Bone repair and ultrasound stimulation: an insight into the interaction of LIPUS with the bone through a multiscale computational study

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- FDA approval since 1994
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But how?
Open question!

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Bone Tissue

How is cortical bone tissue organized?

- Multiscale porosity:
  - vascular porosity (HV): Havers and Volkman canals (Ø ≃ 100 µm)
  - lacuno-canalicular network (LCN): lacunae (Ø ≃ 10 µm) + canaliculi (Ø < 1 µm)
  - collagen-hydroxyapatite porosity (Ø ≃ 10 nm)
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Interstitital fluid (IFluid) shear stress on **osteocytes**

⇒ bone remodelling
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(Cowin et al. 1991, Weinbaum et al. 1994, Klein-Nulend et al. 1995, etc.)

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$\Rightarrow$ bone remodelling

Cortical bone = double-porosity 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 (poroelasticity)
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Biphasic medium 2D-model + US

- Vascular pores (HV) = fluid phase $\approx$ water
  HV pores reconstructed from binarized $\mu$CT images (22.5 $\mu$m)

- Poroelastic bone matrix (PBM)
  anisotropic solid \cite{Scheiner2015} + LCN full of IFluid $\rightarrow$ equivalent medium (Biot’s model)
Model

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  Boundary conditions
  - continuity of pressure and stress fields
  - open pore conditions (interstitial fluid velocity = fluid velocity)
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+ Ultrasound stimulation (US) from Exogen device
  \( f = 1 \) MHz, pressure = 67 kPa, \( \phi \)transducer = 20 mm,
  duty cycle = 20\%, pulse duration = 1 ms
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FE simulation

Interaction between ultrasound waves and double-porosity medium in water

Software: Comsol Multiphysics

- Time-dependent problem
  ⇒ Weak form of wave equation in poroelastic medium + boundary conditions (Nguyen et al. 2010)
  \[ \Delta x \leq \lambda / 5, \text{ and } \Delta t = 0.1 \mu s \text{ (CFL)} \]
  → 24h to simulate a single cycle propagation.
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- Input parameters:
  - Fluids properties = water
  - Bone material properties = anisotropic poroelasticity \((Scheiner\ et\ al.\ 2015,\ Goulet\ et\ al.\ 2008,\ Nguyen\ et\ al.\ 2010,\ Cowin\ et\ al.\ 2009)\)
  - US stimulation parameters from Exogen device

- Output parameter:
  - IFIuid shear stress: \(\tau = \frac{\mu \| \dot{\omega} \|}{\sqrt{k}}\) \((Goulet\ et\ al.\ 2008)\)
    - \(\tau\): wall shear stress (Pa)
    - \(\mu\): dynamic IFIuid viscosity (Pa.s)
    - \(\dot{\omega}\): IFIuid velocity relative to the solid (m/s)
    - \(k\): LCN permeability (m\(^2\))
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### Time-dependent problem

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Results

Wave propagation:

\[ t = 5 \, \mu s \]

\[ t = 20 \, \mu s \]

\( p \): fluid pressure
\( ps \): IFluid pressure
Results

3 models:
- true geometry and vascular pores
- true geometry without vascular pores
- smoothed geometry without vascular pores
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IFluid shear stress and fluid acoustic pressure maps at 200 $\mu$s
Results

Fluid shear stress and fluid acoustic pressure maps at 1 ms

- Influence of the geometry
- Influence of the vascular pores (Goulet et al. 2008)
- Fluid shear stress localized around medullar canal and vascular pores
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IFluid shear stress 1cycle-average

- Average IFluid shear stress: [0.4 - 1.2] Pa
- Prediction interval of osteocyte activation under physiological loading: [0.3 - 8] Pa

(Weinbaum et al. 1994)
Conclusion and Perspectives

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

⇒ Fluid shear stress level locally in the range of the prediction interval ([0.8-3] Pa) given in literature for physiological loading (Weinbaum et al. 1994)
⇒ Fluid shear stress concentrated around medullar canal and vascular pores
⇒ Influence of the geometry and of the vascular pores

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 healing tissues
- stimulation frequency higher than physiological loading (1 - 100 Hz)
- loading direction
- pulsed ultrasound : 2 frequencies ⇒ repetition frequency and signal frequency
  pulse duration = 1 ms vs signal period = 1 µs
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  $\Rightarrow$ relaxation time of the LCN porosity $\approx$ 1 ms
  $\Rightarrow$ relaxation time for the vascular porosity $\approx$ 1 $\mu$s

(Cardoso et al. 2013)
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Questions:
- fluid shear stress?
- osteocytes?

Other physical phenomena:
- Microstreaming?
- Force radiation?
- Piezoelectricity?
- vascular porosity: osteoblasts / lining cells?
  (Kwon et al. 2010, 2012)

→ LIPUS on culture cells: cells = osteoblasts
  (Doan et al. 1999, Gleizal et al. 2010, Puts et al. 2016)

LIPUS: >1 MHz

[1-100] Hz
Thank you for your attention.

Any questions (or answers)?

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Models

Osteocyte Model

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

ECM: $E = 16.6 \text{ GPa}$, $\nu = 0.38$

Osteocyte: $E = 4.47 \text{ kPa}$, $\nu = 0.3$

- **input parameter**: IFluid P gradient: 30 Pa/μm
- **output parameter**: fluid shear stress on osteocyte: $\tau$
Limitations of the study

- a realistic model of the bone callus?
Conclusion and Perspectives

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

Osteocyte process model

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

*You et al. 2001*
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You et al. 2001

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

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

\[
\sigma = C : \epsilon - \alpha p , \tag{7}
\]
\[
- \frac{1}{M} p = \nabla \cdot w + \alpha : \epsilon , \tag{8}
\]

where \( C(x) \) 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; \( \epsilon(x, t) \) is the infinitesimal strain tensor, which is defined as the symmetric part of \( \nabla u^s \).

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

boundary conditions: pressure and stress fields continuity + *open pore* condition (continuity of the normal relative velocity between fluid and solid)
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
  \[
  \begin{pmatrix}
  2.502 & 2.5 & 0 \\
  2.5 & 2.502 & 0 \\
  0 & 0 & 0.001
  \end{pmatrix}
  \] (GPa)
  \(\phi=90\%\)
  \(\alpha_1=0.98\)
  \(\alpha_2=0.96\)
  \(M = 2.2\ \text{MPa}\)
  \(\rho = 1.01\ \text{g/cm}^2\)

- Cartilage
  \[
  \begin{pmatrix}
  5.98 & 5.3 & 0 \\
  5.3 & 5.98 & 0 \\
  0 & 0 & 0.34
  \end{pmatrix}
  \] (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
  \[
  \begin{pmatrix}
  17.1 & 12.9 & 0 \\
  12.9 & 17.1 & 0 \\
  0 & 0 & 2.1
  \end{pmatrix}
  \] (GPa)
  \(\phi=50\%\)
  \(\alpha_1=0.976\)
  \(\alpha_2=0.955\)
  \(M = 2.55\ \text{MPa}\)
  \(\rho = 1.25\ \text{g/cm}^2\)