Mathematical Biology Seminar

Monday, February 27, 2023

3 pm MST (Virtual)

Join Zoom Meeting

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Meeting ID: 984 9769 5684
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Untangling Small-Molecule Interactions Driving Intracellular Phase Separation

An emerging mechanism for intracellular organization is liquid-liquid phase separation (LLPS). Found in both the nucleus and the cytoplasm, liquidlike droplets condense to create compartments that are thought to localize factors, such as RNAs and proteins, and promote biochemical interactions. Many RNA-binding proteins interact with different RNA species to create droplets necessary for cellular functions, such as polarity and nuclear division. Additionally, the proteins that promote phase separation are frequently coupled to multiple RNA binding domains and several RNAs can interact with a single protein, leading to a large number of potential multivalent interactions.

We present a multiphase, Cahn-Hilliard diffuse interface model to examine the RNA-protein interactions driving LLPS. Using a 'start simple, build up' approach to model construction, we explore how the small-molecule interactions underlying protein-RNA dynamics and RNA species competition control observable, droplet-scale phenomena. Numerical simulations reveal that RNA competition for free protein molecules contributes to intra-droplet patterning and the emergence of a heterogeneous droplet field. More in-depth analysis using layered sensitivity analysis techniques, such as Morris Method screening and Sobol' method, highlights the complicated relationships these small molecules have with each other and with the results we can measure. Further, our approach is also applicable to other phase separated systems; our model predicted that protein annuli associated with amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) were actually part of an intra-droplet shell/core pattern, which was then confirmed experimentally by our biological collaborators.