

# **Modélisation par éléments finis des effets des médicaments sur le remodelage osseux : Approche mécanobiologique**

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## 1. INTRODUCTION

Skeletal bone remodeling is a dynamic process mediated by two distinct cell types, osteoclasts which mediate the production of acids and enzymes to dissolve bone minerals and proteins to resorb bone and osteoblasts, which form new bone. The balance of the functions of these cells contributes to the maintenance of bone and skeletal health. An imbalance between osteoclastic and osteoblastic cell functions generates osteoporosis. Osteoporosis is a metabolic bone disease that results in significant bone loss, bone fragility and increased susceptibility to fracture. Osteoporotic fracture is a risk factor for subsequent long-term morbidity and mortality in elderly, especially postmenopausal women. The incidence of osteoporosis in postmenopausal women continues to increase with progressively aging populations.

The functioning and interaction of osteoblasts and osteoclasts cells are coordinated by the competitive binding of RANK (receptor activator of nuclear factor  $\kappa$ B) receptor and a soluble decoy receptor, osteoprotegerin (OPG), with RANK ligand (RANKL) expressed on the surface of osteoblasts.

Different drug treatments against osteoporosis that influence the turnover of bone have been developed, including administration of estrogen, bisphosphonates, parathyroid hormone (PTH), ranelate of strontium and denosumab.

Denosumab (Prolia, Amgen Inc., Thousand Oaks, CA) was approved for treating osteoporosis. Denosumab exerts its effects by binding to the receptor activator of nuclear factor  $\kappa$ B ligand (RANKL).

Investigation of the effects of such drugs on the risk of proximal femur fracture of osteoporotic patients is very long time consuming, very expensive and clinically difficult due to complex mechanical and biological multiscale interactions between the bone cells governing the bone remodeling combined with the applied local mechanical stress and fatigue damage at a given bone site.

Model-based drug development is a promising alternative to study the evaluation of osteoporosis therapies. Thus, there is a need for models that utilize drug pharmacokinetic (PK) and pharmacodynamics (PD) to predict changes in bone organs BMD. PK/PD models have been developed in the past to describe time courses of biomarkers for ibandronate, pamidronate and denosumab in osteoporosis. But the 3D numerical simulation of drugs effects on bone remodeling is still lacking. Computational combined PK and FE models of denosumab effects were not developed in the past.

In the current work, a combined PK and FE (PK/FE) model was developed and implemented into a FE code (Abaqus) to simulate the effects of denosumab (dose and duration) on proximal femur remodeling in term of BMD, degree of mineralization and fatigue damage accumulation variation.

The integrated model is based coupling a PK model of denosumab drug and mechanobiological FE model of bone remodeling

The denosumab PK model describes the absorption of denosumabin blood serum.

The remodeling model is based on previously developed mechanobiological FE model considering the osteoblasts and osteoclasts cells activities.

The link between the PK and FE models is considered by the modulation in the FE model the autocrine factors representing the RANKL-OPG-RANK regulation by the concentration of the denosumab in blood serum.

To investigate the potential of the proposed unified denosumab PK/FE model, three remodeling simulations on a 3D osteoporotic proximal femur model (female, 72 years old, 52 Kg) were performed for a duration of three years with three loading cases; Case 1: Normal daily applied force without denosumab, Case 2: Low daily applied force without denosumab treatment and Case 3: Low daily applied force with a dose of 60 mg every 6 months.

We showed here that the implementation of an integrated PK/FE model provides realistic prediction strategy to assess the drug effects on bone remodeling compared to existing experimental results.

## 2. MATERIAL AND METHOD

Proposed integrated PK/FE model is built to predict the denosumab effect on bone remodeling in 2 steps (Fig. 1):

- (i) **Step 1** : PK simulation of absorption of denosumabin blood serum based on experimental results.
- (ii) **Step 2**: FE simulation of bone remodeling based on mechanobiological bone remodeling model considering the bone cells activities which are modulated by the denosumab concentration kinetics in blood serum of Step 1.

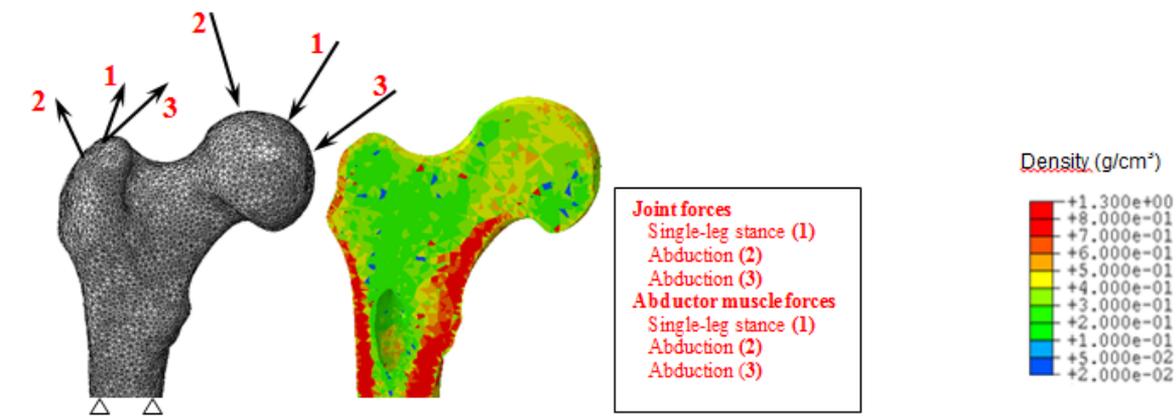
At the remodeling cycle ( $n$ ):

- (i) *The denosumab dose modulates the RANK-RANKL-OPG model parameter (decrease of osteoclast differentiation and activity).*
- (ii) *The applied load generates mechanical stress, strain and fatigue damage states at every FE of the mesh.*
- (iii) *A stimulus is then sensed by the osteocytes at every bone site and converted into signals which control the osteoblast and osteoclast interactions. Bone formation and removal is performed by competition between osteoblast and osteoclast growth at the given bone site.*

The corresponding PK/FE denosumab-remodeling model was implemented in the Abaqus code (UMAT subroutine) using a time step of 1 day.

To illustrate the potential of the current integrated PK/FE remodeling model, three remodeling simulations were performed on 3D human proximal femur model for duration of 3 years under different denosumab treatment conditions (dose and duration) combined with a low load intensity applied to the proximal femur.





(a) Boundary conditions (b) Heterogeneous initial density for cortical and trabecular bone.

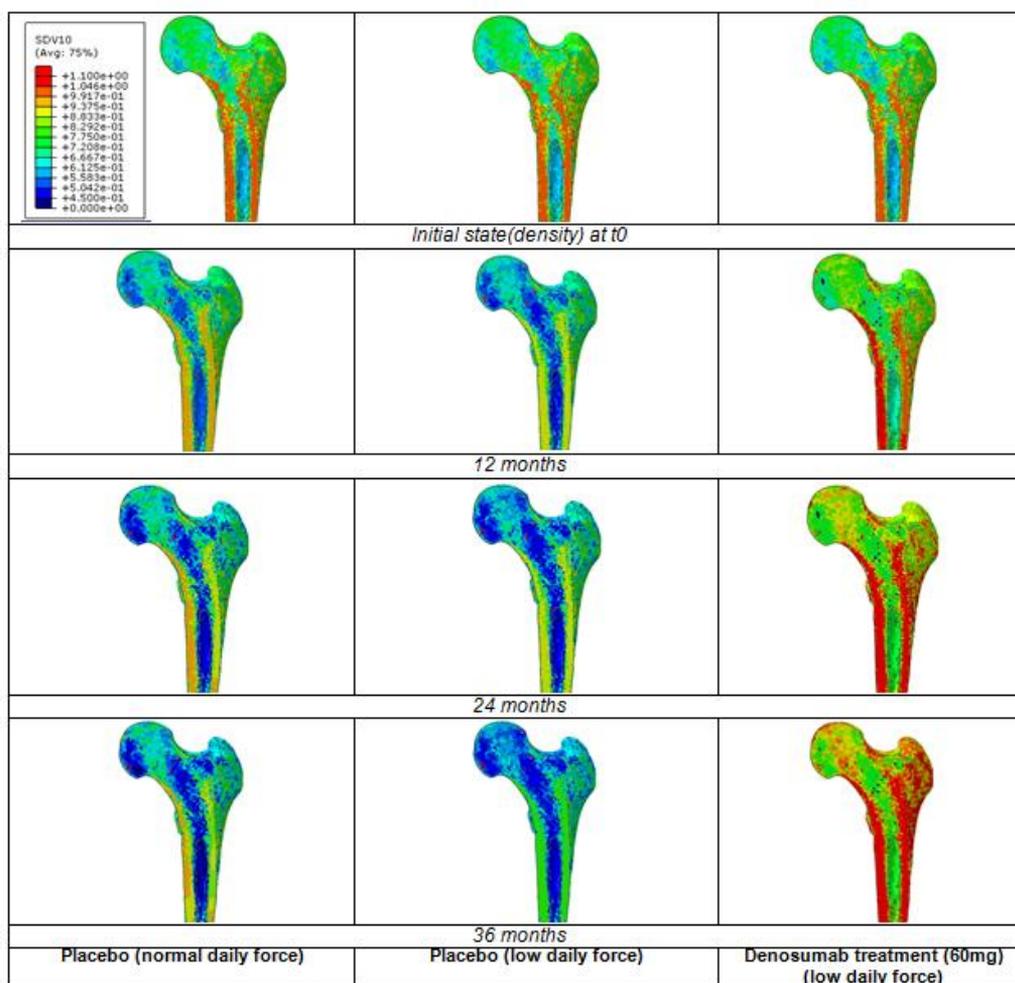
Figure 2. 3D FE model of the proximal femur: (a) Boundary conditions and applied loads, (b) Cross section showing the assigned initial density for cortical and trabecular bone.

The 3D proximal femur model retained in this study corresponds to a female, 72 years old and 52 Kg. simulated administration of 60mg twice a year for duration of 3 years corresponds to a simulated denosumab dose of 1.154 mg/Kg (60mg/52Kg).

#### 4. RESULTS

An example of the bone adaptation of the proximal femur is given in Fig.3. The figure shows the predicted contours of bone BMD at different sequences for the three different remodeling cases (case1: Normal daily force without denosumab case2: Low daily force without denosumab and case3: Low daily force with denosumab).

Predicted results indicate that the bone starts to adapt its density after about 3 months and undergoes nonlinear continuous adaptation. It can be observed that density contour is similar to regional densities observed clinically and the density distribution was consistent with many features observed in femoral morphology: trabecular bone of varying density in the head and trochanter, and dense cortical bone in the diaphysis and calcar region of the neck.



**Figure 3.** Predicted bone adaptation sequences in the form of bone mineral density (BMD) variation in ( $\text{g}/\text{cm}^3$ ) for placebo and denosumab treatment.

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