Master 2 research internship in Integrated Structural & Cell Biology in Grenoble

Supervisor(s):
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https://www.ibs.fr/spip.php?lang=en

Title of the M2 research internship:
Intrinsically disordered proteins under liquid-liquid phase separation: the case of tau involved in neurodegeneration

Project summary:
Background: Liquid-liquid phase separation (LLPS) of biological macromolecules is a hot research topic at the interface between biology, physical chemistry and biophysics. LLPS leads to dense droplets, enriched in macromolecules, that coexist with a depleted phase. Major drivers of intracellular LLPS are intrinsically disordered proteins (IDP) that lack a well-defined 3D structure. A major finding in the past few years was that LLPS can promote pathological amyloid-fiber formation of proteins involved in neurodegenerative diseases (see e.g. Wegmann et al. 2018 EMBO J). Yet, the basic properties of the proteins under LLPS have been scarcely characterized, and the processes leading LLPS to promote IDP aggregation are unknown. The internal protein dynamics of IDPs under LLPS are currently discussed to be important for LLPS, but experimental evidence is missing.
Aim of M2 internship: The aim of the internship project is to link protein dynamics in LLPS with the aggregation-promoting capacity. The medically important IDP tau will be studied, amyloid fibers of which are pathological hallmarks in Alzheimer's disease. The approach is expected to reveal fundamental properties of tau under LLPS and the basis for their pathological behavior.
Method: Neutron spectroscopy (NS) will be the main method used in this project. NS provides spatially-averaged information on ns-ps motions of hydrogens in proteins that are widely acknowledged to play a role in protein functioning and malfunctioning. NS experiments will be carried out at the Institut Laue Langevin in Grenoble that will have ended its extended shutdown when the internship project will be conducted.
Previous results: We have used NS to study the dynamics of tau (Fichou et al. (2015) PNAS 112, 6365) before and after formation of amyloid fibers and to study the dynamics of lysozyme (Pounot et al. (2020) J Phys Chem Lett 11, 6299) during aggregation. We now want to study the dynamics of tau under LLPS.

Keywords:
instrinsically disordered proteins, liquid-liquid phase separation, molecualr dynamics

Relevant publications of the team:
Schirò G, Fichou Y, Brogan APS, Sessions R, Lohstroh W, Zamponi M, Schneider GJ, Gallat F-X, Paciaroni A, Tobias DJ, Perriman A, Weik M (2021) Diffusivelike Motions in a Solvent-Free Protein-Polymer Hybrid. Physical Review Letters 126: 088102

Pounot K, Grime GW, Longo A, Zamponi M, Noferini D, Cristiglio V, Seydel T, Garman EF, Weik M, Fodera V, Schiro G (2021) Zinc determines dynamical properties and aggregation kinetics of human insulin. Biophys J 120: 886-898

Pounot K, Chaaban H, Fodera V, Schiro G, Weik M, Seydel T (2020) Tracking Internal and Global Diffusive Dynamics During Protein Aggregation by High-Resolution Neutron Spectroscopy. The journal of physical chemistry letters 11: 6299-6304

Fichou Y, Schiro G, Gallat FX, Laguri C, Moulin M, Combet J, Zamponi M, Hartlein M, Picart C, Mossou E, Lortat-Jacob H, Colletier JP, Tobias DJ, Weik M (2015) Hydration water mobility is enhanced around tau amyloid fibers. Proc Natl Acad Sci U S A 112: 6365-70

Schiro G, Fichou Y, Gallat FX, Wood K, Gabel F, Moulin M, Hartlein M, Heyden M, Colletier JP, Orecchini A, Paciaroni A, Wuttke J, Tobias DJ, Weik M (2015) Translational diffusion of hydration water correlates with functional motions in folded and intrinsically disordered proteins. Nature communications 6: 6490