of a cross section of an artificially generated vertebra. The model includes modelling of micro-damage as well as adaptive remodelling with strain energy density as the mechanical signal. The model was used to show the mechanisms of bone loss and the collateral deterioration of mechanical strength. Nevertheless, the reduction of the model to two dimensions is a drastic limitation making the model less suitable for simulations of bone adaptation in the context of osteoporosis and bone augmentation.

Boyle and Kim [59] used space topology optimisation on a three-dimensional random trabecular structure to create a realistic trabecular distribution of the proximal human femur. The method reorients structures in order to uniform the strain energy of the system. Although the model was used to investigate Wolff's law and started with a randomly generated architecture, it was able to show adaptation to changed loading. A limitation of the model is that space topology keeps bone volume constant and, hence, cannot recreate the bone deterioration due to bone loss.

An iterative mechanical feedback loop for three-dimensional bone remodelling was proposed by Ruimerman et al [60]. This approach is based on a previously developed model of tissue adaptation [61], where formation and resorption are considered as separate events. Similar to the mechanostat principle, formation is mechanically driven (local strain energy density levels) with more deposition for a higher mechanical signal. Bone resorption, however, is modelled as a stochastic process that is happening randomly on the bone surface. The model was able to generate reasonably realistic trabecular structures when compared with pig samples. In a recent study [62], the model was applied to human iliac crest biopsies to simulate increase in bone mass (Figure 6). Appropriate tuning of the settings may allow simulations of long-term adaptation of augmented osteoporotic bone.

Another three-dimensional bone adaptation algorithm was introduced by Adachi et al [63]. Following the mechanostat principle, the model uses stress gradients to define sites of bone formation and resorption, as well as regions of quiescent bone. The procedure is repeated until an equilibrium state is reached and showed smooth morphological changes on the trabecular level. Although using a simple formulation of the bone remodelling algorithm, adaptation of real canine cortical bone to different loading conditions could be simulated. The model was subsequently applied on an artificial human proximal femur, under different loading conditions, which led to characteristic patterns of trabecular bone found in humans [64].

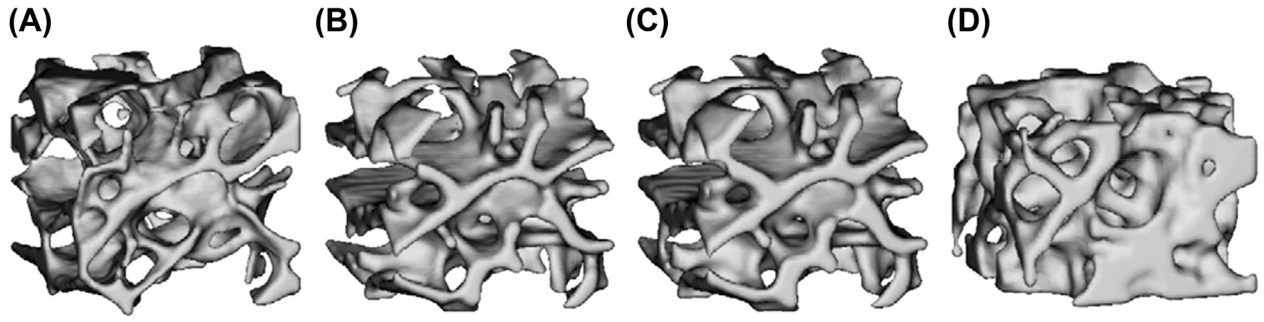


**Figure 6** Bone micro-architecture of the (A) initial; (B) adapted; (C) simulated hypoparathyroidism with 140% osteocyte mechanosensitivity; and (D) clinical hypoparathyroidism biopsies. *Note*. From "Patient-specific bone modelling and remodelling simulation of hypoparathyroidism based on human iliac crest biopsies," by P. Christen, K. Ito, R. Müller, M.R. Rubin, D.W. Dempster, J.P. Bilezikian, et al, 2012, *Journal of Biomechanics*, *45*, p. 2411—6. Copyright 2012, Elsevier. Reprinted with permission.

Cancellous bone deterioration is simulated in a model described by McDonnell et al [65]. In this model, not only voxels with low principal strains are resorbed, but also the very highly loaded voxels to simulate micro-crack formation. The model was run on specimens of human vertebral trabecular bone and showed the structural degradation of the microarchitecture following bone loss (Figure 7). This model could be particularly interesting for the long-term prediction of augmented bone, as it is able to simulate the formation of possible micro-cracks due to the changed loading environment.

Whole mouse vertebrae have been simulated in a remodelling algorithm presented by Schulte et al [66]. The model is based on a mechanostat approach with strain energy density as a mechanical signal determining locations of bone formation and resorption. Real *in vivo* micro-CT measured data has been used allowing an extensive validation of the static and dynamic changes in morphometric parameters. In later work [67], the model was applied to large datasets and extended to simulate the effects of additional loading and pharmaceutical treatment regimens.

In order to overcome some of the computational challenges linked with three-dimensional microstructural bone adaptation of human bones, efforts are made in the direction of multiscale approaches where the idea is to run the FE on a macroscopic level only [68]. Another possibility is to simulate the local changes of bone mass by integrating structural information at multiple scales and analytically define the consequences on the mechanical stability [69]. At the same time, the previously described Schulte model has been adapted to run datasets of whole human bone [70]. Homeostatic bone adaptation has been simulated on two datasets of whole human vertebrae at high resolution. Having crossed the technical challenge to run simulations on such large volumes, bone remodelling models have the potential to be used to investigate microstructural changes of the trabecular bone due to cement augmentation.

As far as the authors are aware of, no simulations of bone adaptation after bone augmentation have been published so far. Tarala et al [71] have presented an organ level model of bone adaptation after total hip replacement. Looking at bone augmentation, similar to this work the special interest would be in regions of bone loss due to stress shielding. With the necessary simulation tools available, simulating the evolution of the microstructure of the augmented vertebrae should be feasible in the future in order to get better insight into the long-term effectiveness of vertebroplasty.

## Conclusion

Vertebroplasty is a promising minimally invasive approach to stabilise fractured vertebrae and may be used to prevent vertebral fractures in the future. Although pain reduction has been reported consistently [13—17], the biological mechanisms leading to pain reduction are still unclear and the mechanical effectiveness is controversial, with strong potential for improvement. Computational tools have thus a great potential to give better insight into the augmentation procedure, the stability after augmentation and the long-term consequences on bone biology.

In particular, the work of Widmer et al [29—32] gives a clear description of the injection patterns during vertebroplasty. This multiscale approach cannot only be used to predict augmentation volumes for individual vertebrae and help deciding where the augmentation material should be injected, but it can also be used to design new augmentation materials with better characteristics in the filling process.

Computational modelling of augmentation in the spine has primarily focused in the stability of the vertebra after augmentation. While most studies use organ-scale models, microstructural models for strength prediction have traditionally been limited to two dimensions. However, advances in computational power and parallelisation approaches allow today a three-dimensional analysis of the bone microstructure. There is huge potential in the use of such tools for analysing the changed biomechanics after augmentation to make fracture assessment more accurate and improve treatment planning.

Multiple microstructural bone adaptation models have been proposed and show realistic morphological changes on real trabecular bone volumes. The high computational cost is the main factor why most models are limited to small volumes. Recent developments in bone remodelling simulations, however, are able to simulate microstructural bone adaptation in whole human bones. These models have the

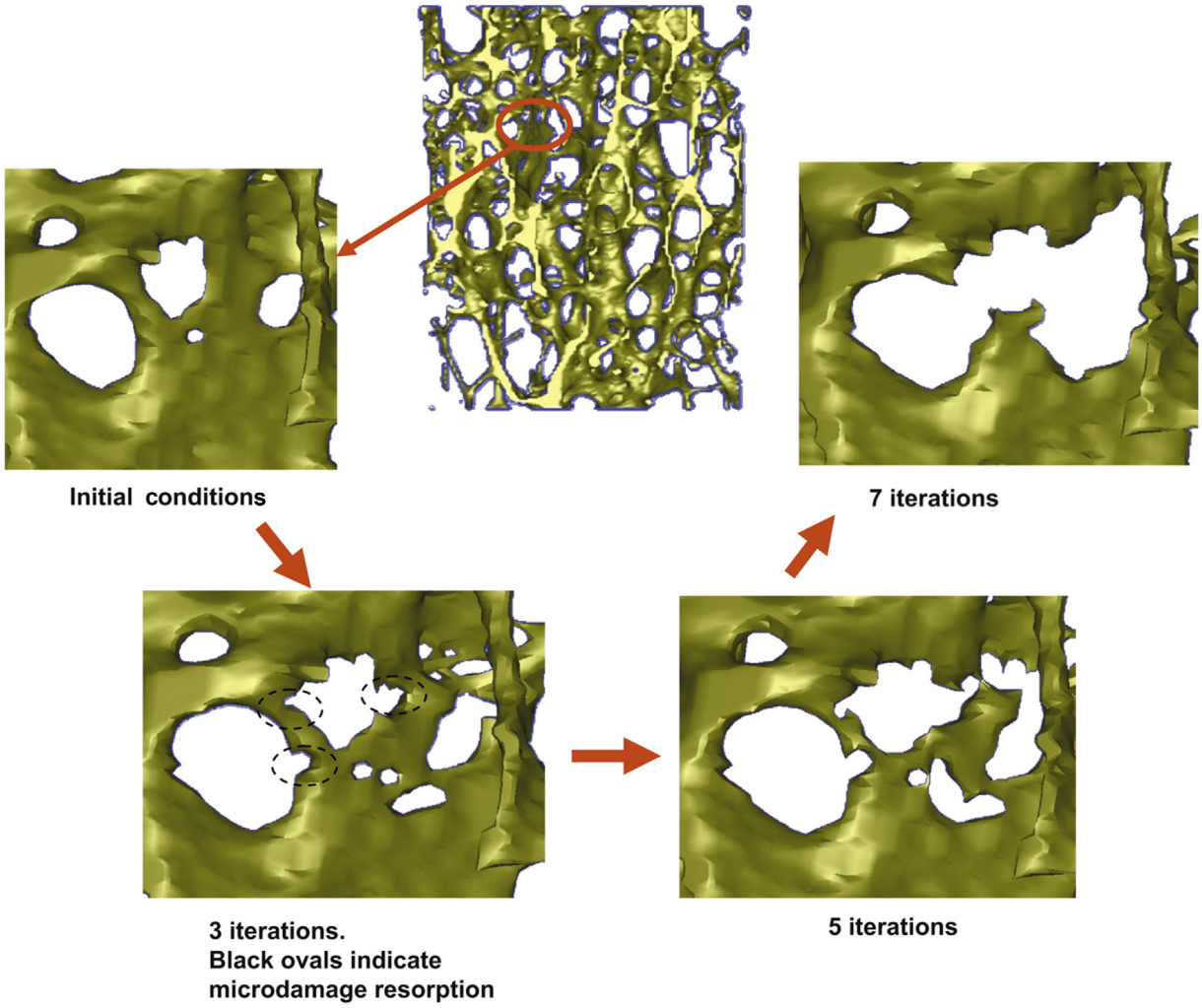


**Figure 7** Close up view of progression of microdamage resorption and perforation of vertical trabeculae. *Note*. From "Simulation of vertebral trabecular bone loss using voxel finite element analysis," by P. Mc Donnell, N. Harrison, M.A. Liebschner, P.E. Mc Hugh, 2009, *Journal of Biomechanics*, *42*, p. 2789—96. Copyright 2009, Elsevier. Reprinted with permission.

potential to show adaptation to cement augmentation in the bone. Not only could this give an insight in the biological processes after the intervention, but also help to better predict the long-term effectiveness of bone augmentation in the stabilisation of fragile bone.

## Conflicts of interest

The authors declare that they have no conflicts of interest.

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