NUS National University of Singapore | Department of Biological Sciences, Faculty of Science

ON-SITE BIOLOGY COLLOQUIUM

Friday, 22 Sept 2023 | 4 pm | LT32

Hosted by Assoc. Prof Lu Gan

Map to Block S1A

Solving the puzzle of large macromolecular assemblies using an integrative approach

By **Shruthi Viswanath**

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Integrative structure determination is a method of determining structures of large macromolecular assemblies by combining data from complementary experimental methods with physical principles, statistical inference, and prior models. It is particularly useful for assemblies which are recalcitrant to direct observation by experiments such as cryo-electron microscopy and X-ray crystallography.

One recent example from our group is the characterization of the desmosomal outer dense plaque (ODP). Desmosomes are large, 300 nm-long protein assemblies that connect the cytoskeleton of adjacent cells and mediate cell-cell adhesion, and play a crucial role in maintaining tissue integrity. We used an integrative approach combining cryo-electron tomography, X-ray crystallography, NMR, immuno-EM, and biochemical studies along with physics principles and statistical inference for determining the molecular architecture of the ODP. Current structural studies posit Plakophilin as a filler protein; in contrast, our model shows that its N-terminal disordered region forms interactions with several ODP proteins, highlighting its key role in the assembly of the ODP. We predict novel protein-protein interfaces as well as rationalize several missense mutations in skin diseases based on our model.

In the second part, we will discuss methods developed by our group; specifically, how we can combine deep learning methods to improve structure prediction of large assemblies in the era of Alphafold.

About the Speaker

Shruthi is from Bangalore India and trained as a computer science engineer during her Bachelors degree at the National Institute of Technology Surathkal. She completed her PhD developing methods for protein-protein docking in the lab of Prof Ron Elber at the University of Texas at Austin. Subsequently she joined the lab of Prof Andrej Sali as a postdoc, developing and applying methods for integrative structural characterization of large macromolecular assemblies, in close collaboration with cell and structural biologists. She continues to work in the field of integrative stucture determination in her own lab at NCBS since late 2019. She is a member of and active contributor to the wwPDB validation group for archiving integrative structures.