A diffusive model to describe the mechanically driven biological stimulus for bone remodeling: following in the footsteps of Roux and Frost

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Cosse-Vita Meeting 12–13 November 2020 on ElastoDynamics and Bio-Materials

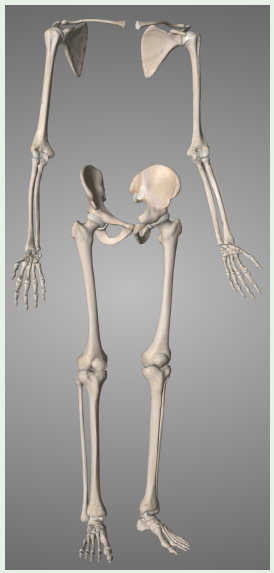
Motivations

Bones

In men and some Vertebrates, bone acts mainly as a structural organ. Functionally, bone can be placed in two major categories:

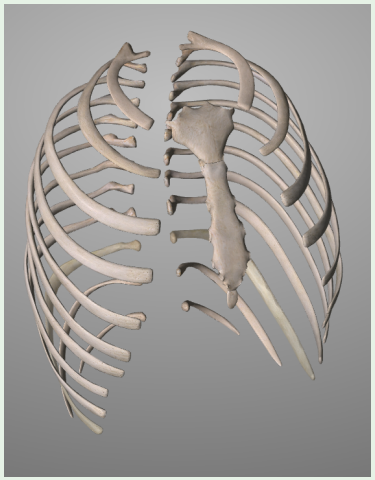
Weight-bearing

spine and appendicular skeleton



Protective

skull and ribs



Introduction

Figura: Wilhelm Roux (9 June 1850 – 15 September 1924).

A biological control process

- Wilhelm Roux, a German zoologist, suggested in 1881 that formation and functional adaptation of trabecular architecture in bone is regulated locally by cells, governed by mechanical stimuli, in a self-organizational process.

Introduction

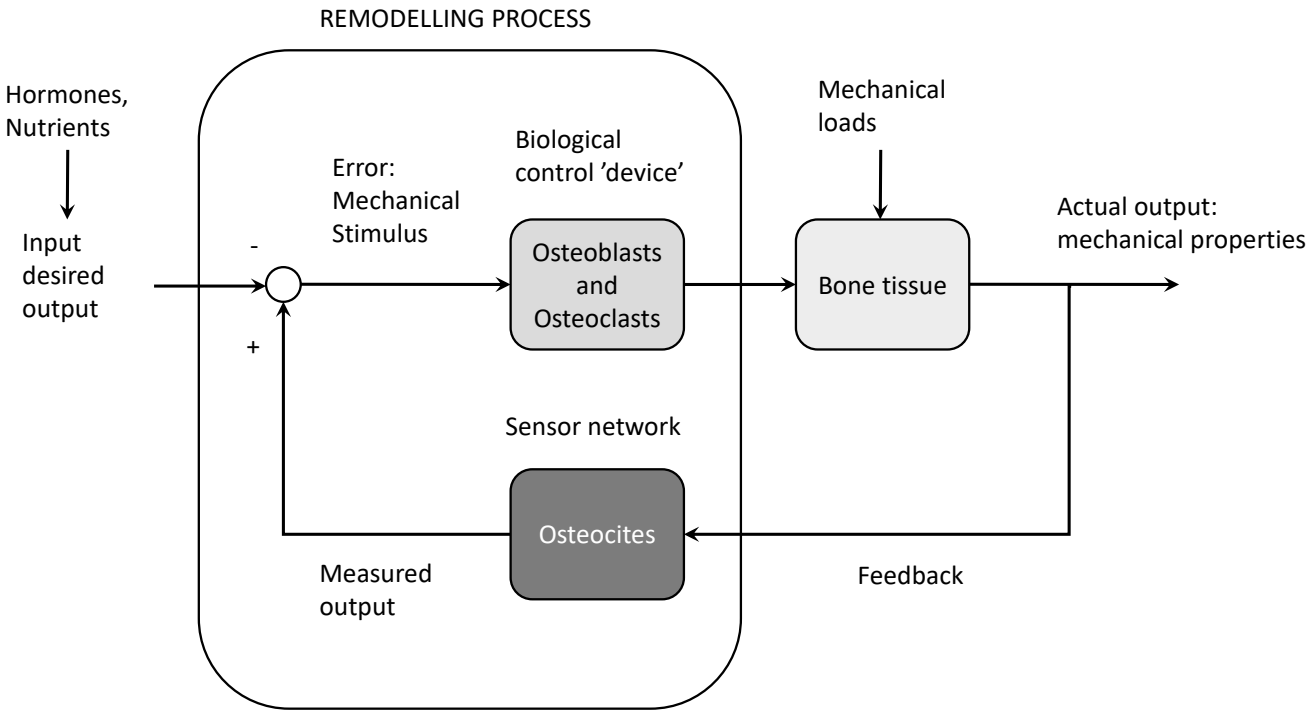


Figura: Feedback scheme for describe the remodelling process.

Frost (1987) who stepped in Roux's footprints

- Frost proposed his conceptual 'mechanostat' theory, in which local strains are assumed to regulate bone mass, as the local temperature in a room regulates the heater through a *thermostat*.

Introduction

Remodelling process

- Bone structure represents an optimum balance between the cost of excessive bone mass and the cost of excessive bone fragility.
- Bone appears to achieve the minimum adequate structure by: (a) Adjusting the distribution of bone mass to maintain desired peak magnitude of 'mechanical strain' within the tissue; (b) Arranging its microstructure in an efficient composite structure.
- Bone is, 'pound for pound', 4 times stronger than concrete, stronger than some steels and more flexible. It is no coincidence that Eiffel considered the bone structure as a reference for the design of his tower.
- Remodelling is the process in which bone is resorbed and replaced *in situ* by new bone. Remodelling repairs micro-cracks and replaces aged bone in a mass turnover process. It can also adjust bone strength, increasing or decreasing its mass and, in turn, its stiffness.

Remodelling as biological control process

Hypotheses

1. Bone is treated in general terms. No distinctions are made concerning the type of bone structure (*i.e.*, cancellous bone, primary Haversian bone, secondary Haversian bone, woven bone, etc). The effects of 'mechanical usage' and biochemical agents probably occur at different rates and in different proportion for different regions of the skeleton. However, the concept of feedback control is pervasive for all weight-bearing bones.
2. The elasticity of bone is treated in a simplified manner. Increases in bone mass are assumed to have direct effects on bone rigidity.
3. The time course for changes in bone rigidity is closely linked to the duration of the remodelling cycle. The minimum time over which a change in bone structure will be completed is about 100 to 120 days in a human being.

Control law

Evolution rule for the functional adaptation in bone tissue

Many of the proposed models fall into the category for which the adaptation law can be symbolically written in the form

$$\frac{\partial \varrho}{\partial t} = A\left(S(\boldsymbol{x}, t) - S_0(\boldsymbol{x}, t)\right)$$

$S(\boldsymbol{x}, t)$ is the feedback signal; $S_0(\boldsymbol{x}, t)$ is a reference value for the stimulus, that is the value for which the bone is in a remodelling equilibrium state. If the evolution rule is expressed in terms of mass density, an additional relation should be formulated. Usually, it is considered an isotropic case for which Young modulus, Y, and mass density, ϱ, are linked by a relation as: $Y = C\varrho^{\gamma}$, where C and γ are positive constants.
In some cases, a direct evolution of the elastic properties of the material is considered:

$$\frac{\partial Y}{\partial t} = B\left(S(\boldsymbol{x}, t) - S_0(\boldsymbol{x}, t)\right)$$

Mechanical Stimulus

Local models for the stimulus

$S(\boldsymbol{x}, t)$ is a stimulus, *i.e.*, the signal that drives bone remodelling. Depending of the mechanosensory effects included in the analysis, it is assumed that the stimulus is proportional to:

1. The strain (Frost 1964, Cowin 1981);
2. Strain energy density, $S = U = 1/2\, \varepsilon_{ij} \mathbb{C}_{ijhk} \varepsilon_{hk}$ (Huiskes, 1987);
3. A level of effective stress, $S = (\sum_i n_i \sigma_i^m)^{\frac{1}{m}}$ where $\sigma_i = \sqrt{2YU_i}$ (Beaupré, Carter 1990);
4. the change in the accumulated damage, $\Delta\omega = \omega - \omega_{RE}$ where $\omega = \sum_i n_i/N_i$ with n_i the number of cycles accumulated at a certain level of stress and N_i number of cycles to failure (Pendergast, Taylor 1994);
5. Amplitude and frequency of load, $S = k \sum_i \varepsilon_i f_i$ where is ε_i peak-to-peak strain magnitude, and f is loading frequency in cycles per second (Turner 1998);

Mechanical Stimulus

Local vs Non-local models for the stimulus

1. The previous local models for the stimulus are not able to describe the interaction between bone tissue and graft of bio-resorbable material or between healthy bone and necrotic tissue in which osteocytes are dead.

Mechanical Stimulus

Non-local models for the stimulus

1. Weighted strain energy density, $S - S_0 = \sum_i^N f_i(\boldsymbol{x})\,(U_i - k)$ in which $f_i(\boldsymbol{x}) = e^{-d_i(\boldsymbol{x})/D}$ (Huiskes, Mullender 1995);
2. Weighted rate of U , $S - S_0 = \sum_i^N f_i(\boldsymbol{x}) \left(\dot{U}_i - k\right)$ (Huiskes 1999);
3. Coupled strain-damage energy density, $S = \sum_i^N f_i(\boldsymbol{x}) S_i$ where $S_i = \frac{1}{2}\frac{(1-D)\sigma_{ij}\varepsilon_{ij}}{\varrho}$ and $Y = C(1-D)\varrho^{\gamma}$ (Hambli 2011)
4. Integral form of the strain energy density (Lekszycki, dell'Isola 2012),
$$S(\boldsymbol{X}, t) = \int_{\Omega} U(\boldsymbol{X}_0, t)\, \varpi(\boldsymbol{X}_0, t)\; f(\boldsymbol{x})\, \mathrm{d}\boldsymbol{X}_0$$
5. Dissipation due to the viscous fluid flow (Kumar, Jasiuk 2011),
$$S(\boldsymbol{X}, t) = \frac{\int_{\Omega} \left(\int_0^t -n_p \boldsymbol{v}^{fl} \cdot \nabla p \, \mathrm{d}\tau \right) f(\boldsymbol{x}) \mathrm{d}\Omega}{\int_{\Omega} f(\boldsymbol{x}) \mathrm{d}\Omega}$$

where n_p is the porosity, p the pressure and $\boldsymbol{v}^{fl}$ the fluid velocity.

Mechanical Stimulus

Stimulus modelling without time delay

If we assume that the signal from sensor cells is instantaneously transmitted (*i.e.*, the transmission time scale is negligible when compared with the characteristic time of the remodelling phenomena), we can adopt the simple equation

$$S(\boldsymbol{x},t)=\int_{V_t} f(\boldsymbol{x},\boldsymbol{y})U(\boldsymbol{y},t)\varpi(\boldsymbol{y},t)\mathrm{d}\boldsymbol{y} \tag{1}$$

where the function $f(\boldsymbol{x},\boldsymbol{y})$ represents the range of influence of sensor cells and must be decreasing with the distance between $\boldsymbol{x}$ (location of actor cells) and $\boldsymbol{y}$ (location of osteocites) and has been chosen to be equal

$$\exp\left\{-D^{-1}\left\|\boldsymbol{x}-\boldsymbol{y}\right\|\right\} \quad \text{or} \quad \exp\left\{-D^{-2}\left\|\boldsymbol{x}-\boldsymbol{y}\right\|^2\right\}. \tag{2}$$

Here D is the characteristic length-scale parameter. The reader is invited to remark that the aforementioned influence functions resemble greatly Green function for heat equation in their structure.

Mechanical Stimulus: a new proposal

A parabolic evolution equation for stimulus S is proposed

$$\frac{\partial S}{\partial t} = \mathrm{Div}\,(\kappa \nabla S) + r + s,$$

where κ is the permeability to stimulus of considered tissue, which can be a second-order tensor field, in general.
The Stimulus driving source r depends on the state of mechanical deformation

$$r = \varpi(\varrho)\, U(\varepsilon),$$

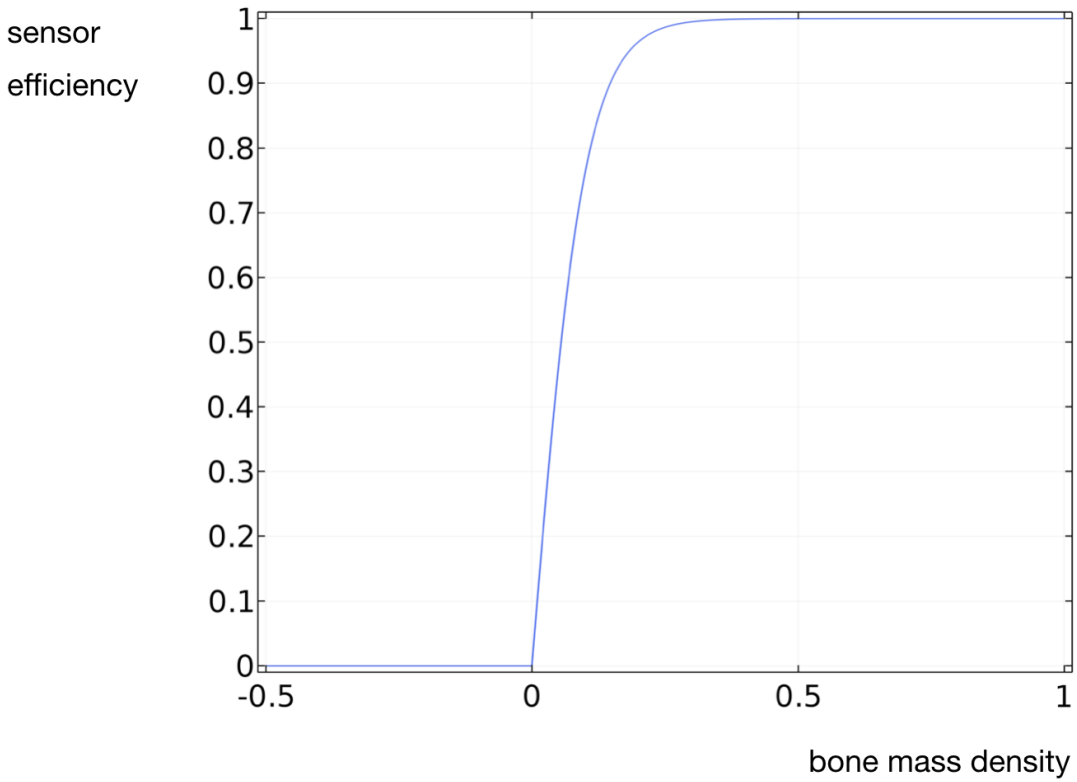
where ϖ is a sort of 'sensor efficiency' depending on the density of sensor cells and their activity.
The sink s is a density field which describes the resorption of stimulus because of metabolic activity. For instance

$$s = -R\, S\, H_v(S),$$

where R is the constant of resorption and H_v is the Heaviside function.

Mechanical Stimulus: sensor efficiency

ϖ is a sort of 'sensor efficiency' depending on the density of sensor cells and their activity. A possible function ϖ is as follows



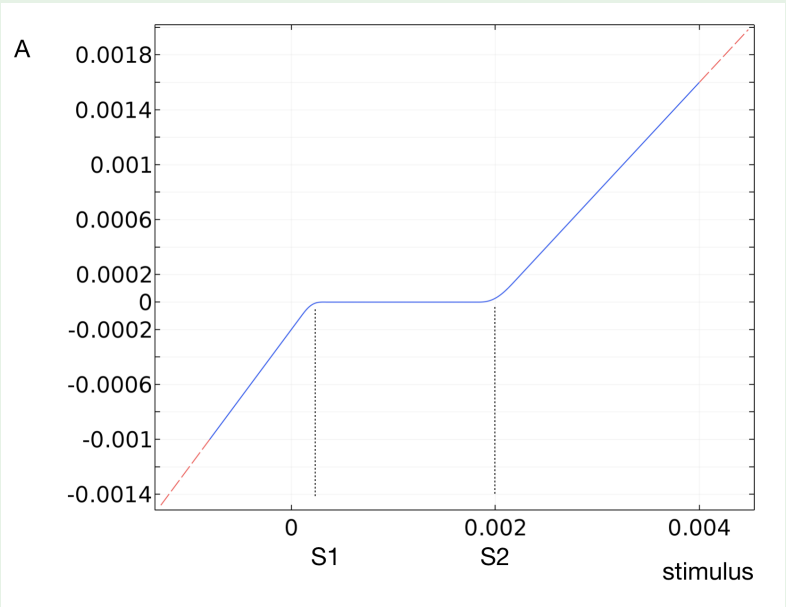
Here, we assume that the number of the osteocytes is an increasing function of the bone mass density, hence, we link the sensor density to the bone mass density.

Evolution rule

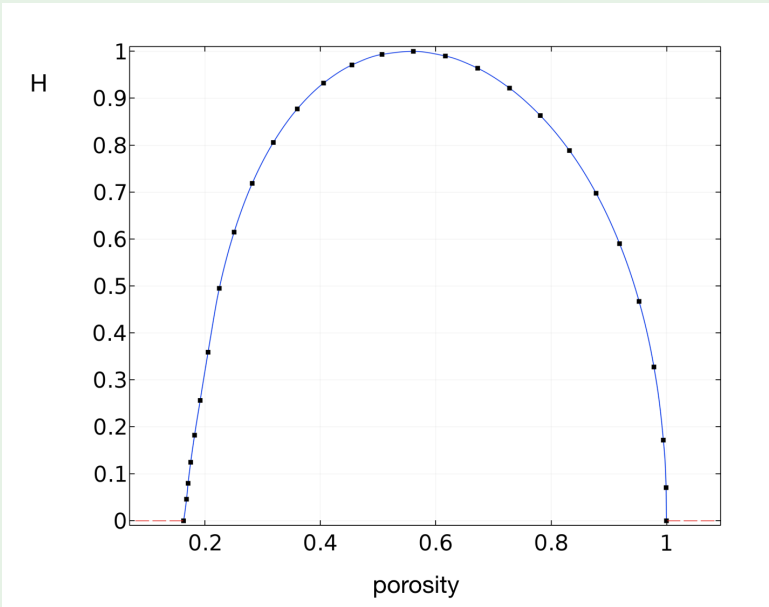
Functional adaptation in bone tissue

$$\frac{\partial \varrho^*}{\partial t} = A(S)\, H(\varphi)$$

Function A



Internal specific surface H



Biot's approach for a porous medium

Stored Energy Density $\mathscr{E}(\varepsilon_{ij}, \zeta; \varrho^*)$

1. The stored energy density $\mathscr{E}$ associated with strain tensor ε and fluid volume distortion from the reference configuration ζ is:

$$\mathscr{E} = \frac{1}{2}\mathbb{C}_{ijhk}(\varrho^*)\varepsilon_{ij}\varepsilon_{hk} + \frac{1}{2}K_1(\varrho^*)\zeta^2 - K_3(\varrho^*)\,\zeta\,\varepsilon_{ii} + \frac{1}{2}K_2\zeta_{,i}\zeta_{,i}$$

where, assuming the hypothesis of isotropic material, the stress tensor is expressed in term of Young's modulus and Poisson ratio

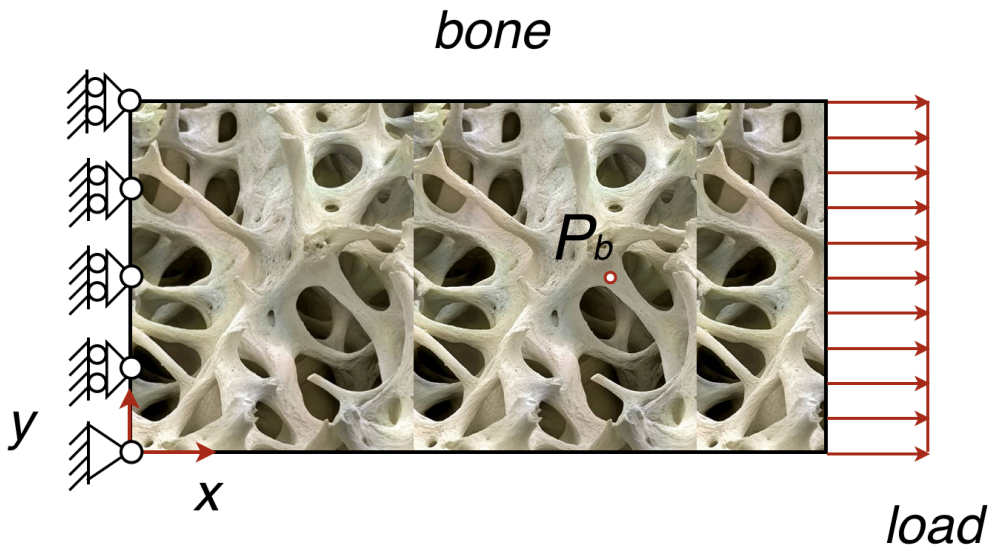
$$T_{ij} = \mathbb{C}_{ijhk}(\varrho^*)\varepsilon_{hk} = \frac{\nu Y(\varrho^*)}{(1-2\nu)(1+\nu)}\,\varepsilon_{kk}\delta_{ij} + \frac{Y(\varrho^*)}{(1+\nu)}\,\varepsilon_{ij}$$

the change of the Lagrangian porosity ζ is:

$$\zeta(\mathbf{X}, t) = \varphi(\chi(\mathbf{X}, t), t) - \varphi^*(\mathbf{X}, t)$$

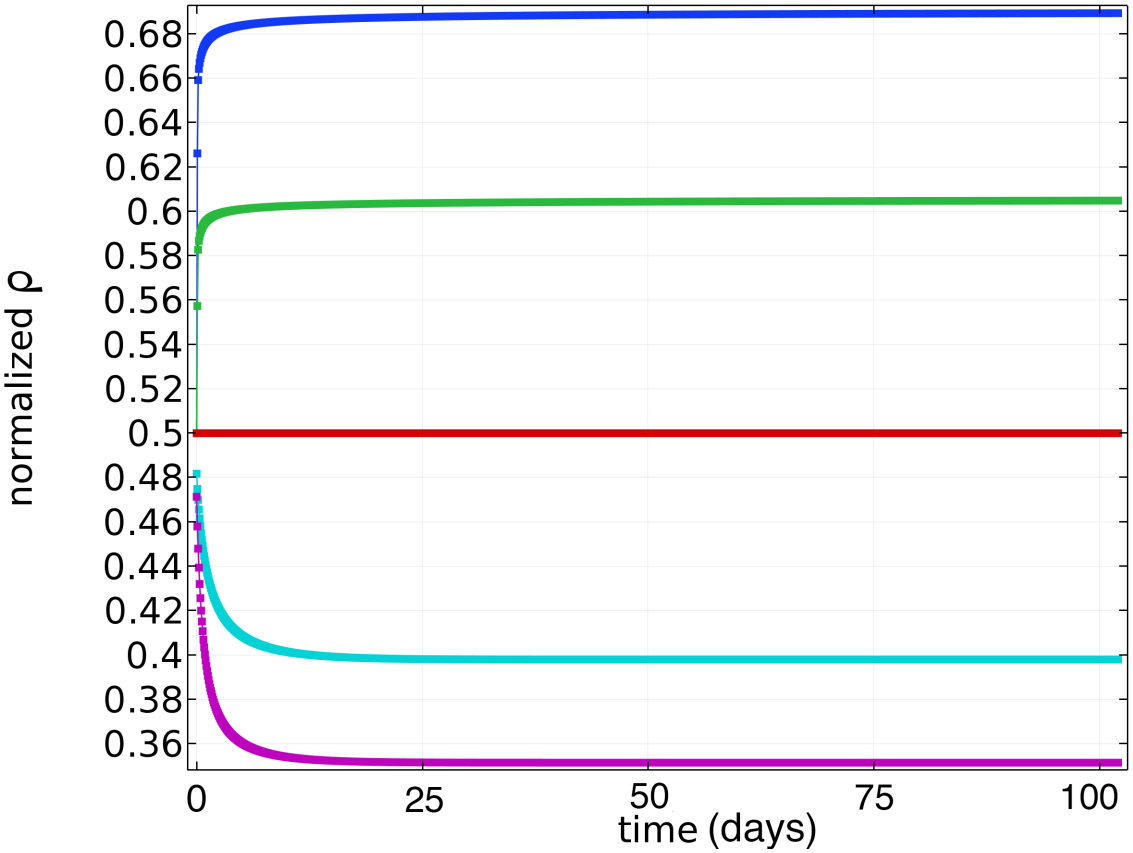
where φ^* stands for the porosity in the reference configuration.

Numerical Results: Case I



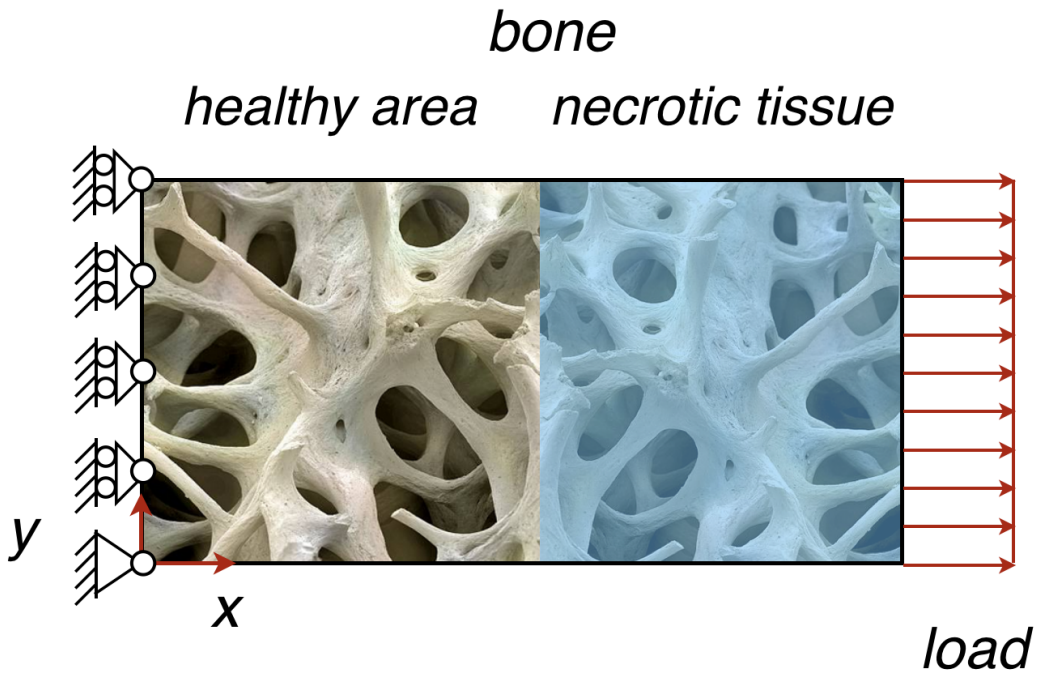
1. Bias extension test with uniform load and initial apparent mass density normalized to the maximal mass density equal to 0.5.

Numerical Results: Case I - Bias extension test



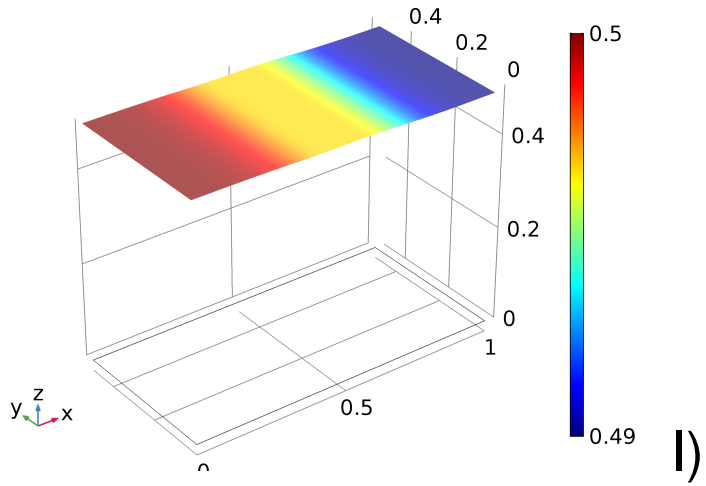
History of the apparent mass density for different values of the external load at probe point P_b.

Numerical Results: Case II

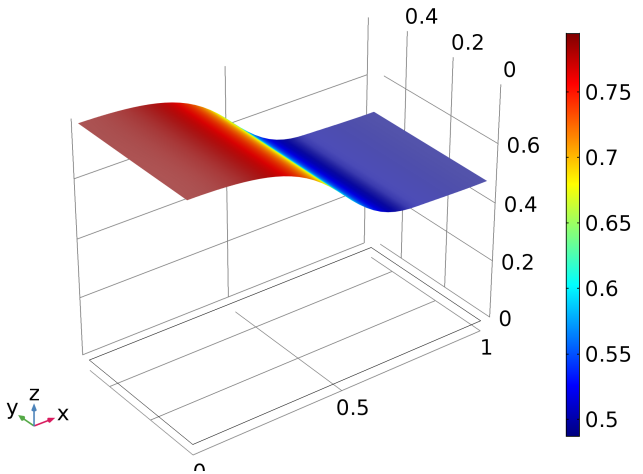


1. Bias extension test with uniform load and initial normalized apparent mass density equal to 0.5. In the necrotic area we assume that all osteocytes are dead.

Numerical Results: Case II



I)



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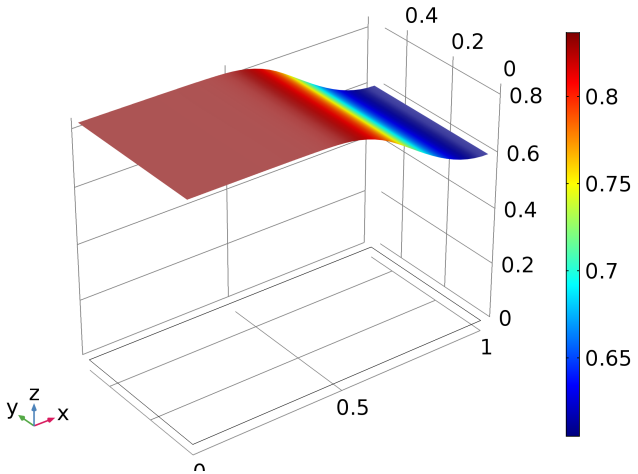
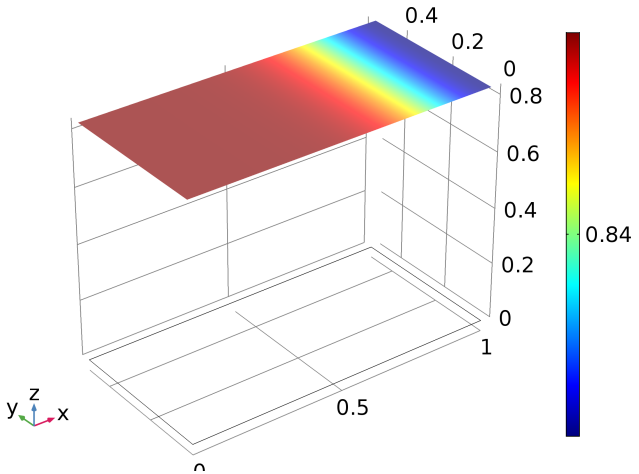


III)



IV)

Distributions of the normalized mass density for four significant stages of the remodelling process.

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Thanks

THANK YOU VERY MUCH FOR YOUR KIND ATTENTION