Multiple mechanisms of protein-protein interaction

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Protein-protein interaction is a fundamental event 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 processes especially the last steps are still unclear. To get the atomistic picture of these steps, we have used real-time molecular dynamic simulation with explicit solvent representation to study the complete binding process of two main classes of protein complexes:

1. The case of hydrophobic interfaces and the role of hydrophobic dewetting.
2. The case of hydrophilic interfaces and water mediation of the interaction.

As an example for the complexes with a hydrophobic interface, we have studied the binding of an SH3 domain with its binding partner [1]. The simulations showed the three phases of binding from diffusion through the intermediate encounter complexes and recovered the known crystal structure of the complex. The analysis of 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 plays a driving force role in the collapse of the interfaces and reaching the specific complex.

In a following study, we have studied the mechanism of protein binding in the case of completely hydrophilic interfaces. For this, we have studied the binding process between Barnase and Barstar. The MD simulations have reproduced the crystal structure of the complex on a time scale of hundreds of nanoseconds. The simulations showed that the structured water in the interfacial gap forms an adhesive hydrogen bond network between the interfaces. This network already plays an important role during the diffusive phase in reducing the dielectric shielding properties of the water and stabilizes early intermediate states before native contacts are formed. The transformation from these intermediates to the stereo-specific complex is then accompanied by maximization of the interfacial water-mediation.

[1] Ahmad, M., W. Gu, and V. Helms, *Angew. Chem. Int. Ed.,* **2008**. 47(40): p. 7626-30.