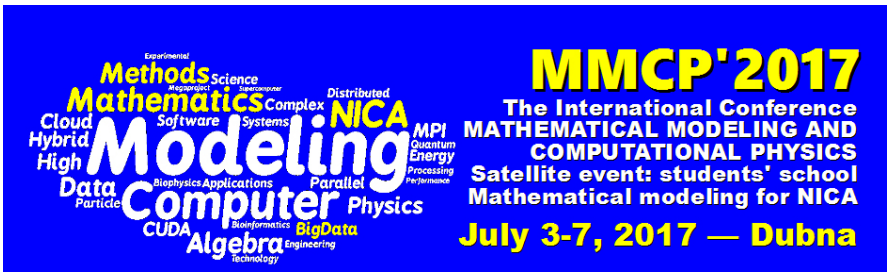

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Density Based Clustering of Brownian Dynamics Trajectories Reveals Predominant Energetically Favorable Orientations in Protein-Protein Interactions

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Protein-protein interactions are of central importance for virtually every process in living matter. Simulation of protein association dynamics is crucial for understanding their functionality. In Brownian dynamics proteins are considered as rigid bodies subjected to electrostatic and random Brownian forces. This rough approximation is rather accurate when protein surfaces do not touch each other, and in combination with molecular dynamics used to simulate close contact of molecules this simulation technique provides complete reconstruction of protein-protein interaction over large temporal and spatial scales.

Brownian dynamics is not so computationally expensive as molecular dynamics, thus allowing exhaustive sampling of relative orientations of protein molecules approaching each other in a virtual reaction space. Long-range electrostatics is the major factor effecting molecule orientation on encounter. To gain some understanding of the role of electrostatic interactions at successive stages of protein-protein complex formation we need to detect and somehow describe intermediate metastable states on the association pathway. To do so we sample frames if electrostatic attraction energy between proteins is above some predefined threshold and analyze similarity of sampled structures in terms of root-mean-square deviation (RMSD) of their atomic positions in aligned to each other structures. Density based clustering technique [Khruschev et al., 2015] allows to find if all sampled structures constitute a single group, or they can be classified into several distinct clusters, and obtain characteristics of such groups (clusters).

We performed a comparative study of diffusional encounter of photosynthetic electron transport proteins cytochrome f and plastocyanin from two species of cyanobacteria (Phormidium and Nostoc) and higher plants. Cytochrome f is an exposed to thylakoid lumen subunit of a large transmembrane cytochrome b6f complex, its redox center is a type C heme. Plastocyanin is a copper-containing mobile carrier performing shuttle electron transfer from cytochrome f to photosystem I. Spatial structures of these proteins are similar, but the amino acid sequences significantly vary. Thus electrostatic properties of the binding sites in all three protein pairs are rather different.

For cyanobacterial proteins formation of structures with electrostatic attraction energy of 4kT or greater is a very rare event (k_on is less than 10^7 M-1 s-1). Several electrostatically favorable binding modes were identified by density based clustering for these species. However, Phormidium plastocyanin always approaches cytochrome f far from its redox center (heme), thus electron transport is very unlikely in these orientations. So we can suppose that electrostatic interactions should not play any significant role in formation of Phormidium plastocyanin-cytochrome f functionally active complex. This can be confirmed by the fact that experimentally obtained reaction rate for these proteins does not depend on solution ionic strength. Salt ions screen protein charges thus addition of salt weakens electrostatic interactions between proteins whereas for Phormidium proteins it does not change the reaction rate.

On the contrary, Nostoc plastocyanin in most cases binds directly to the heme location in two predominant orientations (43% and 40% of all sampled structures). Copper atom is turned toward cytochrome f in all these structures, thus we conclude that electrostatic interactions facilitate the formation of final complex capable of electron transport. Indeed, in experiments we can see strong dependence of electron transfer rate from the ionic strength.

In higher plants, formation of structures with attraction energy of 4kT or greater is much more frequent (k_on is above 10^9 M-1 s-1). The structures constitute one uniformly dense group, in which plastocyanin is located nearby heme of cytochrome f, but its copper atom is turned from the contact area. However, plastocyanin retains noticeable rotational freedom around its center of mass. We sampled protein orientations with even higher energy threshold of 8kT, and k_on still remained rather high (more than 10^7 M-1 s-1), but two distinct groups of plastocyanin orientations were detected. In 57% of structures a flexible single-point joint is formed by oppositely charged areas of two proteins, thus allowing thermal motion to rotate plastocyanin molecule into electron-transfer-capable orientation without breaking electrostatic link. In remaining structures binding of plastocyanin is much more tight, and its orientation suppresses electron transfer. We suppose that in higher plants the process of final complex formation involves at least two stages: the first is diffusive entrapment of plastocyanin by cytochrome f, and the second is orientation adjustment in the transient complex.

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References

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