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A MULTISCALE SYSTEMS BIOLOGY APPROACH FOR COMPUTER SIMULATION-BASED PREDICTION OF BONE REMODELING

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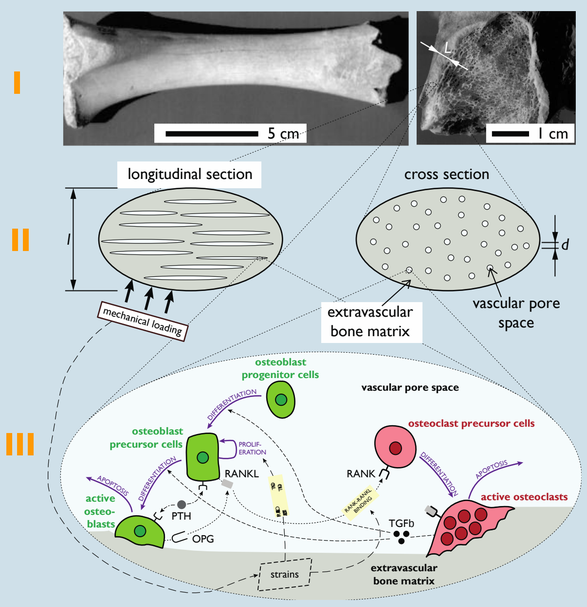
Introduction

Bone remodeling, a remarkable process taking place throughout the whole life of vertebrates, is driven by the cellular activity of bone-resorbing **osteoclasts**, bone-forming **osteoblasts**, and load-sensing **osteocytes**, and governed by biochemical factors, such as the **RANKL/RANK/OPG pathway**, parathyroid hormone (**PTH**), and transforming growth factor beta (**TGF-β**) [1]. Here a mathematical model derived from a previously published modeling strategy [2, 3] is presented, based on which the dynamics of bone remodeling can be accurately predicted. We consider the different length scales found in bone by means of a **multiscale systems biology** approach, and follow the evolutions of osteoclast and osteoblast concentrations due to biochemical factors and changes in the mechanical loading. Thereby, the effects of **porosity changes** are explicitly taken into account. Mechanical regulation of the process is considered by coupling the mathematical systems biology-based model with an experimental, multiply validated **continuum micromechanics** representation of bone [4], and a recently developed multiscale **poromechanics** model [5], based on which the length scale-specific strain states in the vicinity of the bone remodeling-driving cells can be estimated. The model is applied for studying the development of the bone composition in the course of mechanical dis- and overuse, as well as of postmenopausal osteoporosis (PMO).

Materials and Methods

Length scales in bone



I: images of long bone at the macroscopic scale [6]
II: representative volume element (RVE) of cortical bone microstructure (*L* >> *l* >> d [7])
III: main mechanisms involved in bone remodeling

Model assumptions

- Bone remodeling is considered to take place in the **vascular pore space,** where "teams" of osteoblasts and osteoclasts work together
- Cell populations are considered in terms of **molar vascular concentrations** C_i^{vas} [8]
- Biochemical regulation is mainly realized via the **RANKL/RANK/OPG pathway** and **TGF-β**; the concentrations of these factors are also considered at the level of vascular pores, C_j^{vas}
- Mechanical regulation is evaluated by means of the **strain energy density** (SED) of the extravascular matrix Ψ_{exvas}; increased mechanical loading leads to
  - ❑ increased osteoblast precursor proliferation [9]
  - ❑ decreased RANKL-production, downregulation of RANKL-RANK binding and, thus, downregulation of osteoclast differentiation [10]

Mathematical model

Evolutions of the vascular cell concentrations of osteoblast progenitors (OCP), active osteoblasts (OBA) and active osteoclasts (OCA):

$$\frac{dC_{OBP}^{vas}}{dt} = \mathcal{D}_{OBU}(TGF\beta)C_{OBU}^{vas} + [\mathcal{P}_{OBP}(\Psi_{exvas}) - \mathcal{D}_{OBP}(TGF\beta)]C_{OBP}^{vas} - \frac{C_{OBP}^{vas}}{f_{vas}}\frac{df_{vas}}{dt}$$

$$\frac{dC_{OBA}^{vas}}{dt} = \mathcal{D}_{OBP}(TGF\beta)C_{OBP}^{vas} - \mathcal{A}_{OBA}C_{OBA}^{vas} - \frac{C_{OBA}^{vas}}{f_{vas}}\frac{df_{vas}}{dt}$$

$$\frac{dC_{OCA}^{vas}}{dt} = \underbrace{\mathcal{D}_{OCP}([RANKL \cdot RANK], \Psi_{exvas})C_{OCP}^{vas} - \mathcal{A}_{OCA}(TGF\beta)C_{OCA}^{vas}}_{\text{Concentration changes due to biochemical factors}} \underbrace{- \frac{C_{OCA}^{vas}}{f_{vas}}\frac{df_{vas}}{dt}}_{\text{Concentration changes due to geometry}}$$

Definition and evolution of the vascular porosity:

$$f_{vas} = \frac{V_{vas}}{V_{RVE}} \quad and \quad \frac{df_{vas}}{dt} = f_{vas}(C_{OCA}^{vas}k_{res}^{vas} - C_{OBA}^{vas}k_{form}^{vas})$$

Definition of the extravascular strain energy density:

$$\Psi_{exvas} = \frac{\Psi_{macro} - \Psi_{vas}f_{vas}}{1 - f_{vas}}$$

Ψ_{macro}, Ψ_{vas}…macroscopic and vascular SED, respectively, resulting from the multiscale poromechanics model

OBU…uncommitted osteoblast progenitors
$\mathcal{D}$…differentiation rate
$\mathcal{A}$…apoptosis rate
$\mathcal{P}$…proliferation rate
V_{vas}…volume of vascular pores
V_{RVE}…volume of RVE
k_{res}^{vas}…bone resorption coefficient
k_{form}^{vas}…bone formation coefficient

Results & Discussion

Simulation of bone disuse (microgravity)

- Mechanical loading is prescribed in terms of the **stress tensor of cortical bone**:

$$\Sigma_{cort} = \begin{bmatrix} 0 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & \Sigma_{33} \end{bmatrix}$$ **normal:** Σ_{33} = -30 MPa **disuse:** Σ_{33} = -25 MPa

- The increase in vascular porosity due to disuse reaches a plateau with a constant value f_{vas} = 0.21 after approximately 1200 days (Fig. 1), when the cells return to their initial concentrations $C_i^{vas}/C_{i,ini}^{vas}$ = 1 (Fig. 2)
- The simulation is in agreement with experiments on astronauts during and after space flight [11]
- The return of f_{vas} to its initial value after disuse is much more rapid when simulated with the vascular scale-related model, compared to previous, macroscopic formulations [2, 3]

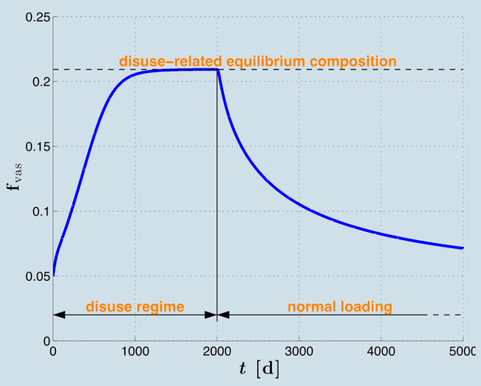


Figure 1: Evolution of the vascular porosity for 2000 days of disuse ($f_{vas,ini}$ = 0.05)

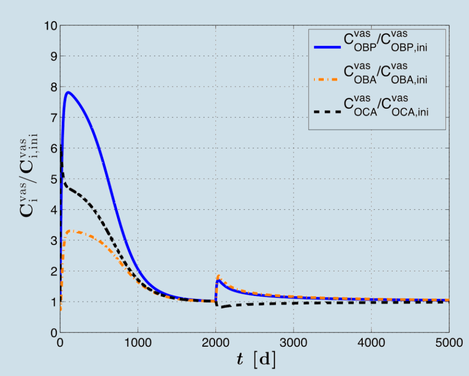
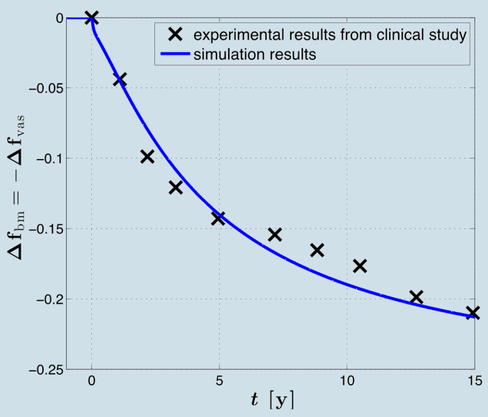


Figure 2: Evolution of bone cell concentrations for 2000 days of disuse

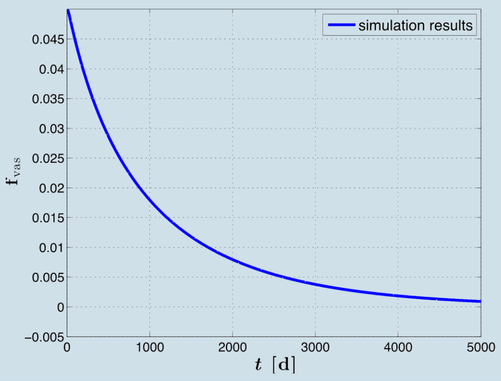
Simulation of postmenopausal osteoporosis

- PMO is modeled biochemically, by introducing [12,13]:
  - ❑ a disease-related increase of the vascular concentration of RANKL (leading to increased osteoclast concentration and bone resorption)
  - ❑ a reduction of the mechanoresponsiveness
- The simulated decrease of the bone matrix volume fraction with PMO agrees well with corresponding clinical data [14]



Simulation of bone overuse

- Overuse is simulated by setting Σ_{33} = -35 MPa
- Compared to previous, macroscopic model formulations, the overuse does not lead to a rapid increase and negative values of the vascular porosity; instead, the increase of f_{vas} over time is slow and never reaches negative values (as shown in the figure)
- The simulation agrees qualitatively with experiments associating long-term sport-specific exercise loading with thicker cortex at certain areas [15]



References

[1] S. Theoleyre et al. (2004). *Cytokine Growth F R*, 15(6): 457–75.
[2] S. Scheiner et al. (2013). *Comput Methods Appl Mech Eng*, 254: 181-196.
[3] S. Scheiner et al. (2014). *Int J Numer Meth Bio.* 30(1):1–27.
[4] C. Hellmich et al. (2008). *Ann Biomed Engrg*, 36(1): 108–122.
[5] S. Scheiner et al. (2015). Submitted to *Biomech Model Mechanobiol.*
[6] S. Weiner and H.D Wagner (1998). *Annu Rev Mater Sci*, 28: 271-298.
[7] A. Zaoui (2002). *J Eng Mech-ASCE*, 128: 808-816.
[8] V. Lemaire et al. (2004). *J Theor Biol*, 229: 293-309.
[9] D. Kaspar et al. (2002). *J Biomech*, 35(7): 873-880.
[10] C. Liu et al. (2010). *Bone*, 46(5): 1449-1456.
[11] L. Vico and and C. Alexandre. *J Bone Min Res*, 7(S2): 445–447.
[12] S. Manolagas (2000). *Endocr Rev*, 21: 115-137.
[13] A. Tomkinson et al. (1998). *J Bone Miner Res*, 13: p1243-1250.
[14] N. Bonnet and S. Ferrari. *IBMS BoneKey*, 7: 235-248.
[15] R. Nikander (2010). *Osteoporosis Int*, 21:1687–1694.

9. Jahrestagung der Deutschen Gesellschaft für Biomechanik, 6. – 8. Mai 2015, Bonn, Deutschland