Integrative approaches for modelling enzyme reaction-modulated assembly of phaseseparated biomolecular condensates

S. Kashif Sadiq*†[1]

[1]Heidelberg Institute for Theoretical Studies – Germany

Abstract

Computational molecular modelling techniques provide a route to integrate existing experimental techniques into a predictive spatiotemporal picture of molecular biology. But important challenges remain to account for the multiple scales involved. Here, I will present several integrative methods that we are developing that aim to bridge these spatiotemporal scales.

I will firstly discuss methods we are developing that couple high-throughput allatom molecular dynamics (MD), Markov state models and Brownian dynamics (BD) simulations to predict the kinetics of conformation-gated slow ligand-binding processes. Furthermore, by combining MD with solution NMR techniques, I will show how we optimally fit spectra and thus identify experimentally validated transitions between relevant conformational ensembles beyond the timescale-reach of MD alone. Focusing on the process of HIV-1 virion maturation and infectivity, I will then discuss how ultra-coarse-grained interaction particle-based reaction diffusion (iPRD) models can be employed to investigate biochemical spatiotemporal reaction networks in the context of crowding, molecular diffusion and macromolecular architecture – guided by experimental data from cryo-EM and super-resolution microscopy techniques.

Finally, I will discuss how we combine modelling methods with AFM and enzymatic assays to probe the condensate behaviour and molecular function of the HIV-1 ribonucleoprotein, an example of a phase-separated membrane-less granule that contains self-assembled RNAprotein mixtures - especially with a view to understanding generally how enzyme reactions in such granules might be modulated and specifically to provide insight into the corresponding biological function in the case of virion maturation.

*Speaker

†Corresponding author: Kashif.Sadiq@h-its.org