Towards Molecular Systems Biology: Dynamic Simulations of Multiprotein Systems

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Abstract

Recent experimental work has highlighted the importance of protein-protein complexes for functioning of biological cells. This concept poses a significant challenge in terms of system size to the field of biomolecular simulations where usually atomic representations are used. In our research group we are developing more efficient residue-scale or even protein-scale representations of particles to allow for coarse-grained dynamics simulations of multi-protein systems over long simulation time scales.

Besides methodological aspects when dealing with multi-protein systems, in contrast to working with single proteins there also exists a big shortage of useful experimental data on association kinetics, thermodynamics, and structural data on complexes. Often, only one of the parameters may be available for particular systems of interest. We have therefore focused our work on the well-established photosynthetic unit and the respiratory chain. In these processes, photochemical and proton-translocation reactions are catalyzed by large, integral membrane proteins. Fortunately, the three-dimensional structures of almost all those membrane proteins could be determined over the past decade, association data is available from kinetic measurements and site-directed mutagenesis, and, at least for the photosynthetic unit, also the three-dimensional arrangement of the proteins inside the membrane is known.

In both systems, the globular water-soluble protein cytochrome *c* functions as electron carrier between two integral membrane proteins. We have modeled the association of cytochrome *c* and membrane-embedded cytochrome *c* oxidase by brownian dynamics simulations in atomic detail (Floeck & Helms) using the SDA package of Gabdoulline & Wade. By investigating two different cytochrome *c* species, we established that the presence of the lipid-bilayer has a very distinct effect on the pre-orientation of the diffusing particles depending on its net charge and dipolar character.

In a separate study we have investigated the association of cytochrome *c* solutions to oppositely charged membranes by browian dynamics simulations. Here, the diffusing particles were modeled as charged spheres with embedded dipoles. These simulations are performed with our new package CESIP (cellular simulation package). In good agreement with experimental data, the simulations reproduce effects of ionic strength and protein concentration of the solution.

In future work we will interface both approaches enabling dynamic simulations of subcellular systems at molecular resolution or “molecular systems biology”