Hong Kong University of Science and Technology
Division of Biomedical Engineering

PhD Thesis Presentation
Bioengineering Graduate Program (BIEN)

Development and Application of Advanced Modelling Algorithms towards a Molecular Understanding of the Aggregation of an Intrinsically Disordered Peptide

by

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Abstract
In this thesis, we use molecular dynamic (MD) simulations to study the conformational dynamics of an intrinsically disordered protein, human islet amyloid polypeptide (hIAPP). Meanwhile, a new algorithm is proposed to help molecular dynamic simulations to gain efficiency in sampling. MD has been emerging as a standard tool in studying the structures and dynamics of large biomolecules at atomistic level. However, it has some drawbacks: the time scales for all-atom MD to reach are still limited to sub-milliseconds and it is easy for straight-forward simulations to be trapped in local energy minima. These limitations make it hard for simulations to study important biological processes as well as exhaustive exploration of the overall configuration space.

To help MD reach longer time scales, Markov state model (MSM) is proposed to build up a Markov chain network model based on short simulations starting from different places in configuration spaces and to propagate the model for long-time dynamics. To help MD sample broader space, different methods have been proposed to help the simulations escape the local minima. However, few of them is targeted at the time spent in exploring the configuration space. We propose a new algorithm to find the optimal weights which minimize the round-trip time of a pair of states in one temperature-based enhancing sampling method. The efficiency improved can be at least 1-2 times for several systems tested.

As one application of MSM, one intrinsically disordered peptide involved in type II diabetes was studied. The model revealed that there are multiple metastable states with similar population. Furthermore, the transitions between different metastable states are surprisingly slow, ranging from hundreds of nanoseconds to hundreds of microseconds. We proposed some small states with $\beta$-hairpin structures and exposed hydrophobic surface area may be a precursor for fibril formation. To test this hypothesis, we performed dimer simulation and found that one major state with cross-$\beta$ structure and the initial contacts to form this structure are mainly formed by hydrophobic residues.

Date : 26 Nov 2014 (Wednesday)
Time : 3:00pm
Venue : Room 5560 (Lift 27-28)

All are welcome!

Examination Committee:
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