Probing protein remodeling mechanisms of AAA+ motors using molecular dynamics simulations and machine learning approaches

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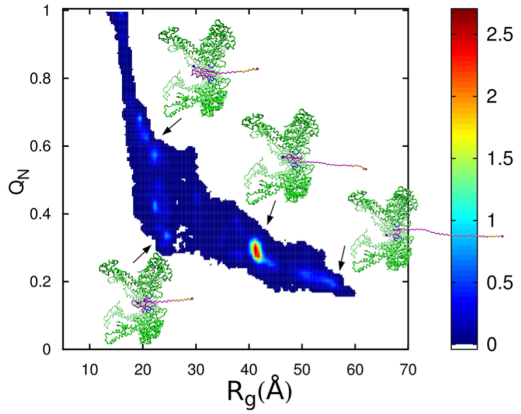

Fig 8. Unfolding and translocation by mechanical pulling with a constant force through a non-allosteric ClpY pore. Probability density map of the fraction of native contacts and radius of gyration for simulations of mechanical pulling through a non-allosteric pore with constant force $F = 125$ pN.

AAA+ nanomachines, such as the hexameric ring-shaped Clp (Caseinolytic protease) ATPases or the 26S eukaryotic proteasome, assist protein degradation and disaggregation by unfolding and translocating substrate proteins through a narrow central channel. Repetitive mechanical forces mediating these actions are affected through flexible pore loops of the ATPase protruding into the channel. All-atom, solvated, simulations of the ClpB disaggregase reveal that requisite dynamic pore stability and flexibility involve a complex interplay between networks of inter- and intraprotomer interactions. Analysis of allosteric pathways, using graph theory approaches, reveals that mutations abolishing ATP hydrolysis weakly affect communication between the nucleotide binding site with pore loop 1, but strongly affect those with pore loops 2 and 3, in accord with results of smFRET experiments. Machine learning approaches identify structural features and their relative importance for characterizing the conformational space of ClpB..