הטכניון - מכון טכנולוגי לישראל

TECHNION - ISRAEL INSTITUTE OF TECHNOLOGY

הפקולטה להנדסה כימית
ע"ש וולפסון
The Wolfson Department of Chemical Engineering

Wolfson Department of Chemical Engineering Seminar

Wednesday, April 15th, 2026 at 13:30

Zoom: https://technion.zoom.us/j/92278627599

Collective Variable-Guided Engineering of the Free-Energy Surface of a Small Peptide

Muralika Medaparambath

MSc Seminar

Advisor: Prof. Dan Mendels
Department of Chemical Engineering, Technion-Israel Institute for Technology

Engineering the free-energy surfaces (FES) of proteins and peptides is central to controlling conformational ensembles and their responses to perturbations. However, predicting how chemical modifications such as point mutations reshape the FES and shift conformational equilibria remains challenging, particularly in data-scarce settings. Building on the Collective Variables for Free Energy Surface Tailoring (CV-FEST) framework, we develop a computational approach that leverages short, unbiased molecular dynamics trajectories to guide mutation analysis. Using the ten-residue β - hairpin CLN025 and a systematic library of its single-point mutants, we apply Harmonic Linear Discriminant Analysis (HLDA) to extract collective variables from the conformational data. We find that the HLDA eigenvector learned solely from short wild-type trajectories provides residue-level insight into the propensity of mutations at specific positions to thermodynamically stabilize or destabilize the folded state. Extending this analysis, we show that shifts in the leading HLDA eigenvalue across mutants, a measure of changes in separability between the conformational ensembles along the HLDA coordinate, correlate strongly with mutation-induced changes in the free-energy difference between states, as reflected in melting temperatures. Benchmarked against Replica Exchange Molecular Dynamics simulations, these findings suggest a promising and computationally affordable route toward guiding the engineering of biomolecular free-energy landscapes.