Modeling the Role of Electrostatics in Macromolecular Recognition

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Electrostatic forces, being long-range forces, are one of the most prominent forces guiding macromolecular recognition. At distance between the partners larger than several angstroms, all other forces are negligible, and electrostatics guides the partners toward their specific orientations and eventually toward their physical binding. However, during the process of association, the electrostatic forces role may change due to complexity of the environment, inhomogeneous charge distribution of interacting partners and conformational changes. Here we investigate the role of electrostatics in three different scenarios: (a) large receptor with intrinsically disordered regions interacting with a protein; (b) set of protein-protein complexes, and (c) a ligand approaching a receptor. We demonstrate that electrostatic interactions are coupled with conformational changes and provide smooth transition from unbound conformational ensemble to bound. Furthermore, we focus on the evolution of the force magnitude and direction as the ligand approaches the receptor. Carrying such an analysis on a large set of protein-protein complexes, we identify four types of force-distance profiles. Particular attention is paid on the cases involving so termed "soft-landing", where electrostatic force attracts the ligand at large distances but opposes binding at short distances, and thus slows down the ligand approach toward the receptor (soft landing). Furthermore, the carry DelPhiForce steered molecular dynamics simulations to reveal the pathway of a ligand approaching the binding site of a particular receptor. It is demonstrated that DelPhiForce provides crucial guidance of the ligand as it approaches the receptor and allows for fast and effective binding.

Bell Hall 143
Friday, October 4, 2019, 10:30 AM