TIFR Centre for Interdisciplinary Sciences
21, Brundavan Colony, Narsingi, Hyderabad 500 075

Seminar

Excluded Volumes of disordered linkers modulates the phase behavior of multivalent proteins

Tyler Harmon

Washington University, St. Louis, USA

Micron-sized, non-membrane bound cellular bodies can form as the result of collective interactions between modules of distinct multidomain proteins. Li et al. have examined the phase diagrams that result for polymers of SH3 domains and proline-rich modules (PRMs) while varying the number of interacting domains. It is noteworthy that flexible, intrinsically disordered linkers connect the interacting units within each polymer. Conventional wisdom holds that linkers play a passive role in determining the phase behavior of multidomain proteins that undergo phase separations. Here, we ask if this view is accurate. The motivation for our work comes from recent studies that have uncovered a rich diversity of composition-to-conformation and sequence-to-conformation relationships for intrinsically disordered proteins. The central finding is that disordered regions of proteins have distinct sequence-encoded conformational preferences. Accordingly, we reasoned that the conformational properties of linkers might be a contributing factor, in addition to polyvalency, to the phase behavior of multidomain proteins.

We have developed and deployed a three-dimensional lattice model to arrive at a predictive framework to query the effects of linkers on the phase diagrams of polyvalent systems. We find that the critical concentration for phase transition can be influenced by the conformational properties of linkers. Specifically, our results show that linkers modulate the cooperative binding between domains of polymers that are already bound together. Depending on their conformational properties, linkers can also block access to the binding domains via excluded volume effects. Additionally, we find that the properties of the linkers can lead to controls over the mixing of proteins in these bodies. Specifically, we find that there are large ranges of parameters for three protein systems where the bodies isolate specific proteins to different regions of the bodies instead of uniformly mixing them. This result is validated by recent findings of organization inside some observed bodies.

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4:00 PM (Tea/Coffee at 3:45 PM)

Seminar Hall, TCIS