Delineating protein-protein curvilinear dissociation pathways and energetics with multi-walker umbrella sampling molecular dynamics simulations

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Proteins-protein interactions are crucial to various cellular functions, such as immune response, signal transduction, transcription and translation, etc. Characterization of such interactions is important for objectives such as designing of next generation protein drugs, developing new protein interactions in protein engineering, and many more. The protein-protein interactions energetics can be obtained by calculating the potential of mean force (PMF) from the umbrella sampling simulations, in which samplings are often enhanced along a predefined vector as the reaction coordinate. However, any slight change in the vector significantly vary the calculated PMF, and therefore the energetics using a random choice of vector would very likely mislead. Here we adopt a non-predefined curve path-based sampling enhancement approach, which is a natural alternative to the aforementioned approach, but was relatively less explored for protein-protein systems. A simple variational principle is applied and the lower-bound PMF was used to derive the standard free energy of binding. Two major dissociation pathways, which includes interactions with the RNA-binding loop and the Val 36 to Gly 40 loop, are observed. Furthermore, we showed that the proposed approach can be used to discriminate the decoys from protein-protein docking studies.