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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Monastery Banz, June 29th, 2017
Ultrasound waves and living tissues

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

*What* is LIPUS? **Low Intensity Pulsed Ultrasound Stimulation**
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Open question!
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Bone Tissue

**How** is cortical bone tissue organized?

- **Porous and multiscale:**
  - Vascular porosity (HV): Havers and Volkman canals ($\varnothing \approx 100 \, \mu m$)
  - Lacuno-canalicular network (LCN): lacunae ($\varnothing \approx 10 \, \mu m$) + canaliculi ($\varnothing < 1 \, \mu m$)

- **Bone cells:** osteocytes

**Mechnotransduction**
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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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)

- Poroelastic bone matrix (PBM)
  anisotropic solid (Scheiner et al. 2015) + LCN → equivalent medium (Biot’s model)
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![Diagram of Models](image)

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<tr>
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Baron, Guvier-Curien et al.

US and bone healing

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Osteocyte Model : ModOst

- Osteocyte cell (solid phase)
- Extracellular matrix, ECM (solid phase)
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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

  \( \Delta x_{\text{bone}} \approx 0.7 \text{ mm}, \Delta x_{\text{water}} \approx 0.4 \text{ mm} \) and \( \Delta t \approx 0.1 \mu \text{s} \)

\( \rightarrow 40 h \) to simulate a single cycle propagation.

(Nguyen et al. 2010)
FE simulation

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- input parameters:
  - US stimulation parameters
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  - 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: IFluid pressure gradient
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Results and Discussion: ModBone

Acoustic pressure and IFluid pressure (Pa)

$t = 4 \mu s$

$\Delta 1.76 \times 10^3 x 10^3$

$\Delta 3.21 \times 10^3 x 10^3$

$\Delta -986$

$\Delta -3.16 \times 10^3$

$t = 20 \mu s$

$\Delta 7.12 \times 10^3 x 10^3$

$\Delta 8.69 \times 10^3 x 10^3$

$\Delta -6.81 \times 10^3$

$\Delta -8.74 \times 10^3$

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

Max|IFluid $P_{\text{periosteum}} - IFluid P_{\text{endosteum}}| \approx 11000 \text{ Pa}

\rightarrow IFluid P gradient = 3.8 \text{ Pa/}\mu\text{m}

IFluid P gradient $\approx 30 \text{ Pa/}\mu\text{m}$ (Anderson et al. 2005, Verbruggen et al. 2012, 2014)

\rightarrow 8\text{-times lower than previous studies considering physiological mechanical loading.}

Fluid shear stress on osteocyte?
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Fluid shear stress on osteocyte?
**FE simulation**

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

- **Input parameter**: IFluid $P$ gradient from ModBone: $3.8 \text{ Pa/\mu m}$
- **Output parameter**: fluid shear stress on osteocyte: $\tau$

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

**Solid domain**: linear elastic,
- ECM: $E=16.6 \text{ GPa}$, $\nu=0.38$;
- osteocyte: $E=4.47 \text{ kPa}$, $\nu=0.3$
Results and Discussion: ModOst

Fluid shear stress on osteocyte (cell body and processes)

\[ \tau_{\text{max}} \approx 0.6 \text{ Pa} \]

(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

(Weinbaum et al. 1994)
Results and Discussion: ModOst

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Limitations of the study

- 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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Vascular porosity?

*Goulet et al. 2008*

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- a realistic model of the lacuno-canaliculi system?

*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 $2.2 \times 10^{-22}$ 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
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1 ms \( \approx \) relaxation time of fluid in canaliculi (*Swan et al. 2004*)
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**Osteocyte process model**

- Zoom on the osteocyte process into the canaliculi
  → GAG fibers → **strain amplification**

*You et al. 2001*
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Drag forces $F_d$

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

$a = 0.22\ \mu m$ : process radius ; $L = 20\ \mu m$ : 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
Wave propagation in the anisotropic poroelastic matrix (from Nguyen et al. 2012)

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

\[ \sigma = \mathbb{C} : \varepsilon - \alpha p, \]  

\[ -\frac{1}{M} p = \nabla \cdot \mathbf{w} + \alpha : \varepsilon, \]  

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

\[ \mathbf{w} = \phi (\mathbf{u}^f - \mathbf{u}^s) \]

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

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

(Scheiner et al. 2015)

Mass density: $\rho = 1.9 \text{ g/cm}^3$

Isotropic LCN permeability: $2.2 \times 10^{-22} \text{ m}^2$ (Smith et al. 2002, Cowin et al. 2009)

Other Biot’s parameters from NGuyen et al. 2016

$\phi = 5\%$, $\alpha_1 = 0.11$, $\alpha_2 = 0.15$, $M = 35.6 \text{ GPa}$. 
Poroelastic healing tissues properties

4 weeks_ Isotropic solid matrix

- **Granular tissue**
  \[
  \begin{pmatrix}
  2.502 & 2.5 & 0 \\
  2.5 & 2.502 & 0 \\
  0 & 0 & 0.001
  \end{pmatrix} \text{(GPa)}
\]
  \(\phi=90\%\)
  \(\alpha_1=0.98\)
  \(\alpha_2=0.96\)
  \(M = 2.2 \text{ MPa}\)
  \(\rho = 1.01 \text{ g/cm}^2\)

- **Cartilage**
  \[
  \begin{pmatrix}
  5.98 & 5.3 & 0 \\
  5.3 & 5.98 & 0 \\
  0 & 0 & 0.34
  \end{pmatrix} \text{(GPa)}
\]
  \(\phi=80\%\)
  \(\alpha_1=0.98\)
  \(\alpha_2=0.96\)
  \(M = 2.4 \text{ MPa}\)
  \(\rho = 1.04 \text{ g/cm}^2\)

- **Woven bone**
  \[
  \begin{pmatrix}
  17.1 & 12.9 & 0 \\
  12.9 & 17.1 & 0 \\
  0 & 0 & 2.1
  \end{pmatrix} \text{(GPa)}
\]
  \(\phi=50\%\)
  \(\alpha_1=0.976\)
  \(\alpha_2=0.955\)
  \(M = 2.55 \text{ MPa}\)
  \(\rho = 1.25 \text{ g/cm}^2\)
## Mechanical properties of healing tissue

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![Graph showing fluid pressure difference over time for different tissue types](image-url)
Mesh