Chemistry Central Journal

Oral presentation

How do proteins associate? A lesson from SH3 domain

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from 4th German Conference on Chemoinformatics
Goslar, Germany. 9–11 November 2008

Published: 5 June 2009

Chemistry Central Journal 2009, **3**(Suppl 1):O22 doi:10.1186/1752-153X-3-S1-O22

This abstract is available from: http://www.journal.chemistrycentral.com/content/3/S1/O22

Protein-protein association is a fundamental event that plays a central role in the regulation of biological processes and in the development of many diseases. Previous experimental and computational studies have provided information about the diffusion phase and the nature of the intermediate complexes. However, the complete mechanism of the binding process especially the transformation from the intermediate complexes to the stereospecific complex, where the desolvation takes place, is still limited by the time scale of this process. Here, the need of a molecular modeling method, that can access the time scale of this process with real dynamics on atomistic scale, is essential to understand the mechanism of protein binding and the driving forces for the binding.

In a recent work [1], we used extensive atomistic molecular dynamics simulations with explicit solvent to study the binding of an SH3 domain with its binding partner as a general example for protein binding mediated by modular protein domains. The simulations showed the three phases of binding from diffusion through the intermediate encounter complexes and could recover the known the crystal structure of the complex. The simulations showed a dual mechanism of binding where the long range electrostatic interactions play an essential role in accelerating and guiding the diffusion phase that finishes with the formation of intermediate encounter complexes of electrostatic nature stabilized by salt bridges. In the last steps of binding, the hydrophobic dewetting that results from the hydrophobic nature of the interfaces, mediates the desolvation of the interfaces to form vapor-like layers around the interfaces. This decrease in the interfacial water density acts as a driving force for the collapse of the interfaces and reaching the stereospecific complex.

References

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