Waves as biosensor for microarchitecture

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Introduction: Recently *in vivo* experiments using Multifrequency MRE (MMRE) have shown that the exponent of the power law derived from MMRE data fitting with a power law could be more sensitive to specific pathologies such as fibrosis, steatosis or even inflammation [1-2]. However these works lack fundamental understanding of the relation existing between the tissue microstructure with its macroscopic nature [3].Therefore - as pointed out in a recent paper [4] - if no theoretical model exists to justify the use of a power law to fit MMRE data and to explain the link between the microscopic and the macroscopic world, critical questions will remain and limit the potential benefits of this technology. As pointed in reference 3, this question has been widely investigated but mainly with the use of lumped mechanical elements such as springs and dashpots to express constitutive equations of the tissue. In this study we develop a full theoretical model of shear wave propagation at the microscopic scale in phantoms containing accurately controlled size distributions of scattering particles and demonstrate that shear waves are able to reveal at the macroscopic scale the hidden micro-architectural properties of the material.

Material and Methods: Gel phantoms were fabricated using an agarose solution at 15g/L (BRL, Type 5510UB). In order to create well defined scattering particle size distributions, colloidal suspensions of polystyrene microspheres with precisely known diameter (10µm diameter, Sigma–Aldrich) and concentrations (1.25-20%) were added to the gel before solidification. MRE was performed on a horizontal 7T imaging scanner (Pharmascan, Bruker, Erlangen, Germany) (Figure 1). The MRE sequence (spin echo, field of view of 30×30 mm^2, 300x300µm in-plane and 0.4 mm slice resolution, TE/TR (ms)= 13-35/270-505, 8 samples for time encoding, excitation frequencies: 600-1000 Hz) was acquired for the three spatial directions of motion in order to obtain volumetric images of the 3D mechanical wave propagating inside the phantom. Data were reconstructed with an isotropic reconstruction technique [5]. A power law fit was used to study the influence of micro–particle size concentration on the real part $\beta \approx \omega^{WSC}$ (WSC as the wave scattering coefficient) of the complex-valued wave vector $k=\beta+i\alpha$ (with β referring to the propagation and α to the attenuation) and to find a formula for its frequency-dependence. Confocal microscopy (lsm 510, ZEISS) using differential interference contrast mode was used to image the distribution of microspheres within the sample and to follow formation of aggregates with time.Theoretically, the heterogeneous medium can be described by a probability density function which represents for a constant and isotropic material the lag time distribution steering the effect of multiple reflections: a characteristic length separates the fractal and the Euclidean regions. This length ζ must follow the simple geometric relationship $\zeta \sim (a\rho)^{-1/d}$, with a and ρ, the radius and the density respectively, of particles submersed in the homogeneous background (d= spatial dimension). As demonstrated in [6] the imaginary part of the Fourier transform of the lag distribution function is equal to the wave propagation coefficient β.

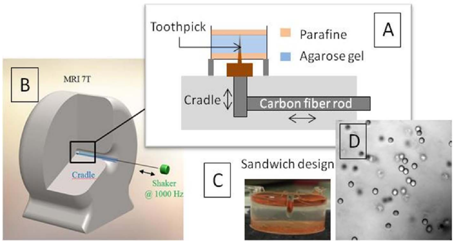

Figure 1: Phantom and experimental set-up. (A) A flexible carbon fiber rod transmits horizontal vibrations from a shaker to a toothpick mechanically coupled to the sandwich design phantoms (C) positioned in a 7T MRI scanner (B). (D) Confocal-microscopy image of the phantom with 1.25% in volume of 10 µm diameter microspheres.

Results and Discussion: Fig.2 presents experimental and theoretical WSC over particle density (a) and over particle radius (b). Dispersion properties of the shear waves are dramatically influenced by the presence of obstacles and are rather well predicted by the theoretical model developed here. WSC reaches a minimum at around 6 % and according to the theoretical model is almost equal to 1 at density above 50% which corresponds to the maximum filling of space with particles organized in a cubic mesh (≈π/6). Given a specific density of obstacles, the present theoretical model is able to estimate the size of the scatterers.

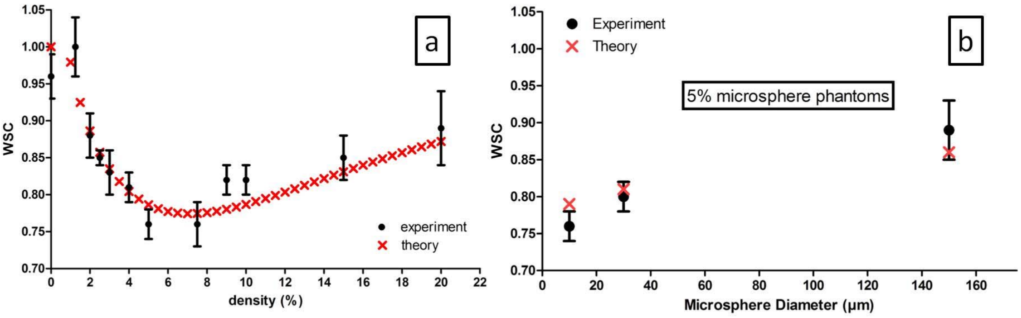

Figure 2: Experimental and theoretical exponent (WSC) of the frequency power-law fit of the propagation constant versus frequency over the density of microspheres (a) and over the microspheres radius (b).

Figure 3: Picture of the tumor cast.

Conclusion and Perspectives: We demonstrated by experiment, and theory that the dispersion properties of shear wave can probe the underlying micro-architecture even if the wavelength is much larger than obstacles. This effect is mainly due to multiple reflections of the shear waves occurring at a microscopic scale and depends minutely on the details of the particle distribution within the material. The theoretical model opens great perspectives for dynamic rheology for many reasons. Firstly, this method is independent from the working frequency and hence allows for tissue rheology comparison using different methods. Secondly, it is the first explanation of macroscopic viscoelastic properties of material based on a microscopic description of shear wave propagation which is the fundamental physical parameter of all elastrographic method. As a preliminary result we measured WSC in a phantom composed of a mouse tumor cast submersed within the previous described agarose gel. WSC was 0.94±0.01 and 0.33±0.01 for the gel without and with the tumor cast respectively. The link between the exponent of the power law and the sub wavelength microarchitecture has an impact on the interpretation of tissue rheology data, but can equally well be applied to the propagation of light.

References: [1] Asbach P. 2010, Radiology 257:80-86.[2] Garteiser P. 2013,ESMRMB,Toulouse.[3] Verdier C., 2003, J of Theoretical Medicine, Vol 5 (2), 67-91 [4] Stumpf M.P.H, 2012, Science,335, 665-666.[5] Sinkus, R, 2005, MRI, 159–165 [6] O'Doherty, RF, Anstey, NA, Geophys. Prospect. 19:430 (1971)