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Effect of cerebral protein aggregates on tissue mechanical properties measured by Magnetic Resonance Elastography

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Introduction

During the first stages of the development of neurodegenerative diseases, some endogenous proteins, usually in a monomeric shape, agglomerate to form beta-sheet stacks called fibrils [1]. The protein involved differs depending on the disease: α -synuclein in the case of Parkinson's disease, β -amyloid for Alzheimer's disease and Tau protein for frontotemporal dementia. Qualitative detection of β -amyloid and Tau fibrils is currently possible by Positron Emission Tomography (PET) using dedicated radiotracers [2]. In MRI, direct detection with contrast agents shows poor sensitivity, and the spatial resolution of structural MRI is not sufficient to discern micrometric scaled agglomerates. Thus, only a late diagnosis can be made, based on a loss in brain volume [3,4]. A non-irradiating, quantitative method to detect any type of aggregate through one unique exam would allow an improved efficiency of the diagnosis procedure. In the case of preclinical trials, being able to follow the evolution of the disease with imaging could be helpful for the development of new drugs. We propose to develop an *in vivo* imaging technique based on the link between the microstructure of the aggregates and the macroscopic observables collected with an MRI experiment.





Figure 3. Evolution of the shear wave speed in a phantom where micro blood vessels are grown, the power factor of the law y increases as the vessels grow [6]

We believe that the fibrillary structure of the protein aggregates could leave its fingerprint in the macroscopic mechanical properties as well. Dedicated experimental developments are mandatory to obtain an adequate image spatial resolution compared to characteristic length of the experiment such as the wavelength.

Development of 3D-printed phantoms with fibril inclusions is ongoing. Those phantoms are, in the meantime, characterized with MRE. After the study of the effect of the fibrils on the mechanical properties of a homogeneous media, *ex vivo* and *in vivo* studies on mice bearing a focal injection of fibrils are scheduled. The main goal is to determine if the "micro/macro" link observed in phantoms persist *in vivo*, where the environment is more complex as it contains other sources of wave scattering than the fibrils.

Finally, a comparison of our results with PET images of the mice will be made to evaluate the MRE technique as a diagnosis tool of neurodegenerative diseases.



Fibrils

mm

MRI resolution # mm

Figure 1. a) Endogenous proteins in their monomeric, healthy shape and grouped to form beta sheet agglomerates (fibrils); b) Presentation of the detection problem with MRI in terms of dimension for the fibril aggregates

Methods

Magnetic Resonance Elastography (MRE) consists in the *in situ* MR imaging of shear waves propagating within tissue. The registered wave is induced by an external driver synchronized with the MRE sequence. Images are acquired at different steps of the wave propagation, and after appropriate reconstruction, different mechanical such as wave speed, attenuation or shear modulus can be obtained.





Figure 4. a) Schema of an agarose phantom containing inclusions of two types of fibrils; b) Inclusion of the same fibril aggregates in a mouse brain, ex vivo

Conclusion

Origin of contrast mechanisms in MRE are poorly understood [7]. This experimental approach will allow identifying the effect of a specific structure on the mechanical properties. By this approach we aim at disentangling the signal coming from the aggregation of proteins, which is the hallmark of neurodegenerative diseases from other structures.

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Figure 2. a) Magnitude and b) phase image of a 3D-printed phantom (PEG-DA hydrogel) and a toothpick (wood) used to propagate shear waves within the phantom. The wave propagation is visible around the toothpick. After analysis, the elasticity found for this sample was 2 kPa

In previous works it has been shown that the frequency dependence of these mechanical parameters can reveal the underlying microarchitecture at the macroscopic scale [5,6]. The behavior of the wave speed inside the material is linked to the multiple scattering undergone by the wave: as frequency (v) increases, wave speed (c_s)increases, following a power-law of the type $c_s = v^y$, where y reflects the fractal aspect of the medium.

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