INSTITUTE FOR MECHANICS OF MATERIALS AND STRUCTURES
TECHNISCHE UNIVERSITÄT WIEN
Vienna University of Technology

NAMABIO
COST Action MP1005 – 3rd Joint Meeting
August 29-30, 2013, Patras, Greece

Integration Of Systems Biology And Multiscale Bone Mechanics For Computational Simulation Of The Cortical Bone Remodeling Progress In Health And Disease

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Introduction

The process by which bone renews itself is termed **bone remodeling** [1], with **bone-resorbing osteoclasts and bone-forming osteoblasts** as key players. Bone remodeling is governed by a number of **biochemical factors** and by the **prevailing mechanical loading** applied onto the skeleton [2].

Anticipating the temporal progress of bone remodeling based on experimental observations alone is difficult (if not impossible), owing to **complex interactions between cells, biochemical factors, and mechanical loading** [2].

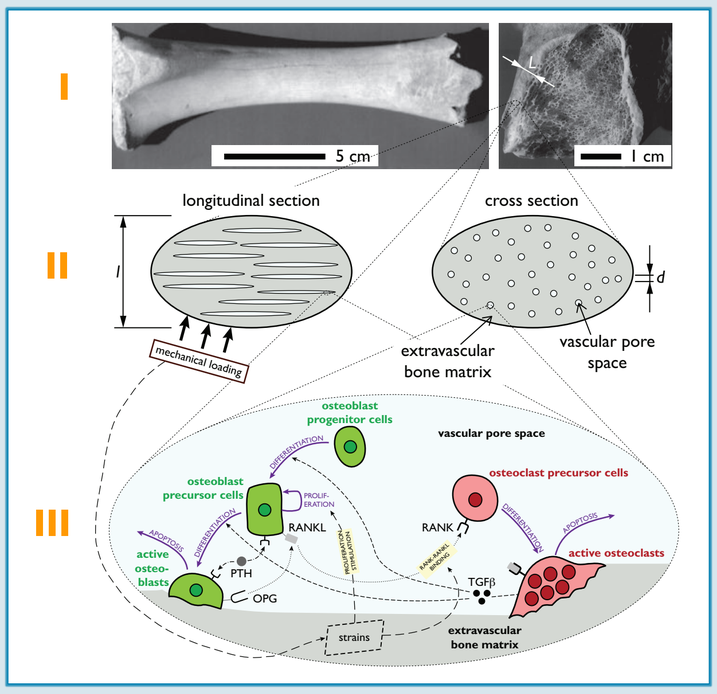
In order to contribute to resolving this issue, **a mathematical model [3,4] is presented, integrating the concepts of**

- **systems biology**, considering biochemical regulation of bone remodeling, and
- **multiscale bone mechanics**, for quantification of the bone straining.

The proposed model is applied for studying the composition evolution of a piece of cortical bone, while the latter is subjected to **specific mechanical load cases, bone pathologies, and drug intervention**.

Materials and Methods

Length scales of interest



I: images of long bone [5]
II: representative volume element (RVE) of cortical bone microstructure ($L >> l >> d$ [6])
III: main mechanisms involved in bone remodeling

Mathematical models

Bone cell population model:

- Populations of cells considered in terms of **molar concentrations** [7]
- Biochemical regulation: **RANK-RANKL-OPG system and TGFβ** [8]
- Mechanical regulation: Increase of mechanical loading leads to
  - **increase of osteoblast precursor proliferation** [9]
  - **decrease of RANKL-production** and thus downregulation of osteoclast differentiation [10]

⇒ general model structure:

change of concentration of cell *i* (C_i) over time *t*; activation and repression functions related to biochemical or mechanical stimuli *j, k, l, or m*

$$\frac{\mathrm{d}C_i}{\mathrm{d}t} = D_{i-1}C_{i-1}\pi^{j}_{\mathrm{act/rep}} + C_i\left(P_i\pi^{k}_{\mathrm{act/rep}} - D_i\pi^{l}_{\mathrm{act/rep}} - A_i\pi^{m}_{\mathrm{act/rep}}\right)$$

differentiation rate and concentration of cell *i*-1 (preceding developmental stage); proliferation, differentiation, and apoptosis rates of cell i

⇒ leads to a system of **three ordinary differential equations**

Model for drug intervention of osteoporosis:

- PK model of the **anti-catabolic drug denosumab** gives its concentration following specific administration regimes [4]
- Model calibration against experimental data for different drug doses [10]
- Consideration in bone cell population model through **competitive binding with RANKL**

Microelastic bone model:

Mechanical stimulus: **bone matrix strain energy density**

$$\Psi_{\mathrm{bm}} = \frac{1}{2}\boldsymbol{\varepsilon}_{\mathrm{bm}} : \mathbb{c}_{\mathrm{bm}} : \boldsymbol{\varepsilon}_{\mathrm{bm}}$$

The **strain tensor of the extravascular bone matrix** follows from a micromechanical model of the bone stiffness [6]:

$$\boldsymbol{\varepsilon}_{\mathrm{bm}} = \mathbb{A}_{\mathrm{bm}} : \left[(\mathbb{C}_{\mathrm{cort}})^{-1} : \boldsymbol{\Sigma}_{\mathrm{cort}}\right]$$

$\mathbb{c}_{\mathrm{bm}}$ = bone matrix stiffness tensor (known from ultrasonics tests)
$\mathbb{A}_{\mathrm{bm}}$ = bone matrix strain concentration tensor [6,9]
$\mathbb{C}_{\mathrm{cort}}$ = macroscopic stiffness tensor [6,9]
$\boldsymbol{\Sigma}_{\mathrm{cort}}$ = macroscopic stress tensor (prescribed)

these tensors are functions of the bone composition, governed by the osteoclast and osteoblast concentrations: **COUPLING TO THE SYSTEMS BIOLOGY MODEL**

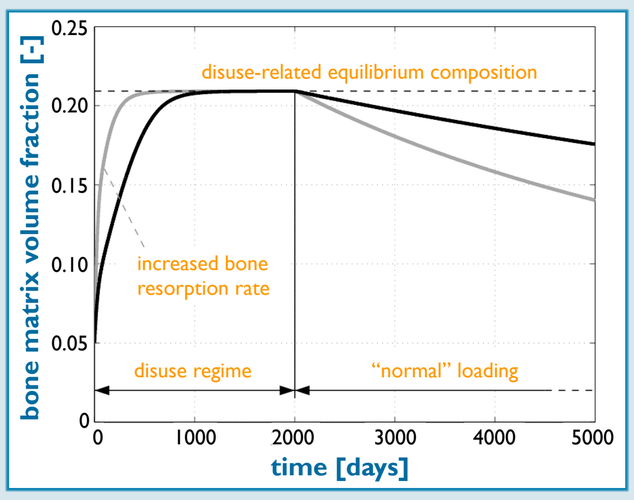
Results of Numerical Simulations

Mechanical loadcase: Disuse (microgravity)

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

$$\boldsymbol{\Sigma}_{\mathrm{cort}} = \begin{bmatrix} 0 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & \Sigma_{33} \end{bmatrix}$$

normal: Σ_{33} = -30 MPa
disuse: Σ_{33} = -25 MPa



☑ The predicted **bone loss rate** (black graph, 0.42%/month) **agrees well with clinical data** [11].
☑ Bone loss varies strongly between species, calling for **species-specific model calibration** (grey graph).
☑ **Very efficient** simulations.

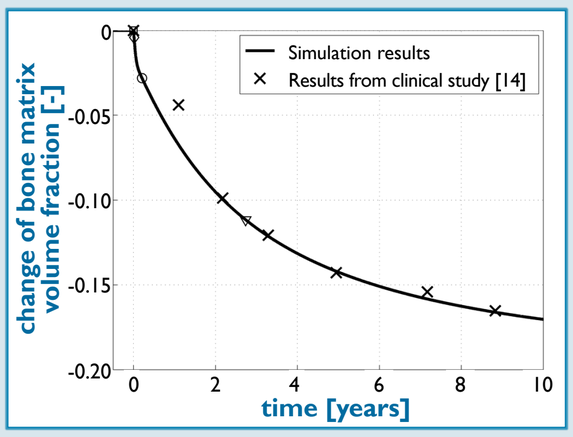
☐ Extension to **"true" multiscale systems biology approach**.
☐ **Model reduction**.
☐ **Mechanoregulation according to experimental evidence**.

Biochemical loadcases: Osteoporosis without and with drug intervention

1. Simulation of postmenopausal osteoporosis (PMO)

PMO modeled by considering the disease-related increase of RANKL/OPG-ratio and reduction of the mechanoresponsiveness [12,13]:

☑ Onset of simulated PMO initiates a catabolic bone remodeling regime.
☑ Simulation results show **adequate bone turnover kinetics**.
☑ The related **porosity increase** agrees well with clinical data.



2. Additional consideration of denosumab administration

☑ In simulations, PMO shows **long-term deceleration, without significant bone gain**, and reasonable **agreement with clinical biomarker measurements** [15].

☐ Clinically observed bone gain [16] ***must* be caused by mineralization effects** [17].

References and Acknowledgments

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Financial support by the European Research Council (ERC), through the project *MULTISCALE POROMICROMECHANICS OF BONE MATERIALS, WITH LINKS TO BIOLOGY AND MEDICINE* FP7-257023), and by the Australian Research Council (ARC), through the project *MULTISCALE MODELING OF TRANSPORT THROUGH DEFORMABLE POROUS MATERIALS* (DP-0988427), is gratefully acknowledged.