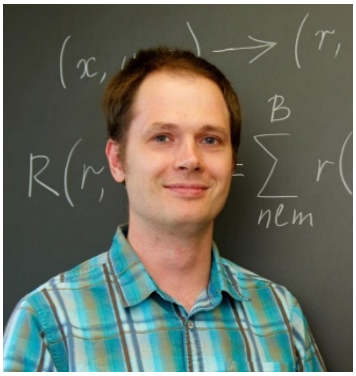
Genome Informatics Seminar

Modeling of macromolecular interactions using Fast Fourier Transforms on the rotational manifolds



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Abstract:

The proteomics revolution provided the blueprint for the networks of molecular interactions in the cell, however full understanding of how molecules interact comes only from three-dimensional structures. Despite recent progress in structure determination of individual proteins using X-ray or NMR, structures of complexes remains difficult to obtain. Additionally, modulating protein interactions for therapeutic purposes has become one of the modern frontiers of biomedical research. Thus, modeling of protein interactions has important motivations. My talk consists of three parts. First, I will describe the development of a fast protein-protein docking method, based on a simplified but accurate and exactly solvable statistical physics model, using the Fast Fourier Transform on rotational manifolds (FMFT). I will demonstrate that the model is accurate enough not just to model the structure of the complex, but also provides insight in protein-protein association, and reveals that the protein interaction energy landscape resembles a canyon-like terrain where the low energy areas lie in a lower dimensional subspace. The second part of the talk will focus on generalizing the approach to flexible global protein peptide and ligand interactions. I will describe successful validation of FMFT based approaches in blind protein-protein and protein-ligand docking community experiments CAPRI and D3R. In the third part I will focus on understanding the key principles of disrupting protein-protein interactions using small molecules, macrocycles or other compounds. This will be done by introducing the concept of hot spots of protein-protein interactions, i.e., regions of surface that disproportionally contribute to binding free energy. Hotspots will be determined by modeling the interaction of proteins with a number of small molecules used as probes. The method is a direct computational analogue of experimental techniques, and it also uses the FFT based sampling approach similar to the one described above. I will demonstrate that the hot spots provide information on the "druggability" of protein-protein interactions, i.e., on the ability to bind drug-like small molecules, in good agreement with available data.

Date & Time
10th December
14:00-16:00

Venue
BIKEN Hall

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