Abstract:

Compartmentalization at the cellular and sub-cellular levels is essential for biological functions. Organelles bound by lipid membrane, e.g., mitochondria and nuclei, serve this purpose. Compartments can also be non-membrane-bound. These include stress granules, germ granules, nucleoli, and many others. These bodies possess physical properties similar to those of mesoscopic liquid droplets. Referred to collectively as “biomolecular condensates”, their formation is underpinned largely by liquid-liquid phase separation (LLPS) of intrinsically disordered proteins (IDPs), intrinsically disordered regions (IDRs) of proteins, and nucleic acids. Behaviors of biomolecular condensates are fundamentally governed by the information encoded in the sequences of proteins and nucleic acids involved. To gain basic physical understanding of this fascinating phenomenon, we developed analytical theories and coarse-grained explicit-chain simulation models for sequence-specific LLPSs of IDPs/IDRs. Our theoretical predictions rationalize experimental data and elucidate the effects of net charge, sequence charge pattern, π-related aromatic interactions, pH and salt on biomolecular LLPS. Our results point further to a “fuzzy” mode of molecular recognition by charge pattern matching that afford physical insights into how different IDP species may be miscible or demix upon LLPS to achieve desirable compartmentalization and sub-compartmentalization. We have also taken a first step toward rationalizing the temperature and pressure dependence of LLPS by considering empirical and atomic models of solvent-mediated hydrophobic interactions.