Biomolecular association on funneled free energy landscapes

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Protein-protein interactions are key components of most biological processes. On the one hand, about half of all cellular proteins appear to be parts of large stable protein complexes. On the other hand, transient, pairwise protein-proteins interactions are crucial parts of bioenergetic and signal transduction pathways. Complementary electrostatic interactions often accelerate the association processes by several orders of magnitude so that they are amenable to Brownian and molecular dynamics (MD) simulations.

First, we have studied the association free energy landscape for the barnase:barstar complex by Brownian Dynamics simulations [1]. We will use this system to introduce the concept of diffusional protein-protein association on conformational energy landscapes.

Secondly, unbiased MD simulations were used to study the binding process of a proline-rich peptide to an SH3 domain [2]. In this case, stable complexes were formed within 20 - 130 ns of simulation. Association was governed by long-range electrostatic effects and by partial dewetting at contact distances.

Finally, atomistic MD simulations reproducibly recovered the native bound state of the Barnase:Barstar complex [3]. The water in the interfacial gap forms an adhesive hydrogen-bond network between the interfaces stabilizing early intermediates before native contacts are formed. The interfacial gap solvent showed a reduced dielectric shielding up to distances of few nanometres during the diffusive phase. The interfacial gap solvent generates an anisotropic dielectric shielding with a strongly preferred directionality for the electrostatic interactions along the association direction.

References

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