Acoustic streaming in bone pericellular fluid under ultrasound stimulation

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1. Introduction

The use of ultrasound (US) stimulation for bone healing is a therapeutic approach that dates back over half a century. Nevertheless, the therapeutic efficacy of US stimulation of bone remodelling remains an open question, as the underlying mechanisms involved are still poorly understood. Among the possible hypotheses, the propagation of ultrasonic waves in bone tissue could generate acoustic streaming (AS) resulting in fluid shear stress exerted on the wall of osteocytes known as the mechanosensitive conductors of bone remodeling. Osteocytes are dendritic cells surrounded by a viscous pericellular fluid (PCF), ubiquituous in the bone extra-cellular matrix (ECM) forming a complex micrometric 3D network called the lacuno-canalicular network (LCN). A first finite-element (FE) model is proposed to investigate the AS induced by a US stimulation inside the PCF considered as a viscous fluid. The resulting wall shear stress (WSS) applied on the osteocyte process is estimated for different shapes of PCF space and different viscosities of PCF.

The aim is to explore the relevance of two simplifying assumptions commonly used in the literature: a geometry of the space occupied by the PCF equivalent to an annular-section tube, and a PCF viscosity equal to the viscosity of water. Finally, its quantification is questioned in regard of stress levels that can trigger a biological response.

2. Methods

It has been clearly demonstrated that the most sensitive parts of the osteocyte are its processes. According to the ratio of the transverse dimensions of the canaliculus (~0.1 µm) to its length (~10 µm), a 2D FE model is implemented on Comsol Multiphysics (v. 6.0) representing a cross-section of an osteocyte process surrounded by a layer of viscous fluid representing the PCF bounded by a wall representing the ECM.

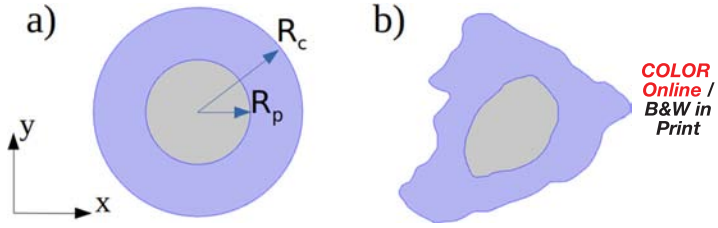

Figure 1. (a) Idealized I-model and (b) realistic R-model of PCF (in blue) and process (in gray). $R_c = 0.25\,\mu m$ is the canaliculus radius, $R_p = R_c/2$ is the process radius.

The goal of this work is to estimate the influence of the shape of the canaliculi and process on the WSS (averaged WSSav and maximum value WSSmax along the contour of the process). An idealized (I-model) geometry of two concentric circles is compared to realistic (R-model) contour extracted from images published in (Kamioka et al. 2012) (Figure 1).

The acoustic properties of the cell process and of the PCF are similar to those of water, except that the viscosity of the PCF is supposed to vary between 0.65×10^{-3} Pa s (viscosity of water at 37 °C) and 0.05 Pa s (Lee et al. 1993). The ECM/PCF interface is considered as a wall.

To mimic the influence of US stimulation, we assume that the walls are oscillating in the x-direction. A first order oscillating velocity $\mathbf{U1}(f) = i2\pi f d0\mathbf{ex}$ parallel to the x-direction is imposed along the ECM/PCF interface to model a harmonic acoustic wave at frequency f of 1 MHz with an amplitude of displacement d0.

The Navier-Stokes equations are solved inside the PCF domain using the perturbation method in order to calculate the acoustic streaming velocity V2 (time average of the 2nd order term) and to deduce the resulting WSS applied at the PCF/process interface. In Comsol Multiphysics 6.0, the Thermoviscous Acoustics module (in frequency domain) is used in order to resolve the first order acoustic field. Then, the acoustic streaming is taken into account by using the Laminar Flow module and weak form formulations (Muller and Bruus 2014).

3. Results and discussion

The acoustic streaming velocity V2 is calculated inside the PCF space.

Considering the PCF as water at 37 °C ($\mu PCF = \mu water = 0.0065$ Pa s), and the amplitude of the oscillation $d0 = 0.4$ nm the I-model provides a $V2max = 0.09\,\mu m/s$ whereas the R-model gives $V2max = 0.11\,\mu m/s$ (Figure 2).

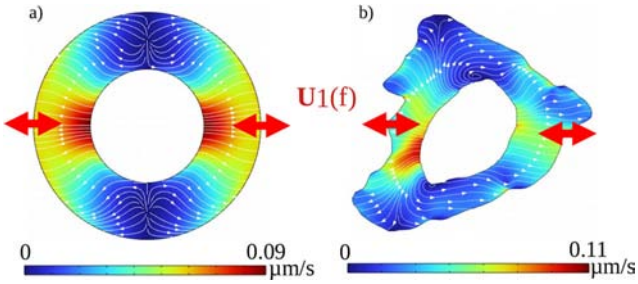

Figure 2. Acoustic streaming velocity V2 for (a) idealized and (b) realistic contours of PCF and process.

Table 1. Ratios of WSS between idealized (I-model) and realistic (R-model) contours for 3 values of PCF viscosity.

µPCF/µwater	1	3.85	7.7
WSSav(R-model)/WSSav(I-model)	2.5	3	3
WSSmax(R_model)/WSSmax(I-model)	16	19	19.5

The influence of the geometry is quite the same whatever the viscosity (Table 1). WSS_{max} is more dependent to the geometry of the contours as expected (Table 1). It is worth noting that the WSS_{av} values for the R-model is more than 2 times higher than WSS_{av} for the I-model and up to 20 times for WSS_{max} values (Table 1) showing that it is necessary to take into account a realistic geometry to relevantly investigate US stimulation effect on osteocytes.

Regarding the potential biological response of osteocytes under US stimulation, it is interesting to know that for viscosity higher than µref, a value of d0 = 0.8 nm is sufficient to induce WSSmax higher than 0.8 Pa which has been defined as the threshold to trigger osteocyte mechanotransduction (Weinbaum et al. 1994). The WSSav reaches this threshold for an oscillation amplitude d0 = 2 nm if µPCF = 0.025 Pa s and for d0 = 1.8 nm if µPCF = 0.05 Pa s. Note that WSSav along the process contour is proportional to $d0^2$ for the two geometries.

Although the model is 2D and has the limitations mentioned above, it tends to confirm that acoustic streaming can be induced by US stimulation in such a way that it can trigger biological response. Moreover, one of the strengths of this model is to easily investigate other contour shapes to test the WSS pattern associated with. One can notice that these realistic geometries can be further complicated including the tethering elements and ECM protrusions present inside the PCF space. In addition, the viscous fluid model of PCF and cell can be improved considering them as poroelastic medium and viscoelastic solid respectively. These considerations will affect the fluid velocity patterns obtained. Some further investigations are in progress to question the choice of mimicking US stimulation by an oscillating velocity. Moreover the low intensity ultrasound stimulation used in therapeutics is a pulsed stimulation, which needs to develop a model in time domain. This work can give new insights on stimulation of bone remodeling and could help to understand the underlying mechanisms in order to a better care for the patient.

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