Bone repair and ultrasound stimulation : an insight into the interaction of LIPUS with the lacuno-canalicular network of cortical bone through a multiscale computational study.

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MSME Laboratoire Modélisation et Simulation Multi Echelle

Ultrasound waves and living tissues

UltraSounds (US) interact with living tissues : destroy (HIFU) and repair (LIPUS)

What is LIPUS ? **L**ow **I**ntensity **P**ulsed **U**ltrasound **S**timulation
LIPUS stimulates bone healing :

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But how ?
Open question !
(*Claes et al. 2007, Padilla et al. 2014*)

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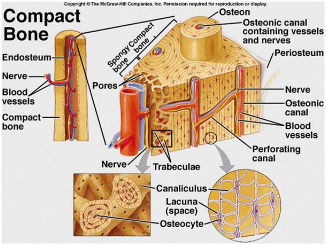

- Porous and multiscale :
  - vascular porosity (HV) :
    Havers and Volkman canals (Ø$\simeq$ 100 μm)
  - lacuno-canalicular network (LCN) :
    lacunae (Ø$\simeq$ 10 μm) + canaliculi (Ø$<$ 1 μm)
- Bone cells : osteocytes

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Fluid shear stress on osteocyte $\rightarrow$ bone remodelling

Cowin et al. 1991, Klein-Nulend et al. 1995

Cortical bone = double-level porous medium

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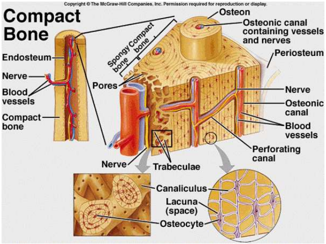

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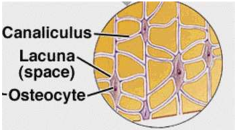

Cortical bone = double-level porous medium

Hypothesis and aims

Hypothesis : US excitation at meso-scale level induces fluid shear stress on osteocytes at micro-scale level

Locks :

- Multiscale phenomena to understand and analyze
- Multiphysics : acoustics, fluid and structure
- Coupling multiscale and multiphysics

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Models

Biphasic medium Model + US : ModBone

- Vascular pores (HV) = fluid phase
  HV pores reconstructed from binarized μCT images (22.5 μm)

RX image

- Poroelastic bone matrix (PBM)
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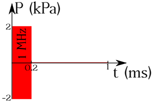

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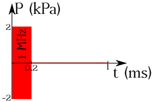

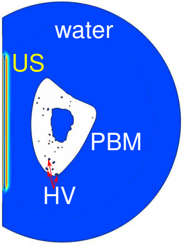

Models

Osteocyte Model : ModOst

- Osteocyte cell (solid phase)
- Extracellular matrix, ECM (solid phase)
- Interstitial Fluid (IFluid) (fluid phase)

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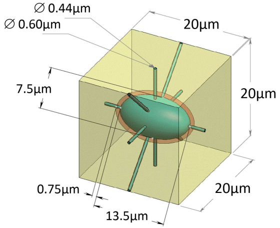

FE simulation

2D and 3D coupling between acoustics and fluid and fluid-solid interaction
Software : Comsol Multiphysics

- ModBone (2D) : US stimulation at the mesoscale
  Time-dependent problem
  Weak form of wave propagation in poroelastic medium
  + boundary conditions

  (Nguyen et al. 2010)

  $\triangle x_{\mathrm{bone}} \approx 0.7$ mm, $\triangle x_{\mathrm{water}} \approx 0.4$ mm and $\triangle t \approx 0.1 \mu s$
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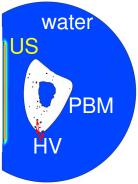

  - input parameters :
    US stimulation parameters
    f=1MHz, pressure=2 kPa, duty cycle=20%, pulse duration=1 ms, Øtransducer=10 mm
    surrounding fluid properties = water
    bone material properties = anisotropic poroelasticity
    (Scheiner et al. 2015, Goulet et al. 2008, Nguyen et al. 2010, Cowin et al. 2009)
  - output parameter : |Fluid pressure gradient|

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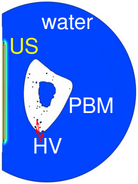

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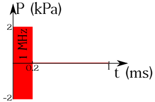

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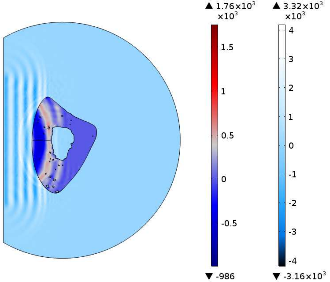
Acoustic pressure and IFluid pressure (Pa)

t = 4 μs



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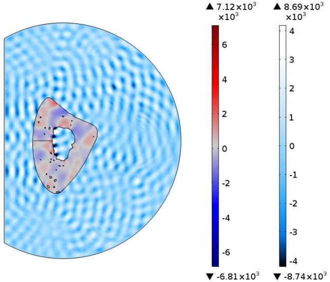

- IFluid pressure (IFluid P) difference induced by US stimulation on 1 cycle

$$\mathrm{Max}|\mathrm{IFluid\ P}_{\mathrm{periosteum}} - \mathrm{IFluid\ P}_{\mathrm{endosteum}}| \approx 11000\ \mathrm{Pa}$$

$\longrightarrow$ IFluid P gradient = 3.8 Pa/μm

- IFluid P gradient $\approx$ 30 Pa /μm *(Anderson et al. 2005, Verbruggen et al. 2012, 2014)*
  $\longrightarrow$ 8-times lower than previous studies considering physiological mechanical loading.
- Fluid shear stress on osteocyte ?

Results and Discussion : ModBone

Acoustic pressure and IFluid pressure (Pa)

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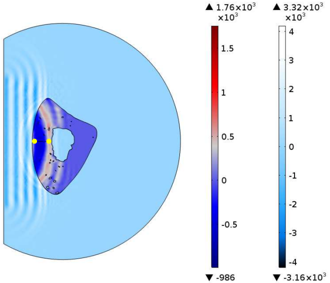

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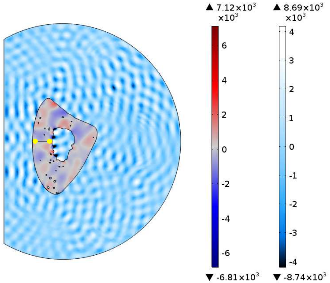

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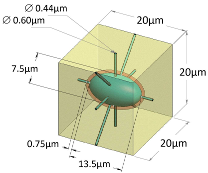
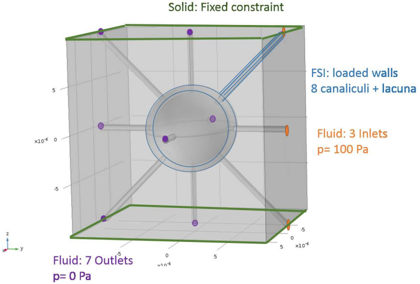
FE simulation

- ModOst (3D) :
  Fluid Structure Interaction Model (one-way coupling)



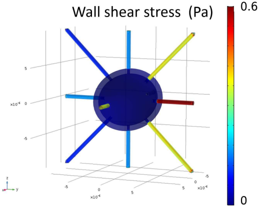
  - input parameter : IFluid P gradient from ModBone : 3.8 Pa/μm
  - output parameter : fluid shear stress on osteocyte : τ



IFluid domain : newtonian,
ρ=997 kg/m^3,
μ=885$\times$ 10^{-4} kg.m^{-1}.s^{-1}

Solid domain : linear elastic,
ECM : E=16.6 GPa, ν=0.38 ;
osteocyte : E=4.47 kPa, ν=0.3

Results and Discussion : ModOst



Fluid shear stress on osteocyte
(cell body and processes)
$\tau_{max} \approx 0.6$ Pa

(McGarry et al. 2004)

- Shear stress patterns obviously related to simple symmetrical geometry and boundary conditions
- Shear stress levels in agreement with literature and consistent patterns with higher values on processes than on cell body

  (Anderson et al. 2005, Verbruggen et al. 2014)
- Theoretical shear stress interval for osteocyte under physiological load : 0.8-3 Pa

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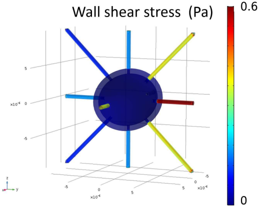

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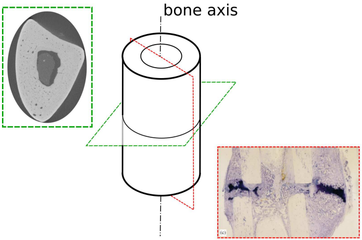
- a realistic model of the bone callus ?
  - geometry
  - healing tissues properties



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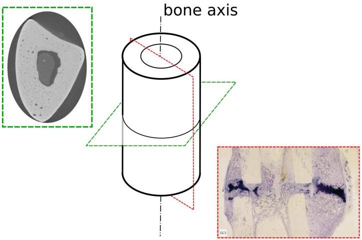

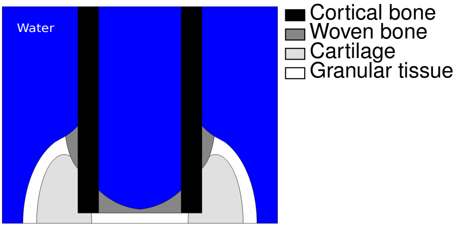

Bailon-Plaza et al. 2001, Claes et Heigele 1999

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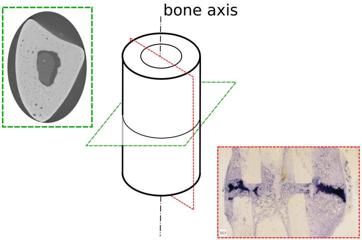

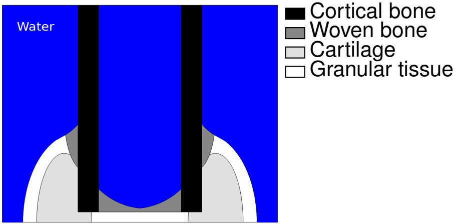

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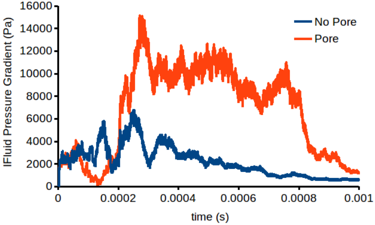
Vascular porosity ?

Goulet et al. 2008



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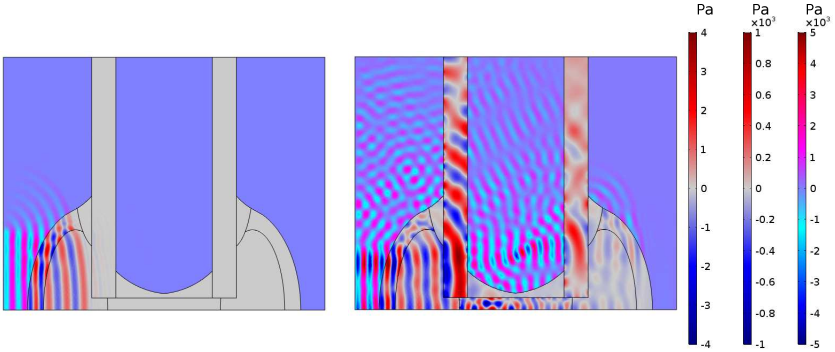

Limitations of the study

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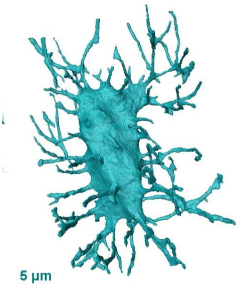
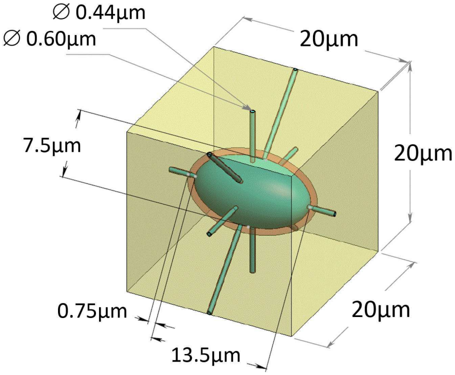


Image from Creatis (Lyon, France)



Conclusion and Perspectives

2-scale numerical model to investigate the mechanical effects of LIPUS on osteocytes.

⇒ Fluid shear stress ≈ **lower than the lower bound of prediction interval under physiological load**

Poroelastic model and US

- LCN permeability 2.2×10^{-22} m^2 *(Cowin et al. 2009)*
- treatment duration (15 min) vs 1 cycle (1 ms) : cumulative effect to investigate
- stimulation frequency higher than physiological loading (1 - 100 Hz)
- pulsed ultrasound : 2 frequencies ⇒ repetition frequency and signal frequency
  pulse duration = 1 ms **vs** signal period = 1 μs

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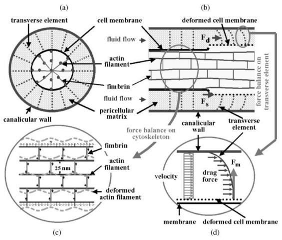
- Zoom on the osteocyte process into the canaliculi
  $\rightarrow$ GAG fibers $\rightarrow$ **strain amplification**



You et al. 2001

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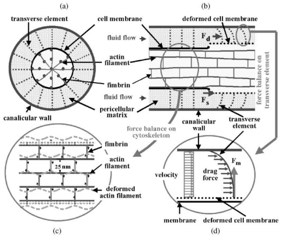


You et al. 2001

Drag forces F_d

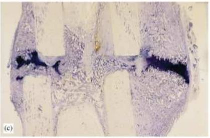
$$F_s = 2\pi a L \tau \approx 16.10^{-12}\text{N} \Rightarrow F_d \approx 330.10^{-12}\text{N}$$

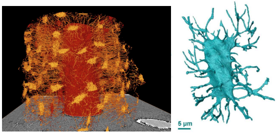
a = 0.22 μm : process radius ; L = 20 μm : process length.

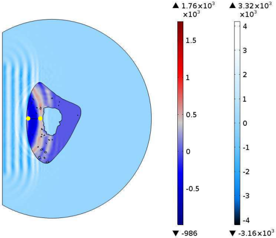
Conclusion and Perspectives

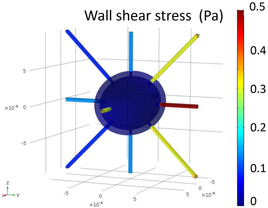
Tissue scale

Microscopic scale









Thank you for your attention.
Any questions (or answers) ?

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carine.guivier@univ-amu.fr

Equations

- Wave propagation in the anisotropic poroelastic matrix (from *Nguyen et al. 2012*)

The constitutive equations for the anisotropic linear poroelastic material are given by

$$\boldsymbol{\sigma} = \mathbb{C} : \boldsymbol{\epsilon} - \boldsymbol{\alpha}\, p\,, \quad (7)$$

$$-\frac{1}{M}\, p = \nabla \cdot \boldsymbol{w} + \boldsymbol{\alpha} : \boldsymbol{\epsilon}\,, \quad (8)$$

where $\mathbb{C}(\boldsymbol{x})$ is the elasticity fourth-order tensor of drained porous material; $\boldsymbol{\alpha}$, which is a symmetric second-order tensor, is the Biot effective tensor; M is the Biot scalar modulus; $\boldsymbol{\epsilon}(\boldsymbol{x},t)$ is the infinitesimal strain tensor, which is defined as the symmetric part of $\nabla \boldsymbol{u}^s$.

$\boldsymbol{w} = \phi(\boldsymbol{u}^f - \boldsymbol{u}^s)$

- boundary conditions : pressure and stress fields continuity + *open pore* condition (continuity of the normal relative velocity between fluid and solid)

Poroelastic cortical bone properties

Transverse isotropic extralacunar matrix

$$\begin{pmatrix} 22.88 & 10.14 & 0 \\ 10.14 & 29.60 & 0 \\ 0 & 0 & 6.98 \end{pmatrix} (GPa)$$

(Scheiner et al. 2015)

Mass density : ρ=1.9 g/cm^3
Isotropic LCN permeability : 2.2×10^{-22} m^2 *(Smith et al. 2002, Cowin et al. 2009)*
Other Biot's parameters from *NGuyen et al. 2016*
ϕ=5%, α_1=0.11, α_2=0.15, M = 35.6 GPa.

Poroelastic healing tissues properties

4 weeks_ Isotropic solid matrix

- Granular tissue

$$\begin{pmatrix} 2.502 & 2.5 & 0 \\ 2.5 & 2.502 & 0 \\ 0 & 0 & 0.001 \end{pmatrix} \text{(GPa)}$$

ϕ=90%
α_1=0.98
α_2=0.96
M = 2.2 MPa
ρ= 1.01 g/cm^2

- Cartilage

$$\begin{pmatrix} 5.98 & 5.3 & 0 \\ 5.3 & 5.98 & 0 \\ 0 & 0 & 0.34 \end{pmatrix} \text{(GPa)}$$

ϕ=80%
α_1=0.98
α_2=0.96
M = 2.4 MPa
ρ= 1.04 g/cm^2

- Woven bone

$$\begin{pmatrix} 17.1 & 12.9 & 0 \\ 12.9 & 17.1 & 0 \\ 0 & 0 & 2.1 \end{pmatrix} \text{(GPa)}$$

ϕ=50%
α_1=0.976
α_2=0.955
M = 2.55 MPa
ρ= 1.25 g/cm^2

Mechanical properties of healing tissue

	E (GPa)	ν	k (m^2)	p	GradPress (Pa/μm)	τ_{max} (Pa)
Cortical bone	18	0.28	2.2×10^{-22}	0.05	3.8	0.6
Woven bone	9	0.28	2.2×10^{-22}	0.05	9	1.4
Immature bone	1	0.325	10^{-13}	0.8	8.5	1.3

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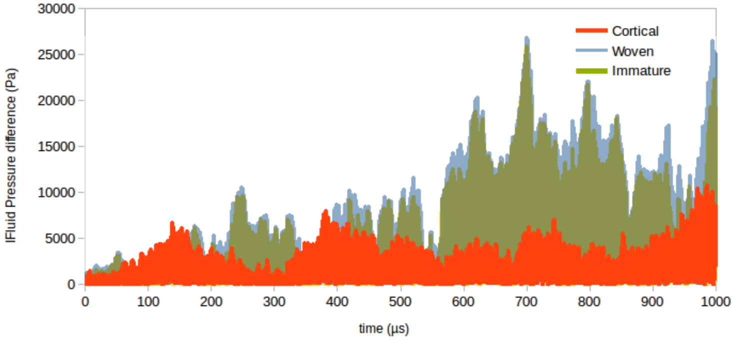

Mesh