

GPU Computing for Bionanotechnology

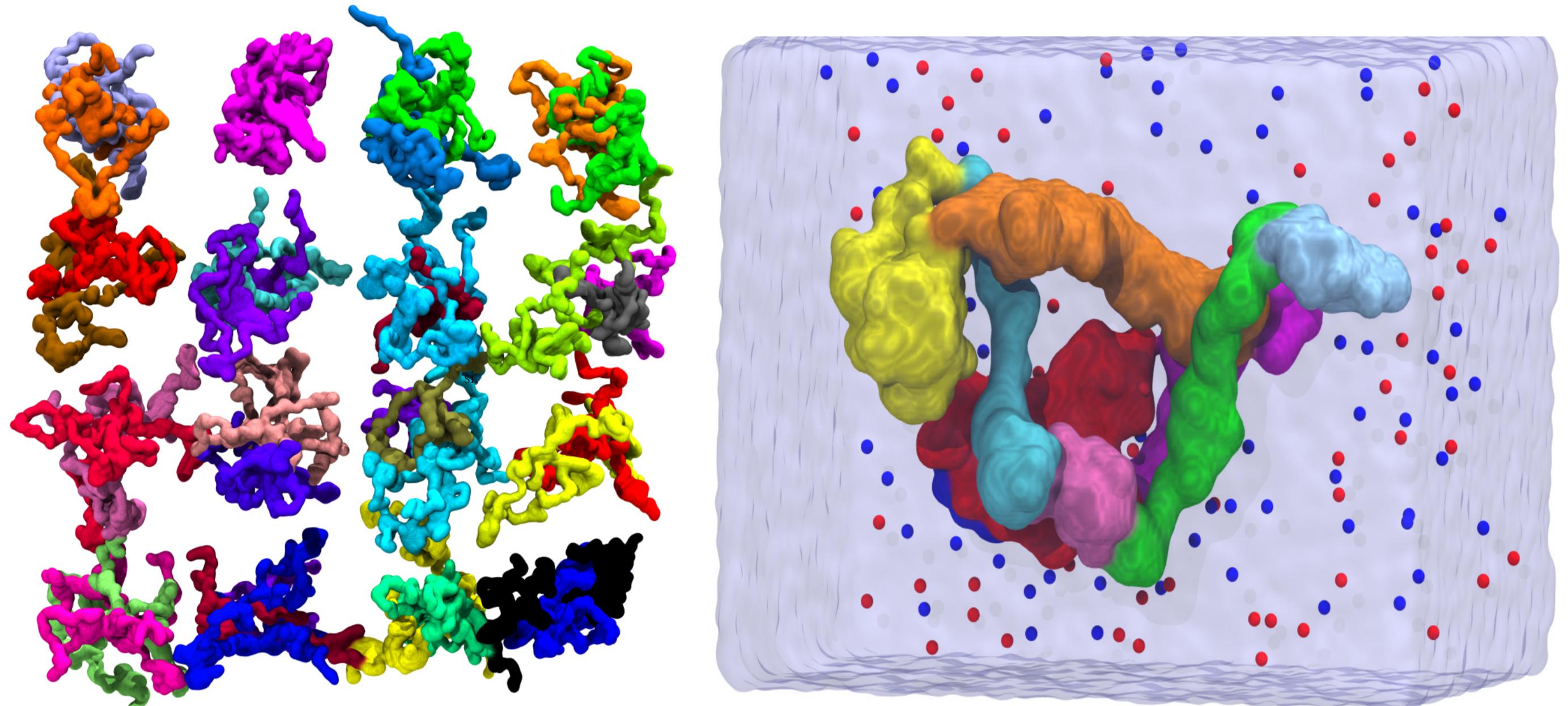
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Introduction

Biomolecular condensates are membraneless organelles found in Eukaryotic cells that are formed by liquid-liquid phase separation (LLPS) and display liquid-like properties. An important constituent of certain condensates is the Fused in Sarcoma (FUS) protein, which is an RNA-binding protein involved in various cellular processes such as DNA repair, RNA transport and damage response. The FUS protein is essential for the condensate to undergo the LLPS process *in vivo* and the FUS protein itself undergoes LLPS *in vitro*.



Aim

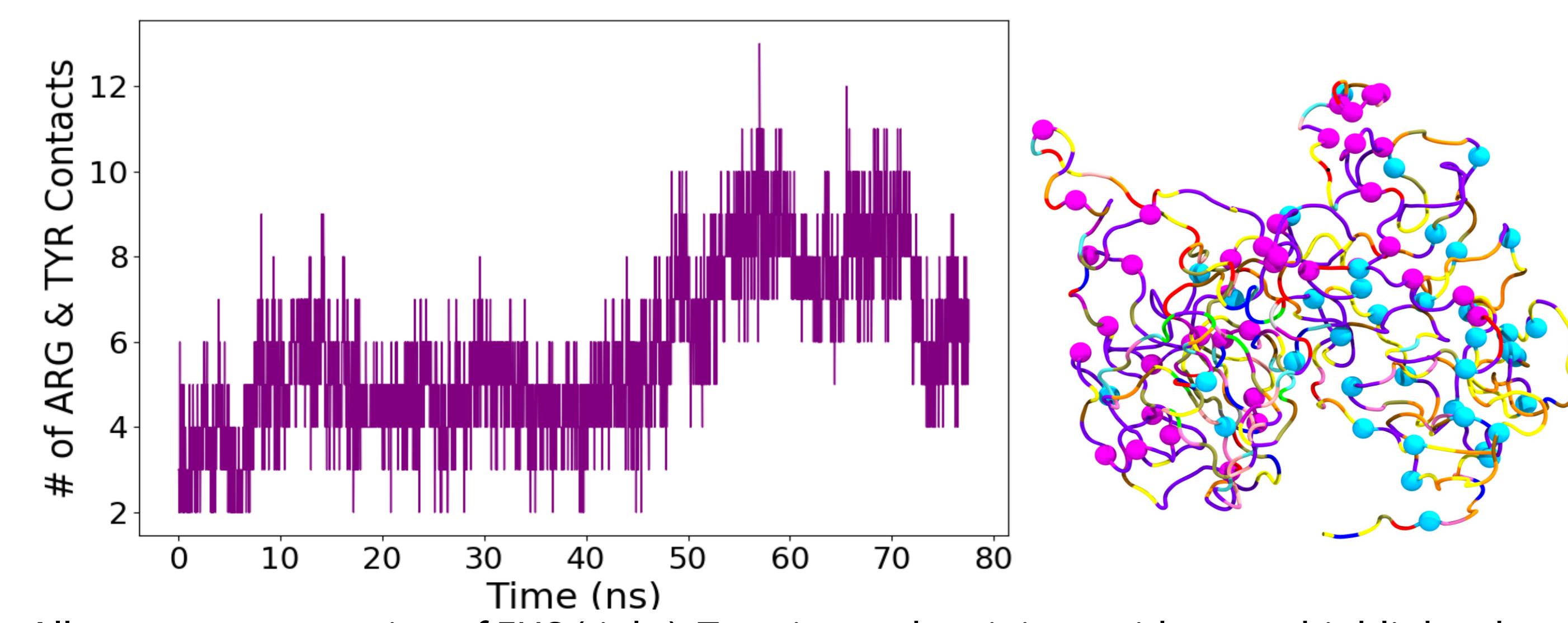
Computationally investigate phase separation in the FUS protein by first studying the phase separation process of wild-type (WT) FUS under temperatures ranging from 295K to 450K in order to understand the temperature dependence of the LLPS process.

Significance

- The properties of biomolecular condensates are involved in the pathology of neurodegenerative diseases such as amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD).
- In particular, mutations in FUS can lead to fibrous aggregates, which are thought to underlie the pathogenesis of both ALS and FTD.

Fused in Sarcoma (FUS)

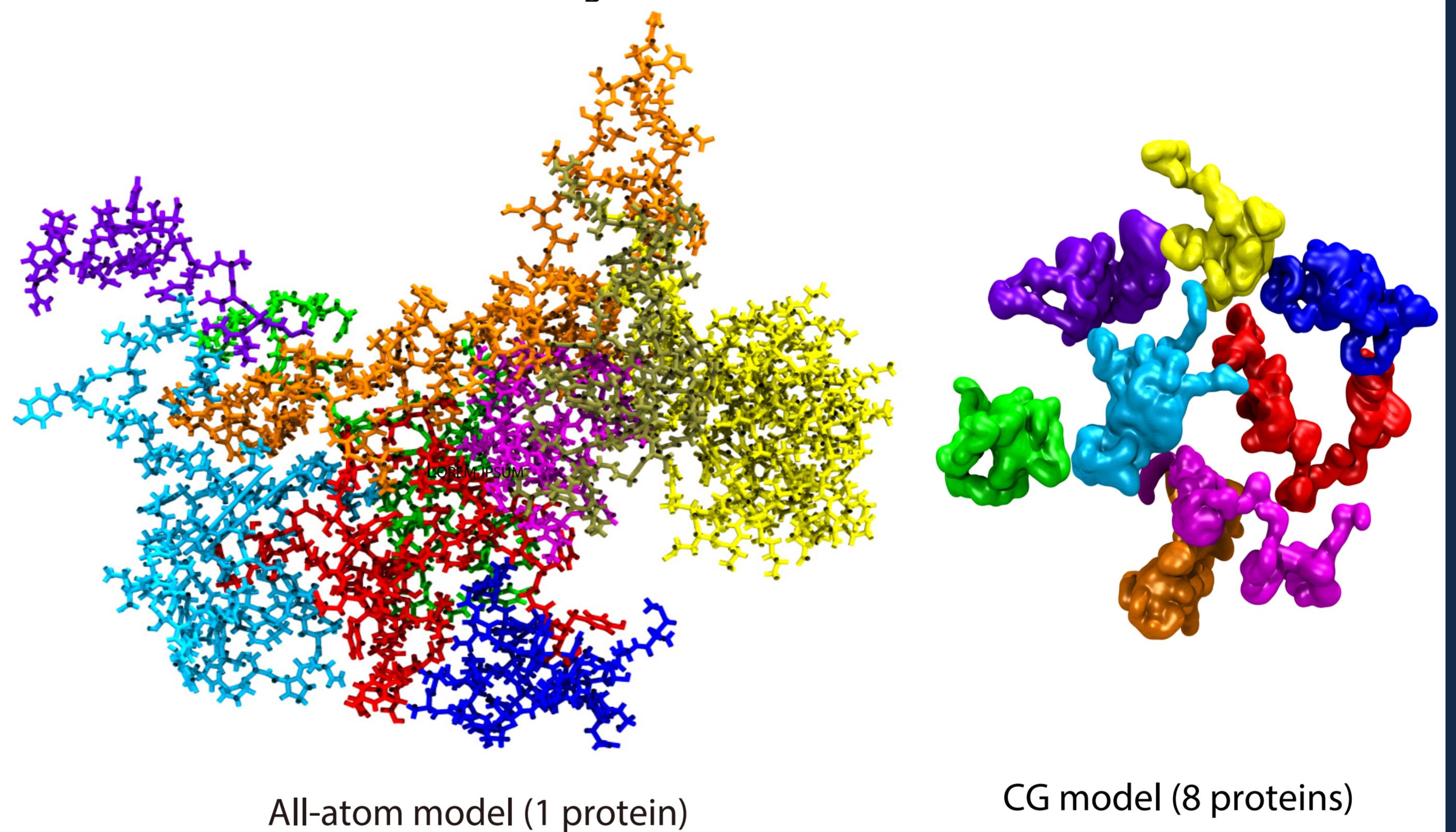
- An individual FUS protein is made up of 526 amino acids.
- Structure can be divided into RNA-binding domains (RBDs) and prion-like domains (PLDs), each of which have ordered and disordered regions.
- Phase separation of FUS protein has been shown experimentally to be primarily driven by the interactions between tyrosine residues from PLDs and arginine residues from RBDs.



All-atom representation of FUS (right). Tyrosine and arginine residues are highlighted blue and magenta, respectively.

Methodology

- Phase separation process is simulated using all-atom Molecular Dynamics (MD) and Atomic Resolution Brownian Dynamics (ARBD).
- Building all-atom model of FUS protein using publicly available data from Protein Data Bank for the ordered region and the disordered regions are constructed from the amino acid sequence.
- From the all-atom model, coarse-grained (CG) model is built.



- The raw output data from both simulations give the trajectory of all atoms (or coarse-grained particles) of the system. Trajectory is then analyzed to gain insight into phase separation process.

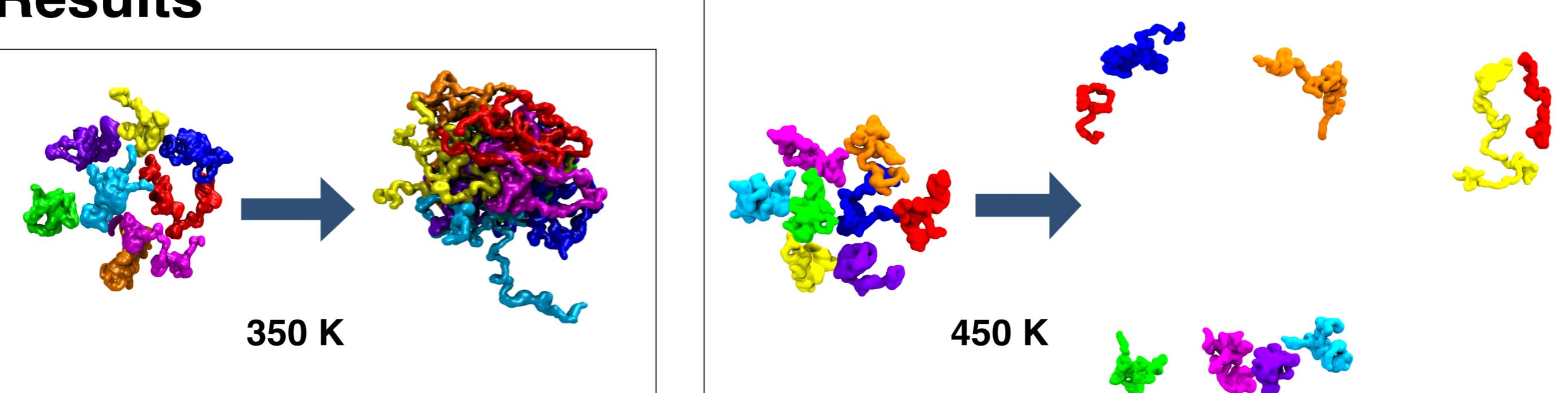
Software & Applications Used

- ARBD is a GPU-enabled code that takes advantage of the processing power of the GPUs to facilitate fast simulations and achieves better computational efficiency for large systems.
- Python script is used to run ARBD simulations.
- All-atom simulations are done using NAMD software on Stampede2 supercomputer.
- Visualizations are done using VMD and all-atom model of FUS is built using VMD software.
- Programming language used for analysis were Tcl and Python.

Simulation Conditions

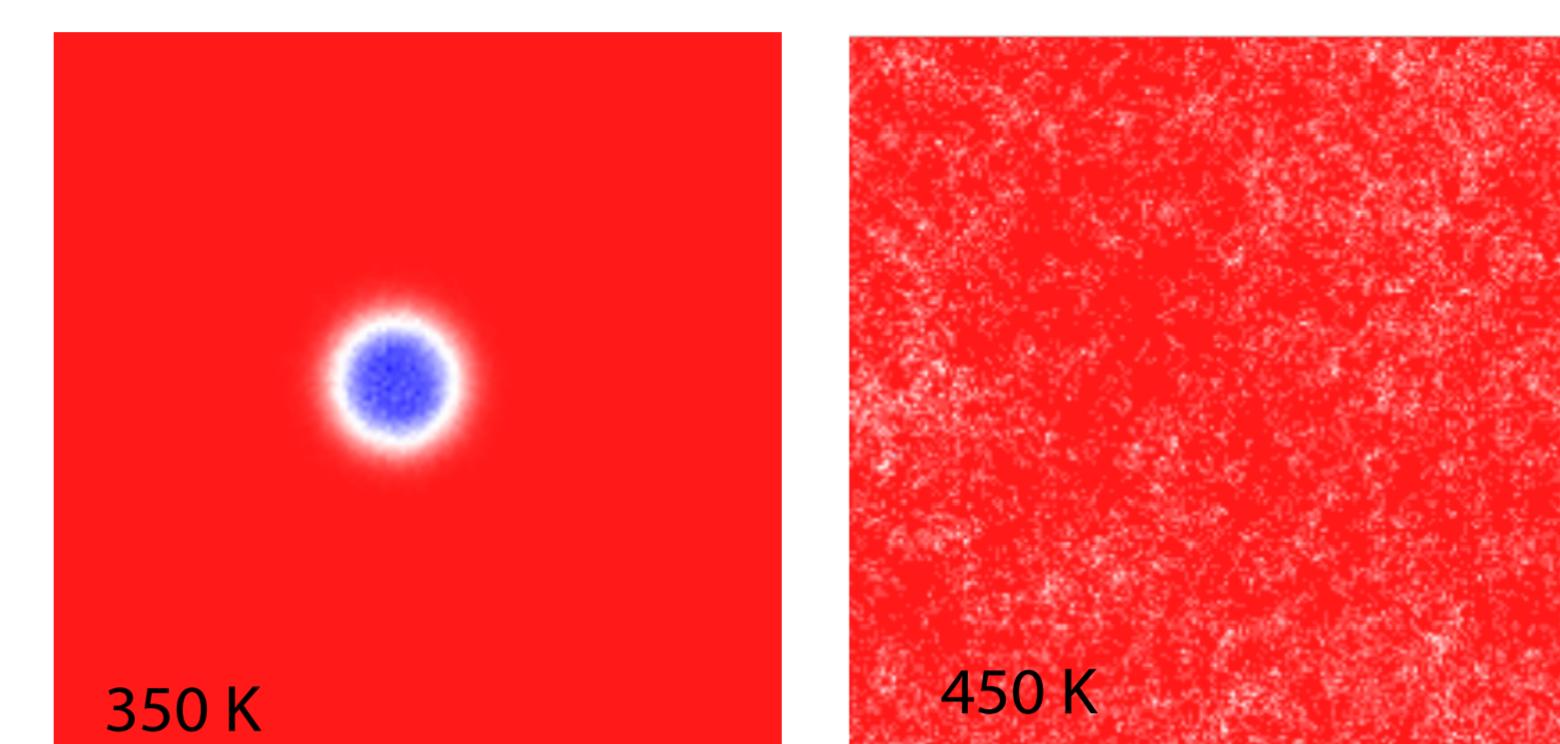
- All-atom simulation of wild-type (WT) FUS protein is run at 300K in NPT-ensemble for 100 ns in 0.15 M of KCl solution in periodic boundary conditions. Total atoms = 320332
- The ARBD simulation of WT 8 FUS proteins are run at 295K, 350K, 400K, 410K, 415K, 420K, 425K, 430K, 440K, 450K in NVT-ensemble for 10 μs. Total atoms = 4344
- The simulation box volume is 825³ Å³ and thus, the concentration is 23.65 μM.

Results



The state of 8 FUS proteins at the start and at the end of 10 μs simulation.
The 350 K system aggregates (left) and the 450 K (right) did not.

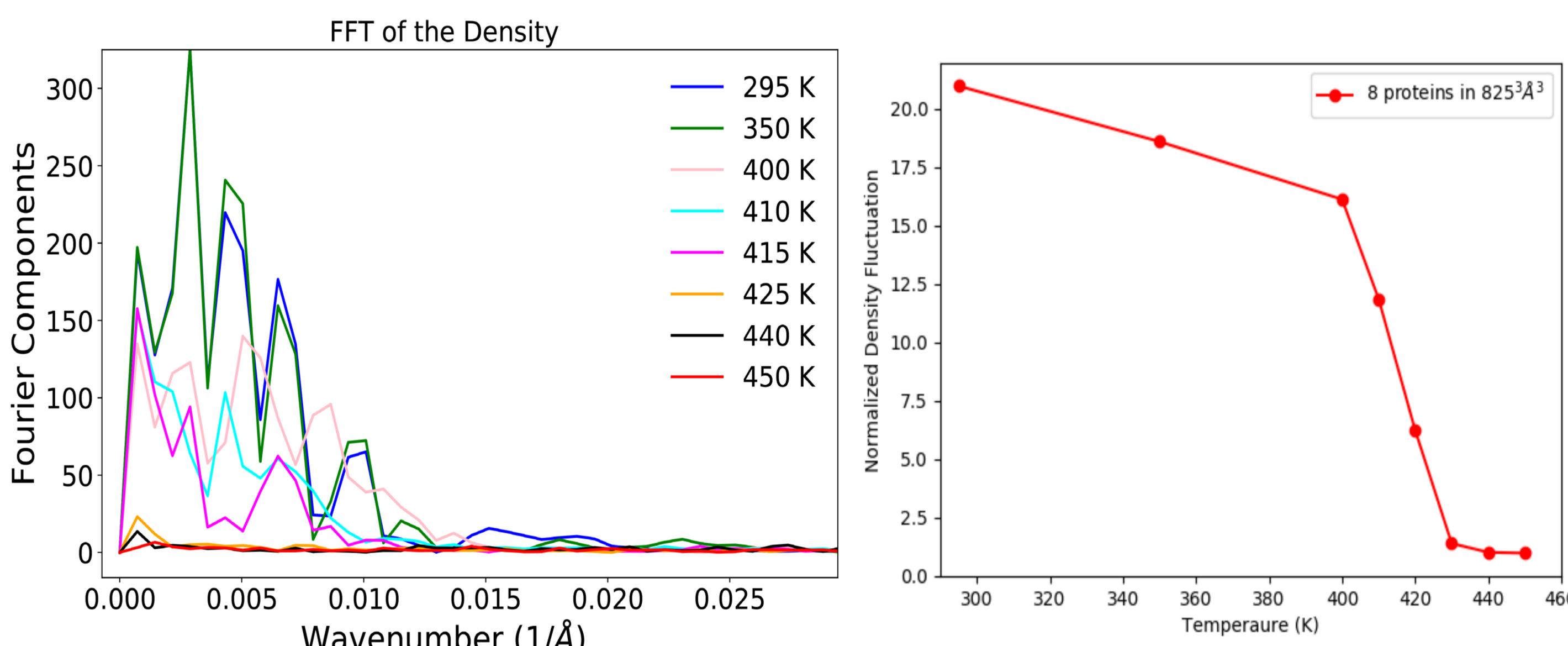
Results



The distribution of the density is quite uniform for the system (right) that didn't coalesce unlike the other system (left) which formed a dense region, reflecting the cluster formation.

The density maps of FUS proteins obtained using the data from ARBD simulation.

Results



- If the system is inhomogeneous, there are more density fluctuations yielding closely spaced wave lengths and hence, a large wavenumber. On the other hand, if the system is homogeneous, the density fluctuations are more uniform resulting in larger wave lengths and hence, a smaller wavenumber.
- Around 415K, we can see a transition from inhomogeneous to homogeneous phase, where the density fluctuation becomes almost zero.

Conclusion & Future Directions

The liquid-liquid phase separation process is highly temperature dependent as at temperatures higher than 415K, the proteins didn't coalesce at all. However, at room temperature or temperatures lower than 415K, the proteins aggregate. Hence, the threshold temperature at which LLPS occurs appears to be at 415K.

Additional simulations at various concentrations of FUS protein should be run to find out the concentration threshold for the LLPS process, akin to how we determined the temperature threshold. Another promising direction is to compare the relevant behavior of the WT FUS protein with that of the mutant FUS protein. The results of this comparison would provide insight into how certain mutations affect the phase separation properties of FUS. Moreover, it would help us determine exactly which regions of the protein are most involved in LLPS, for mutations in an essential region should disrupt the LLPS process much more than mutations in nonessential regions.

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