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"*Discovering rough mountain peaks in the dark by using Transition Path Sampling Elucidating the mechanism and role of solvent for β -lactoglobulin dimerization*"

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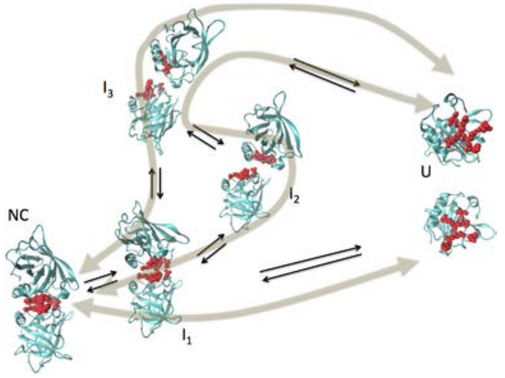
Αίθουσα «Νίκος Κουμούτσος» Σχολής Χημικών Μηχανικών

Abstract

We present a novel Transition Path Sampling shooting algorithm [1], denoted "spring shooting" for efficient sampling of complex (biomolecular) activated processes with asymmetric free energy barriers. The method employs a fictitious potential that biases the shooting point toward the transition state. The method is similar in spirit to the aimless shooting technique by Peters and Trout [2], but is targeted for use with the oneway shooting approach, which have been shown to be more effective than two way shooting algorithms in systems dominated by diffusive dynamics. We illustrate the method on a 2D Langevin toy model, the association of two peptides and the initial step in dissociation of a β -lactoglobulin dimer. In all cases we show a significant increase in efficiency.

Many proteins associate to their native complex structure with a rate much slower than the Smoluchowski diffusion rate, while much faster than the rate of a random binding. This implicitly signifies the presence of non-specific encounter complexes that relax towards the native dimer state [3]. By using spring shooting TPS, we resolve the mechanism and the transition state ensemble for the dimerization of β-lactoglobulin. The association process is found to occur via (at least) three distinct mechanisms: 1) a one step aligned association to the native dimer state, 2) a two step misaligned association at non native sites followed by hop towards the native state and 3) a two step misaligned association followed by sliding of the protein towards the native state. We find that the native dimer state is stabilized by salt bridging interactions and hydrogen bond bridging waters. Interestingly, water at the native interface can be found in two dynamical hydration states, a glassy one and a tetrahedral one [4]. The crevice introduced upon binding increases the glassy populations as well as increases the average tetrahedrality of water, mainly at the vicinity of hydrophobic residues.



[1] Z. F. Brotzakis and P. G. Bolhuis, J. Chem. Phys. 145, 164112 (2016)

[2] B. Peters and B. L. Trout, J. Chem. Phys. 125, 054108 (2006)

[3] S. H. Northrup and H. P. Erickson, Proc. Nat. Acad. Sci. USA 89, 3338 (1992)

[4] Z.F. Brotzakis, I.K Voets, P. G. Bolhuis, in preparation.