



PhD Research Proposal Form China Scholarship Council (CSC) - ENS Group

FIELD: Biology/Biophysics

Thesis subject title: Molecular Modeling of Alpha-Synuclein Interactions at the Lipid Droplet–Mitochondria Interface in Parkinson’s Disease

Name of the French doctoral school : ED 205 - EDISS Interdisciplinaire Sciences et Santé

Name of the Research team : Dynamics and Control of Biological Assemblies and Macromolecular Machines (part of LBMC - Laboratoire de Biologie et Modélisation de la Cellule)

Website : <https://www.ens-lyon.fr/LBMC/equipes/dynamics-and-control-of-biological-assemblies-and-macromolecular-machines>

Name of the Supervisors:

main supervisor: Paulo C. TELLES DE SOUZA, Email: paulo.telles_de_souza@ens-lyon.fr

co-supervisor: Luís BORGES-ARAÚJO, Email: luis.borges@ens-lyon.fr

Lab Language : English

Research Proposal Abstract :

Parkinson’s disease is characterized by the misfolding and aggregation of alpha-synuclein, an intrinsically disordered protein that plays a central role in neuronal lipid metabolism. Recent findings from LBMC show that alpha-synuclein promotes the accumulation of PLIN2-positive lipid droplets in neurons, suggesting that lipid environments and organelle interfaces influence its pathological behavior. However, the molecular mechanisms by which alpha-synuclein interacts with lipid droplets and mitochondria, and how these interactions contribute to neuronal dysfunction, remain poorly understood. This PhD project aims to elucidate these mechanisms using computational biophysics. Recent advances from our simulation group now allow us to model the conformational dynamics of alpha-synuclein with improved accuracy. Building on these developments, we will investigate how alpha-synuclein binds to lipid droplet surfaces with different lipid compositions and curvatures, including PLIN2-decorated monolayers, and determine how membrane interactions affect its conformation and aggregation propensity. We will also model the lipid droplet–mitochondria interface, focusing in particular on the mitochondrial import receptor TOM20, to explore whether alpha-synuclein facilitates or stabilizes organelle contact sites that may contribute to metabolic stress. The work will rely on multiscale molecular dynamics simulations (coarse-grained Martini and atomistic approaches) and will be developed in close partnership with experimental studies at LBMC. Computational results will be integrated with lipidomics and neuronal imaging data generated in the team of Prof. Bertrand MOLLEREAU. The PhD student (Zaihang YE, candidate pre-selected) will be supervised by Dr. Paulo C. TELLES DE SOUZA with co-supervision from the CNRS researcher Dr. Luís BORGES-ARAÚJO, ensuring strong expertise in molecular simulation and protein–lipid interactions. The project will also include a 3–6-month research stay at Sichuan University – China, with Dr. Yang LIU to receive advanced training in modeling intrinsically disordered proteins, biocondensates and their interactions with membranes. Together, this interdisciplinary project will provide new molecular insight into how lipid environments influence alpha-synuclein function and dysfunction in Parkinson’s disease.

References :

- Girard, V. et al. (2021) Abnormal accumulation of lipid droplets in neurons induces the conversion of alpha-synuclein to proteolytic-resistant forms in a *Drosophila* model of Parkinson's disease. *PLoS Genetics* 17(11): e1009921.
- Wang, L. et al. (2025) Martini3-IDP: improved Martini 3 force field for disordered proteins. *Nature Communications* 16: 2874.
- Liu, Y. et al. (2023) Capturing coacervate formation and protein partition by molecular dynamics simulation. *Chemical Science* 14: 1168–1175.
- Ingólfsson, H. I. et al. (2023) Multiscale simulations reveal TDP-43 molecular-level interactions driving condensation. *Biophysical Journal* 122: 4370–4381.

Type of PhD :

1.Full PhD

- Joint PhD/cotutelle (leading to a double diploma) : NO
- Regular PhD (leading to a single French diploma) : YES

2. Visiting PhD (for students enrolled at a Chinese institution who will be invited to a French institution to carry out a mobility period) : NO