Tsinghua-*Science* Workshops

Computational Structural Biology

Session 9: Computational Structural Biology – Protein Dynamics

Friday, August 20th, 2021 9-11 am (GMT +08:00, Beijing)

09:00 am-09:45 am

Nagarajan Vaidehi, Beckman Research Institute of the City of Hope, USA

Spatiotemporal Determinants and Allosteric Communication Modulate the Ligand Bias in GPCRs

09:45 am-10:00 am Q&A

10:00 am-10:45 am

Haipeng Gong, Tsinghua University, China

Protein structural prediction and conformational sampling

10:45 am-11:00 am Q&A

Host

Prof. Xueming Li

Xueming Li received his Ph.D in condensed matter physics from Institute of Physics at the Chinese Academy of Sciences in 2009. Then, he joined the laboratory of Yifan Cheng at University of California San Francisco as a postdoctoral scholar, and changed his research direction to electron cryo-microscopy (cryoEM) in structural biology. Xueming Li joined Tsinghua University since 2014. He is currently associate professor of the School of Life Science, and principal investigator of Beijing Advanced Innovation Center for Structural Biology and Tsinghua-Peking Joint Center for Life Sciences.

Xueming Li has been engaged in the research of electron cryo-microscopy (cryoEM) methods and techniques, as well as the applications of cryoEM in structural biology, for more than ten years. He

had made remarkable contributions in the development of electron counting detector and beam-induced motion correction algorithm, which promoted the "Resolution Revolution" of cryoEM. In recent years, Xueming Li aimed to develop high-efficient and high-resolution cryoEM technologies, and introduced new algorithms from other fields into cryoEM, such as deep learning in artificial intelligence and particle filter in electronic engineering. Xueming Li also worked on microcrystalline electron diffraction (MicroED) and greatly enhanced the applicability of this technology. His efforts provide new ideas for the development of image processing technology in cryoEM.

Currently Xueming Li's researches are focusing on the methodological and technological development of electron cryo-tomography (cryoET) with a goal to obtaining in situ structures of cellular organelle and biological macromolecules at 1 nm or even atomic resolution, and exploring the possibility of medical application of cryoET technology.

Speakers

Prof. Nagarajan Vaidehi

Nagarajan Vaidehi, Ph.D., is professor and chair of the Department of Computational and Quantitative Medicine (DCQM)at the Beckman Research Institute of the City of Hope in Los Angeles, CA. She is also the Associate Director of the City of Hope Comprehensive Cancer Center. Dr. Vaidehi received her Ph.D. in quantum chemistry from the Indian Institute of Technology in India, where she was honored with the Distinguished Alumni Award in 2016.Following her postdoctoral studies on protein dynamics simulation methods at University of Southern California, and at Caltech, she became the director of biomolecular simulations at the Materials and Process Simulation Center, Beckman Institute at Caltech. Dr. Vaidehi joined City of Hope in 2006 as a Professor and became chair of DCQM in 2018. She has advanced the use of computational methods to meet the challenges of designing therapeutics with lower off target effects. She is an internationally recognized biophysicist for her contributions in developing constrained molecular dynamics simulation methods with emphasis on application to G-protein coupled receptors and drug design.

Spatiotemporal Determinants and Allosteric Communication Modulate the Ligand Bias in GPCRs

The G-protein coupled receptor (GPCR) interaction with the G protein or β-arrestin are inherently often transient and dynamic. However, these interactions exhibit exquisite level of selectivity in some cases or promiscuity in other cases, in coupling to one or multiple partner proteins upon a cell signaling event. Using multi-scale molecular dynamics simulations in combination with FRET experiments and cell based assays we have shown that the spatio-temporal components play a critical role in explaining the selective coupling of GPCRs towards G proteins and β-arrestins. The MD simulations show that reshaping of GPCR-G protein coupling interface explains the promiscuous coupling of some GPCRs to multiple G proteins. Allosteric communication in signaling proteins play an important role in transducing signal across cell membranes. Delineating the amino acid residues involved in this communication would allow us to design ligands that are specific or “biased” to a given signaling pathway. Such “biased ligands” are therapeutically desirable and would enable design of drugs with minimal side effects.

Dr. Haipeng Gong

Dr. Gong received his bachelor’s and master’s degrees in Biophysics in 1997 and 2000, respectively, from Tsinghua University. He obtained his doctor’s degree at Johns Hopkins University in 2007, trained in Prof. George Rose’s lab. Then he joined Prof. Tobin Sosnick’s lab at University of Chicago for postdoctoral training. In 2009, he joined the School of Life Science at Tsinghua University as a principal investigator. His lab focuses on computational study and method development related with protein structures, mainly including the protein structural prediction as well as the protein conformational sampling by simulations.

Protein structural prediction and conformational sampling

Protein structural prediction, predicting the three-dimensional structures of proteins from their amino acid sequences, has experienced rapid progresses, particularly exemplified by AlphaFold2 from DeepMind, which improves the prediction accuracy to an astonishingly high level using artificial intelligence techniques. Here, I will introduce two models we have developed in the past years to improve the prediction of inter-residue contacts and distances, which can be applied as additional constraints to fold the protein structure. Unlike most traditional methods, our models AmoebaContact and GANProDist were constructed using novel ideas including the automatic neural architecture search and adversarial training, respectively, and thus may provide new insights in the further development and refinement of deep-learning-based models for protein structural prediction.

Instead of taking a static structure as provided by most structural prediction and determination methods, proteins frequently experience conformational transition in order to accomplish their biological functions. Here, I will introduce two methods we developed recently to sample such conformational transitions through molecular dynamics simulations. The first method (FEXS) can rapidly expand the conformational sampling space of a protein from one known starting structure by iteratively identifying “frontier” seed structures to restart new trajectories. The second method (unpublished) can quickly produce a kinetically accessible transition path that connects two known conformational states, and the identified path could then be iteratively refined to allow reasonable free energy estimation for the structural transition process.