

Exploring Protein Degradation Machines with Molecular Dynamics Simulations

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E3 ubiquitin ligases are large molecular machines that control protein degradation in human cells. By bringing a target protein close to the ubiquitin-transfer machinery, they determine which proteins are labelled for destruction by the proteasome. Their function depends not only on their composition, but also on transient conformations that cannot be fully captured by static structural biology methods.

This internship is part of the hE3-DC project (Dynamics and Control of human E3 ubiquitin ligases), which combines integrative structural modelling, molecular simulations, AI-assisted protein design and experimental validation. The project focuses on the human CRL4-DCAF1 Cullin-RING E3 ligase, a large protein complex exploited by HIV accessory proteins Vpr and Vpx to redirect protein degradation. The M2 student will use coarse-grained molecular dynamics simulations with the Martini 3 force field to investigate the conformational dynamics of CRL4-DCAF1. Starting from available structural models, they will construct simulations of selected functional states and analyse the flexibility of the complex, including transitions between open, closed and intermediate conformations. The main objective will be to determine how these large-scale motions influence the geometry between the ligase, recruited substrates and ubiquitin-transfer machinery, and thus favour or prevent productive ubiquitination.

The student will analyse trajectories using domain distances, contact maps, interface fingerprints and conformational clustering, and compare the results with available atomistic simulations and structural data. Depending on progress, the project may be extended towards multi-state coarse-grained models or simulations of CRL4-DCAF1 in complex with protein degraders. The internship will provide training in molecular modelling, Martini 3 coarse-grained simulations, high-performance computing, trajectory analysis and structural bioinformatics. The student will work with Paulo C. T. Souza and Luis Borges-Araujo at CBPsmn and LBMC, within the DAMM team, in close interaction with researchers in structural modelling, protein design and cell biology.

The candidate should have an interest in computational biophysics, structural biology, biomolecular modelling or bioinformatics. Previous experience with molecular simulations, programming or Linux is welcome but not required.

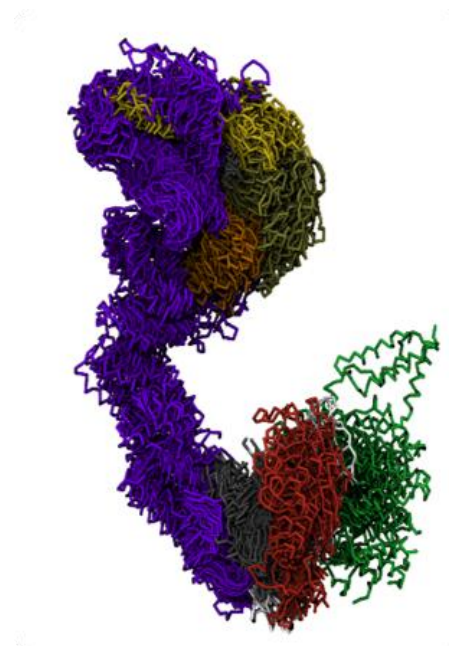


Figure: MD simulations of E3 Ligase.