BioISI - Biosystems & Integrative Sciences Institute

Molecular Mechanisms of Amyloid Aggregation in Neurodegenerative Diseases

Place of work: BioISI – FCUL, Edificio C8, piso 5

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Abstract / MSc thesis project proposal

Protein aggregation is implicated in several human disorders, including Alzheimer's and Parkinson's disease (PD). The former involves the aggregation of tau and amyloid-beta peptides and the latter the aggregation of alpha-synuclein in dementia with Lewy bodies and multiple system atrophy, in addition to PD. a-synuclein is a 140 amino acid intrinsically disordered protein, product of the SNCA gene, mainly expressed in the brain, that aggregates into toxic oligomers and amyloid fibrils, forming protein inclusions, known as Lewy bodies and Lewy neurites[1]. Thus, understanding the molecular mechanisms of a-synuclein aggregation is paramount to the development of therapeutic strategies including the design of novel aggregation inhibitors.

This project aims to study, through molecular dynamics simulations, the hydration and aggregation of key amyloid peptides closely associated with Parkinson's and Alzheimer's disorders. The student will perform fully atomistic molecular dynamics simulations of the monomer and dimer of the peptide(s) of interest in aqueous solution aiming at assessing the hydration and binding free energies. Several free energy enhanced sampling techniques will be used, in addition to molecular analysis tools developed in the group to investigate the role of protein-protein and protein-water interactions in the aggregation process[2]. The investigation of potential drugs targeting specific regions of a-synuclein may also be performed through molecular docking studies, depending on the students' interests.

Bibliography:

[1] Breydo, L., Wu, J. W., and Uversky, V. N. (2012) α-Synuclein misfolding and Parkinson's disease. *Biochim. Biophys. Acta BBA - Mol. Basis Dis.* **1822**, 261–285

[2] N Galamba (2019) On the *Nonaggregation of Normal Adult Hemoglobin and the Aggregation of Sickle Cell Hemoglobin*, J. Phys. Chem. B, 123 (50), 10735-10745