Sub-Voxel Micro-Architecture Assessment by Diffusion of Mechanical Shear Waves

Lauriane Jugé[1], Simon Auguste Lambert[1], Simon Chatelin[1], Leon ter BEEK[2], Valérie Vilgrain[1], Bernard E Van BEERS[1], Lynne E Bilston[3], Bojan Guzina[4], Sverre Holm[5], and Ralph Sinkus[1]

[1]*U773-CRB3, INSERM, Paris, France,* [2]*Philips Medical Systems, Best, Netherlands,* [3]*University of New South Wales, Neuroscience Research Australia, New South Wales, Australia,* [4]*Dept. of Civil Engineering, University of Minnesota, Minneapolis, MN, United States,* [5]*Informatics, University of Oslo, Oslo, Norway*

Introduction: Magnetic Resonance Elastography (MRE) is a technique capable of noninvasively assessing the mechanical properties of tissues. The assessment of these properties is done indirectly via the measurement of low frequency mechanical shear waves traversing the tissue [1]. It can be hypothesized that the presence of micro-obstacles –similar to effects leading to the apparent diffusion coefficient - changes the dispersion relation of propagating shear waves and hence might influence at the macroscopic scale the apparent mechanical properties of the medium [2, 3]. In diffusion weighted imaging (DWI), disordered media can lead to two effects: reduction of the typical diffusion length leading to the apparent diffusion coefficient and/or a mean-square displacement which is not anymore proportional to time but to a fractional power of time not equal to one (so-called anomalous diffusion) [4]. In DWI, micro-structural information is lost due to the massive averaging that occurs within the imaging voxel and can only be revealed when exploring the tissue using different b-values. Similarly here, where the propagation of a mechanical wave enters into the diffusive regime due to multiple scattering effects, the frequency dependence of the mechanical properties could allow the assessment of the sub-voxel micro-architecture. In this study we investigate the propagation of shear waves in calibrated phantoms containing accurately controlled size distributions of scattering particles and demonstrate for the first time that shear waves are able to reveal at the macroscopic scale the hidden micro-architectural properties of the material.

Materiel and Method: Gel phantoms were fabricated using an agarose solution at 15 g/L (BRL, Type 5510UB) prepared in a water bath at 80°C. In order to create well defined scattering particle size distributions, colloidal suspensions of polystyrene microspheres with precisely known diameter (1µm, 5 µm, 10 µm, 30µm and 150µm diameter, Sigma-Aldrich) and concentrations were added to the gel before solidification (Fig.1A). The aim was to maintain for all prepared gels a concentration of 8% of spheres (similar to the volume fraction of blood vessels in tissue). The polystyrene microspheres have an extremely elevated shear modulus (~MPa) and hence can serve as microscopic scatterers in the soft gel (~kPa). Different sample were prepared: gels without spheres serving as reference, gels with only one type of spheres (so-called monosize gel) and gels with particle size distributions which followed a power law and hence possessed fractal properties. Different exponents of power-law particle size distributions (#~d^{γ}, with d the particle diameter) were fabricated (γ= -2, -1, 0). A γ-value of zero indicates a flat distribution meaning that as many small as large particles are present. MRE was performed on a horizontal 7 T imaging scanner (Pharmascan, Bruker, Erlangen, Germany). Mechanical vibrations were generated by a toothpick placed in the center of the sample to induce a circular propagation. An electromagnetic shaker located outside the MR scanner was used to transmit mechanical vibrations via a flexible carbon fiber rod to the toothpick (Fig.1B). Samples placed around the toothpick were always at the same height via a home-made support. A surface receiver coil was placed around the sample at the level of the gel to assure optimal signal to noise. For each phantom a steady-state MRE sequence was applied with a mechanical excitation frequency in the range of 150 to 300 Hz and the following sequence parameter: 8 dynamics, 7 contiguous transverse slices with slice thickness of 0.4 mm, field of view = 25 mm × 25 mm, matrix size = 256 × 256, TE/TR = 27-17/427-353 ms and acquisition time in the range of 6 to 10 min depending on the excitation frequency and on the number of motion encoding gradient periods. The MRE sequence was acquired for the three spatial direction of motion in order to obtain volumetric images of the 3D propagating mechanical wave inside the phantom. In order to take into account a potential temporal evolution of the gel during the entire acquisition time (up to 300mins!), the first experiment was repeated at the end of the acquisition time. This allowed correcting for potentially drying effect. Data were reconstructed with an isotropic reconstruction technique [5].

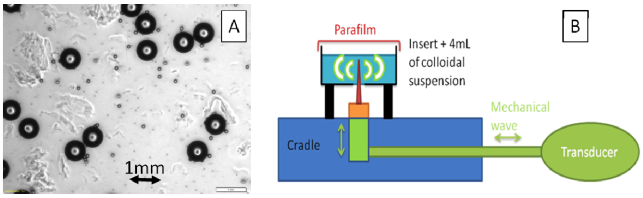

Figure 1 : A) Light microscopy image of a colloidal gel specimen at magnitude ×50 (LEICA Microscope). Clearly, particles of different sizes can be identified. The thereby measured diameter distribution per volume corresponded to the expected theoretical value hence validating the desired micro-architectural properties of the gel; B) Schematic depiction of the experimental setup. The gel is filled into an insert which is mounted on to the MRE setup.

Results:The complex-shear modulus (G*) of each phantom increased by a maximum of 10 % between the beginning and the end of the multifrequency-MRE experiment due to aging effects. As presented in Figure 2, results show that the macroscopic shear modulus is frequency-dependant for the four investigated samples and follows a power law with $|G^*(\omega)|=\alpha.\omega^{z0}$. The power coefficient z_0 of a gel with the 10 µm-monosize distribution of microspheres is almost unchanged as compared to z_0 of the reference gel (Fig.2A). However, in the presence of a fractal distribution of microspheres, z_0 increases significantly compared to the reference gel by a factor of 2.2. All other fractal gels demonstrated equally a significant increase in z_0.

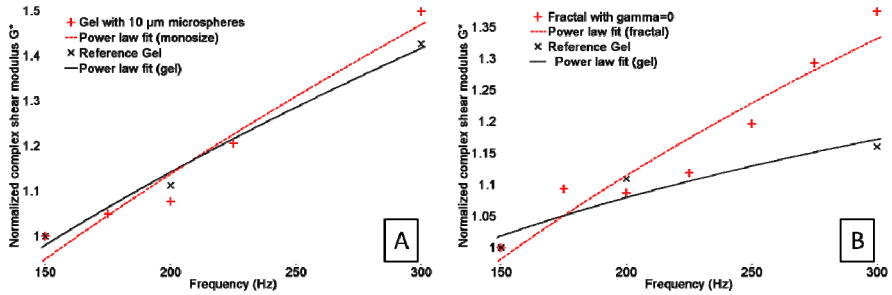

Figure 2 : Normalized complex shear modulus (|G*|) as function of mechanical excitation frequency. A power-law fit according to $|G^*(\omega)|=\alpha.\omega^{z0}$ was applied to the experimental data A) The power coefficient of the gel containing only 10 µm-spheres is unchanged (×1.2-red dashed line) compared to the reference gel (black line). B) A significant increase of z0 (factor of 2.2) is observed in the case of the fractal gel with a flat particle size distribution (γ=0).

Conclusion, discussion and perspectives: For the first time we demonstrated that the frequency-dependence of mechanical shear wave diffusion can allow probing sub-voxel distributions of scattering structures and as a consequence overcome the spatial resolution limitation relying intrinsically on the MR imaging sensitivity. These experimental results have been theoretically [2] and numerically via FEM simulations confirmed (not shown). However, in this study mechanical properties of the gel were critically relying on the fabrication process and only relative slopes of different gels have been compared. The solidification process of the colloidal gels must be improved and additional imaging modalities should be involved such as CT-scans in order to image the microspheres distribution in phantoms after solidification of the gel that probably induces microspheres aggregation into fractal flocs [6]. Moreover, the studied gels consisted of very simplified biphasic structural arrangements with particles being about 1000 times stiffer than the background gel. Biological tissue represents a far more complex arrangement with variations not only in size, but also in stiffness contrast and length distribution. Phantoms with microspheres exhibiting multi-size distributions and multiple elasticity properties would be better to simulate real tissue. The here observed effect might play an important role in understanding the influence of microscopic tissue components on mechanical properties as measured by elastography techniques. It opens the perspective of detecting and describing micro-inclusions, such as small metastases or neo-vascularisation, from elastography data, which are not directly detectable by MRE.

References [1] Muthupillai, R, et al, Science, 1995. 269(5232) p. 1854 [2] Holm S, Sinkus R, J. Acoust. Soc. Am. 127:542 (2010) [3] O'Doherty, RF, Anstey, NA, Geophys. Prospect. 19:430 (1971) [4] Zhou XJ et al, MRM 2010 Mar;63(3):562-9 [5] Sinkus R, Tanter M, et al., Magn Reson Imaging 23:159 (2005).[6] Coussot P, Soft Matter, 2007, 3, 528-540