PhD Proposal 2022-2025

Title of the project: Protein dynamics and aggregation from a graph perspective

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Opening a new avenue of research

As demonstrated experimentally by Anfinsen (1972 Nobel Prize), a protein folds in its minimum of Gibbs free energy, named its native state, in physiological conditions, both *in vitro* and *in vivo*.[1] Protein folding can be described as global[1] and local[2,3] first-order phase transitions. Misfolding leads to toxic aggregation, as for example in Parkinson Disease (PD) and Alzheimer Disease (AD). Misfolded alpha-synuclein (PD) and Abeta (AD) toxic aggregates are landmarks of these two neurological pathologies.

Very recently, the prediction of the folded structure of a protein from its amino-acid sequence was achieved by deep learning algorithms[4], solving an issue 50 years old. Despite of this major success of artificial intelligence,[4] how the folding pathways are encoded in the amino-acid sequence, how to characterize the apparent fuzzy dynamics of an intrinsically disordered protein, as alpha-synuclein, are fundamental questions remaining unanswered. They are relevant to characterize the molecular origin of AD and PD. Atomistic molecular dynamics (MD) simulations of proteins at different temperatures contain implicitly the answers to these fundamental questions. The major issues are i) to identify collective variables and properties which allow to build a comprehensible model of the biopolymer dynamics and aggregation from the apparent chaotic motions of its atoms, ii) the huge conformational space and complexity of misfolding structures and aggregates **which cannot be explored by MD due to the limitations of current computer technology**.

Therefore, we propose a new "Divide and Conquer" method which consists in a multi-scale strategy: from a topological description of proteins to coarse-grained MD simulations. We will develop a new *graph theoretical approach* of the protein conformational dynamics and structures to identify relevant order parameters of a graph *free-energy landscape*. Two types of approaches will be explored. First, based on preliminary results found in a previous[5] and current internships[6], global and local robustness of a simple structure-based graph will be used as well as other topological invariants to cluster protein conformations. Second, we will build a free-energy model for a protein graph parametrized on a database of protein experimental structures[5] and on an ensemble of MD data of alpha-synuclein dimers[7].

References

[1] Principles that Govern the Folding of Protein Chains, C. B. Anfinsen, Science 181:223-230 (1973)
[2] Statistical model to decipher protein folding/unfolding at a local scale, P. Grassein, P. Delarue, H.A. Scheraga, GG Maisuradze, P. Senet, J. Phys. Chem. B 122: 3540-3549 (2018)
[3] Curvature and Torsion of Protein Main Chain as Local Order Parameters of Protein Unfolding, P. Grassein, P. Delarue, A. Nicolaï, F. Neiers, H.A. Scheraga, G.G. Maisuradze, P. Senet, J. Phys. Chem. B 124: 4391-4398 (2020)
[4] 'It will change everything': DeepMind's AI makes gigantic leap in solving protein structures, E. Callaway, Nature 588:203-204 (2020); Improved protein structure prediction using potentials from deep learning, Senior, A. W. et al. Nature 577, 706–710 (2020); Highly accurate protein structure prediction with AlphaFold, J. Jumer et al., Nature 596: 583-589 (2021)
[5] Protein folding from a graph perspective, S. Tyler, UBFC (2021)
[6] Protein d conformational dynamics from graph theory, R. Guo, UBFC (2022)
[7] Adrien Guzzo, PhD thesis, UBFC (2022)

Type of project: Theory/Numerical simulations/Collaboration with experimentalists
Required skills: Mathematics/ Molecular Dynamics /Programming