How to understand the effects of LIPUS on bone healing? A multiscale computational investigation

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July 13, 2016

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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Open question !

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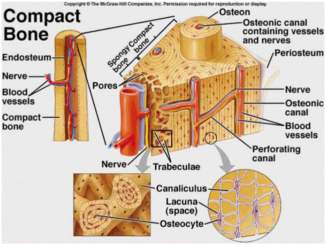


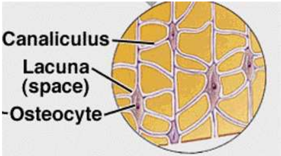
- Multiscale and two-level porosity : Havers-Volkmann network (HV) and lacuno-canalicular network (LCN)
- Bone cells : osteocytes
- Multiphasic (solid bone matrix, interstitial fluid and water)

Mechanotransduction

Fluid shear stress on osteocyte

$\rightarrow$ bone remodelling

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



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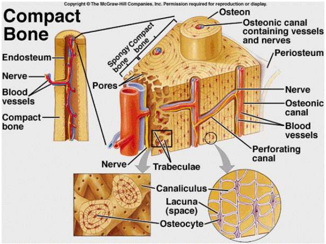

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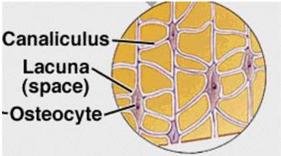

Hypothesis and aims

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

Cortical bone = double-level porous medium

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

Biphasic medium Model : ModBone

- poroelastic bone matrix (PMB)

anisotropic solid *(Scheiner et al. 2015)* + LCN
$\rightarrow$ equivalent medium (Biot's model)

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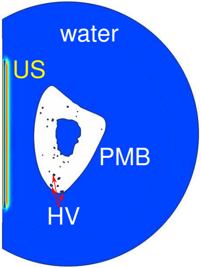

Osteocyte Model : ModOst

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

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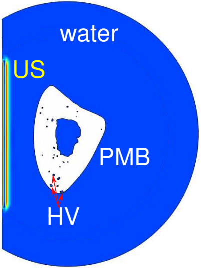

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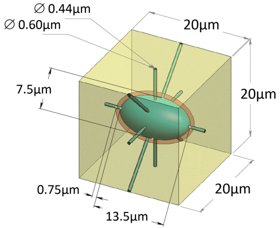

FE simulation

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

- ModBone (2D) : US stimulation at the mesoscale
  HV from CT scan images (22.5 μm)
  Time-dependent problem
  Weak form of wave propagation in poroelastic medium
  (Nguyen et al. 2010)
  $\triangle x_{\mathrm{bone}} \approx 0.7$ mm, $\triangle x_{\mathrm{water}} \approx 0.4$ mm and $\triangle t \approx 0.1 \mu s$
  $\rightarrow$ 40h to simulate a single cycle propagation.

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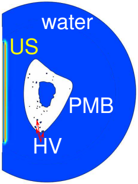

- input parameters :
  US stimulation parameters (from Exogen device)
  f=1MHz, pressure=2kPa, duty cycle=20%, pulse duration=1ms, Øtransducer=10mm
  surrounding fluid properties = water
  bone material properties = anisotropic poroelasticity *(Scheiner et al. 2015, Goulet et al. 2008, Nguyen et al.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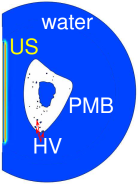

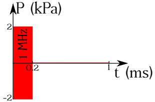

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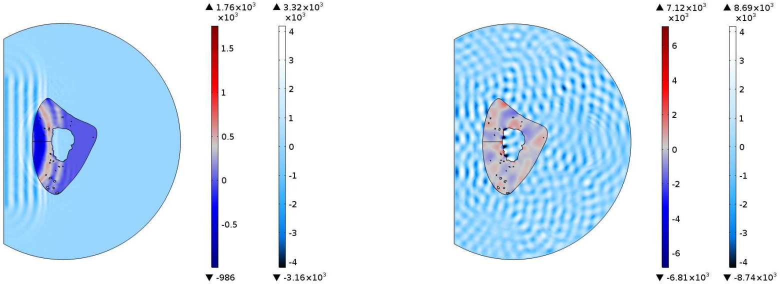
Acoustic pressure and IFluid pressure (Pa)

t = 4 μs | t = 20 μs



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

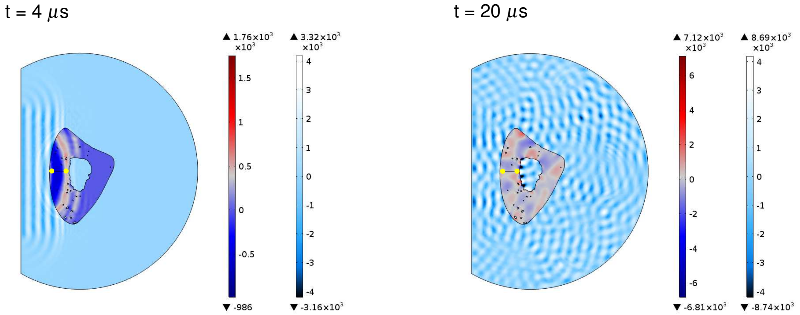
$$\mathrm{Max}|\mathrm{IFluid\ P}_{\mathrm{periosteum}} - \mathrm{IFluid\ P}_{\mathrm{endosteum}}| \approx 15000 \text{ Pa}$$

$\longrightarrow$ IFluid P gradient = 5 Pa/μm

- IFluid P gradient $\approx$ 30 Pa /μm *(Anderson et al. 2005, Verbruggen et al. 2012, 2014)*
  $\longrightarrow$ 6-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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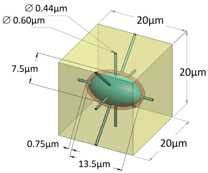
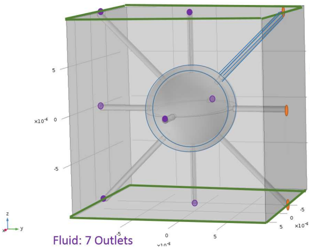
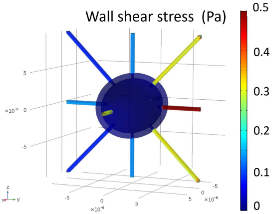


- ModOst (3D) :
  Fluid Structure Interaction Model (one-way coupling)
  - input parameters : lFluid P gradient from ModBone : 5 Pa/μm
  - output parameters : fluid shear stress on osteocyte : τ



lFluid 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



Fluid shear stress on osteocyte
(cell body and processes)
$\tau_{max} \approx 0.8$ Pa

- Shear stress patterns obviously related to simple symmetrical geometry and boundary conditions
- Theoretical shear stress interval for osteocyte activation : 0.8-3 Pa *(Weinbaum et al. 1994)*
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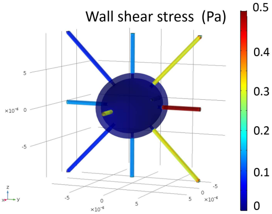

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What about *fluid drag forces* and strain amplification phenomenum ?
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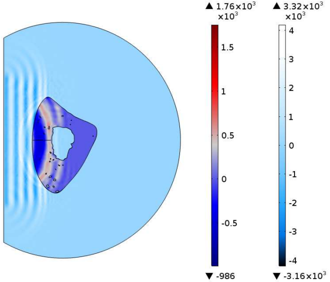

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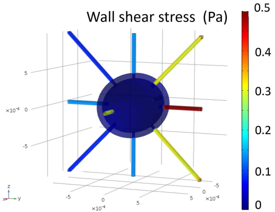

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Poroelastic bone properties

Transverse isotropic extralacunar matrix

$$\begin{pmatrix} 22.88 & 8.93 & 10.14 & 0 & 0 & 0 \\ 8.93 & 22.88 & 10.14 & 0 & 0 & 0 \\ 10.14 & 10.14 & 29.60 & 0 & 0 & 0 \\ 0 & 0 & 0 & 14.72 & 0 & 0 \\ 0 & 0 & 0 & 0 & 14.72 & 0 \\ 0 & 0 & 0 & 0 & 0 & 13.96 \end{pmatrix} (GPa)$$

(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*

Mesh