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Laboratoire des Systèmes et Applications des Technologies de l'Information et de l'Energie UMR CNRS 8029

Rheological monitoring for tau protein aggregation process

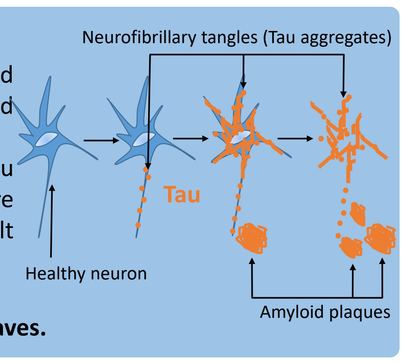
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Introduction

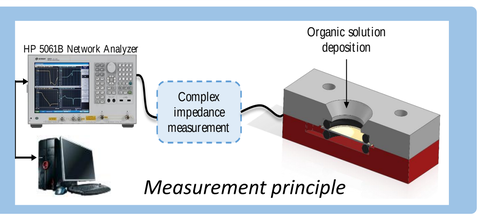
In the human body there are many proteins for which the polymerization can induce pathology. Diseases result from abnormalities in the structure and conformation of proteins, called conformational disease. Tau protein aggregation (Tubulin-Associated Unit) is associated with many neurological disorders grouped under the term Tauopathies. It was originally described as the "Tau factor" means an element capable of inducing polymerization of tubulin into microtubules.
Neurofibrillary tangles are amassed from filaments having a straight or paired helical morphology, they are composed of the microtubule-associated protein tau under hyperphosphorylation form. Death of polymer-laden neurons is evidenced by the presence of insoluble tangle remnants to induce degeneration, they are implicated in the necrotic process of synapses. They will aggregate and probably cause cell death. The aggregation's mechanism is poorly understood and difficult to study.



In this work, a microsystem is developed for tau protein detection based on real time monitoring micro-rheological parameters by high frequency ultrasonic waves.

Measurement principle

Tau protein polymerization is followed thanks to the thickness shear mode resonator developed in this study. The acoustic wave transducer has a resonance frequency due to its intrinsic properties (materials type, quartz dimensions, crystal cut) and mechanical properties, which will vary with biological species deposition on its surface.
Complex impedance is measured by a vectorial network analyzer after introducing piezoelectric transducer in a thermostated cell during the experiment.



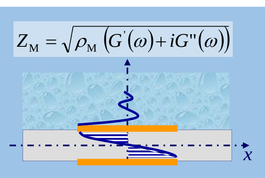
Measurement principle

Transducer characterization: Electrical response

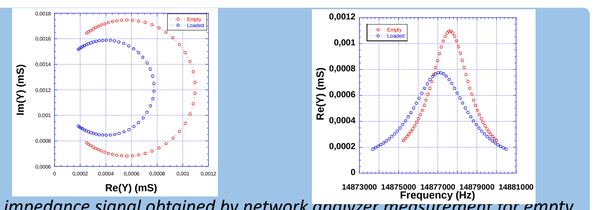
During a deposition of chemical or biological species to the quartz surface, its resonance frequency and its electrical properties are changed and characterized by a network analyzer.

Biological species deposition is characterized by complex impedance Z_M, which depend on the viscoelastic parameters of tested solution.

$$Z_M = \sqrt{\rho_M \left(G'(\omega) + iG''(\omega)\right)}$$



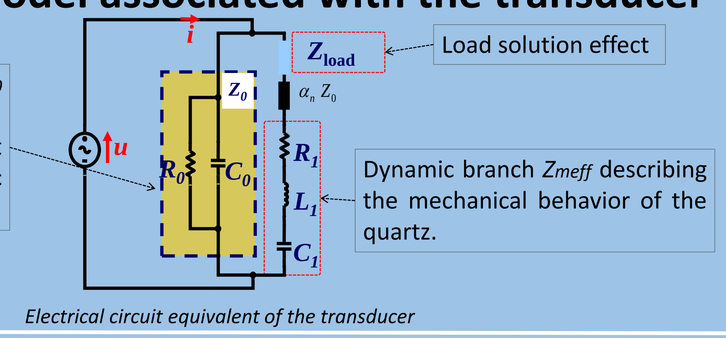
Acoustic wave propagation in the transducer and analytes.



Complex impedance signal obtained by network analyzer measurement for empty (orange) and loaded (blue) system

Electrical model associated with the transducer

Static branch *Z0* describing capacitive effect *C0* and dielectric loss effect *R0*



Electrical circuit equivalent of the transducer

Extraction of viscoelastic parameters

Elastic modulus (G') and Viscous modulus (G'') are extracted from Z_{load} :

Electro-mechanical coupling factor — **Mass effect**

$$Z_{Load} \cong i\,Z_0 \frac{(2n+1)\pi}{4K_{eff}^2} \frac{Z_M}{Z_{m_eff}} \cong K\left(\sqrt{\rho_M \left(G'(\omega)+iG''(\omega)\right)} + i\,\omega\,\rho_M\,h_{eff}\right) = R + iX + i\,K\omega\,\rho_M\,h_{eff}$$

Rheological parameters

$$G' \propto \frac{R^2 - X^2}{\rho_M}$$ **elastic modulus**

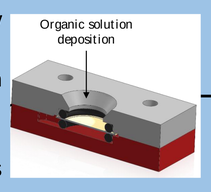
$$G'' \propto \frac{R \times X}{\rho_M}$$ **viscous modulus**

(*R*, *X*) or (*G'*, *G''*) give information on the evolution of the material

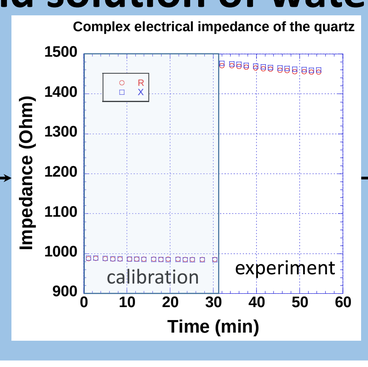
Viscoelastic parameters G' and G'' for a pure water and solution of water/glycerol:

Measurements revolves around three phases:

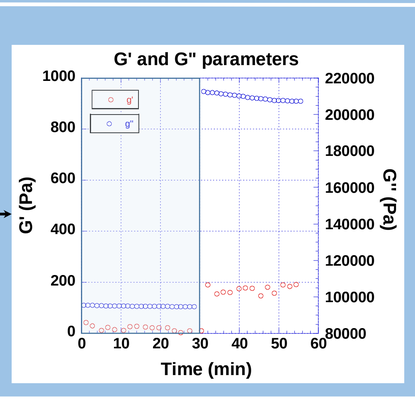
- **First phase** consisted in **system initialization**, with the determination of the sensor electrical parameters and quality factor.
- **Second phase** consisted in deposition of a purely Newtonian liquid (DI water) on the quartz surface to **calibrate experiment**.
- **Third phase** is the **experimental phase**. the Newtonian liquid is removed and biological solution is deposited on the quartz substrate measurement for the record in line of complex impedance.



Complex impedance measure

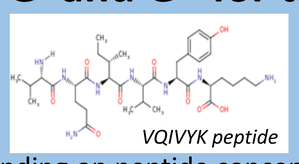


Viscoelastic parameters G' and G'' extracted with electrical model



Viscoelastic parameters G' and G'' for tau protein polymerization

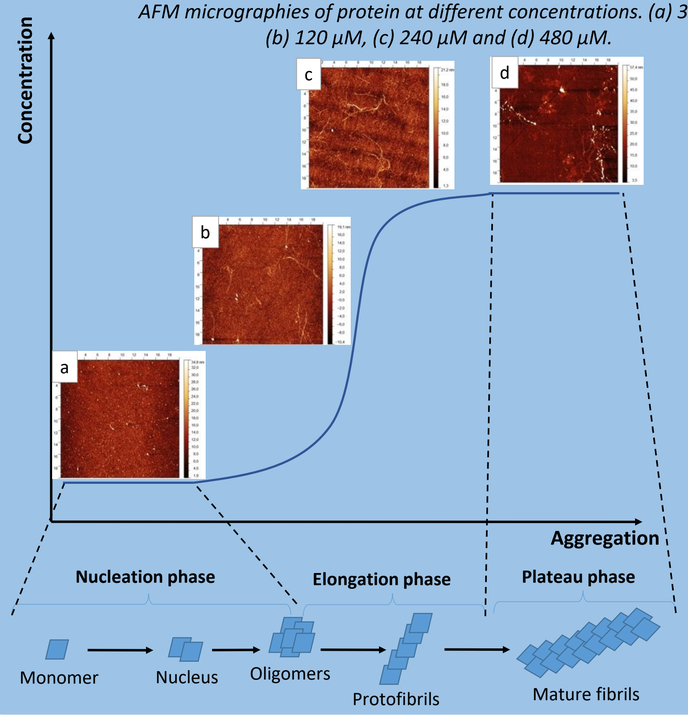
Protein sequence : VQIVYK


VQIVYK peptide

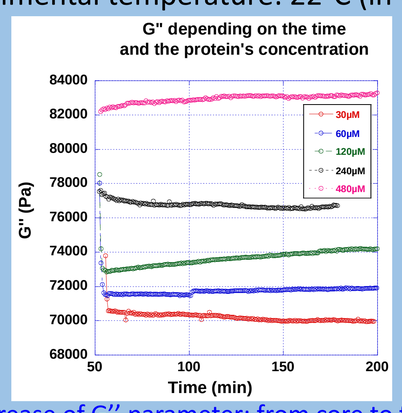
Conformational states of protein depending on peptide concentration

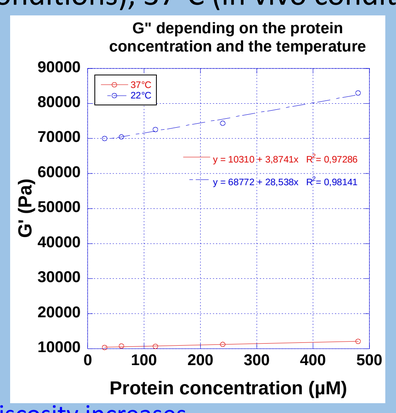
The choice of this peptide is justified by its presence in the tau protein in position 306-311 and is sufficient for the self-assembly of tau

Biological model of the polymerization of the tau protein.
AFM micrographies of protein at different concentrations. (a) 30 µM, (b) 120 µM, (c) 240 µM and (d) 480 µM.



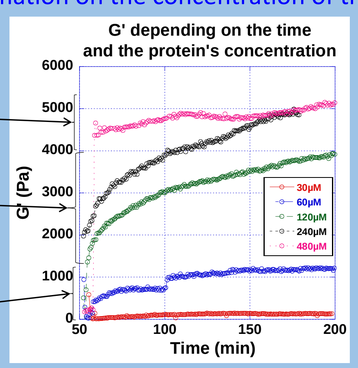
-> Different concentrations of protein are deposited on the quartz.
Experimental temperature: 22°C (in vitro conditions), 37°C (in vivo conditions)

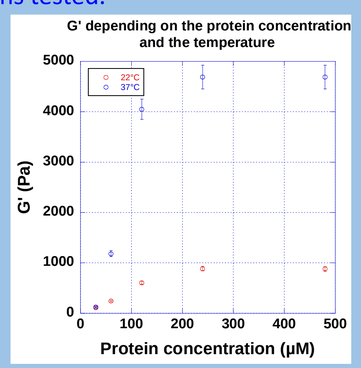




Increase of G'' parameter: from core to fibers, viscosity increases
-> Information on the concentration of the solutions tested.

Plateau phase
Elongation phase
Nucleation phase





Variations of G' parameter: follow proteins polymerizations and detection of peptides conformations changes are possible.

Conclusions

Development of an instrumentation system allowing:

- Detection of different concentrations of proteins in static conditions
- Detection of different conformational states with the plasticity differentiation
- Differentiation between protein concentrations of tau ranges from 30-480 µM by measuring their viscoelastic properties with confirmation of the biological model.

