P-1.18

Analysis and Design of Protein Fold Switches Using Physics and Machine Learning Based Methods

Lisa Schmidt [1], Bert L. De Groot [1]

[1] Max Planck Institute for Multidisciplinary Sciences, Goettingen, Germany

Protein fold-switches are proteins that adopt multiple stable structural states encoded within a single sequence. They play crucial roles in various biological processes and exhibit remarkable structural diversity, making them ideal targets for protein design efforts aimed at creating programmable proteins with novel functions. Despite significant advances in protein design in recent years, the de novo design of fold-switching proteins remains a challenging task. To investigate fold-switching behavior, we integrate dynamical, structural, and sequence-level analyses of known switches, and employ molecular dynamics simulations and free energy calculations (GROMACS, pmx) alongside established machine learning tools (e.g. AF3, Foldseek). This approach enables us to identify residues and interactions that are critical for switching. Furthermore, we apply our analysis to introduce additional layers of control into existing switches, such as the dopamine receptor (protein domain switch). Finally, we have designed a new fold switch based on ubiquitin that transitions between the ubiquitin fold and a barrel-like conformation. This UBI switch (Ubiquitin–Barrel switch I) may modulate the non-covalent binding of ubiquitin-interacting proteins and thus provide a means to influence the ubiquitin pathway.