Finite-size scaling analysis of protein droplet formation

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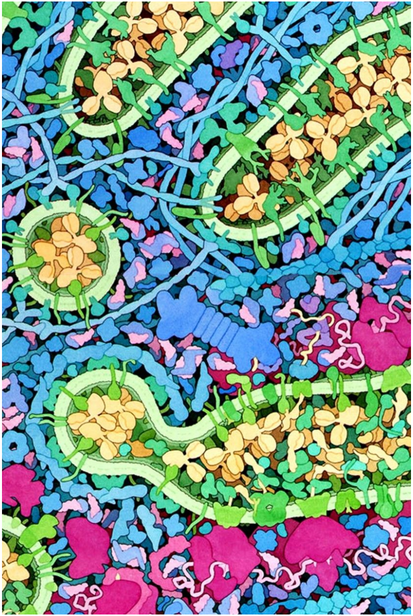
Biomolecular condensates

- Spatial organization is important for cell function.
- Well-known: Membrane-enclosed organelles.
- Structures without membranes also exist.
- Believed to form through liquid-liquid phase separation (LLPS)

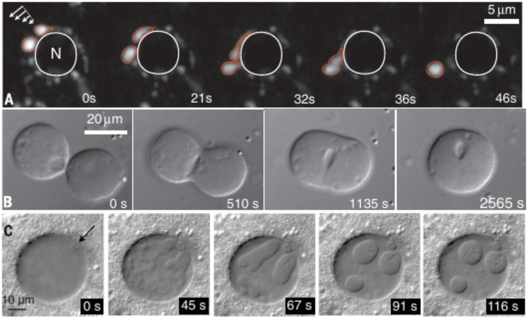


From Goodall, "The machinery of life"

Experimental evidence

Droplet-like behaviour

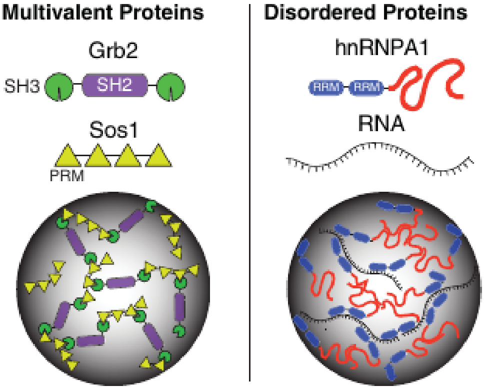
- Concentration-dependent formation
- Spherical
- Coalescence
- Wetting



From Shin, Brangwynne, *Science* 2017

What drives phase separation?

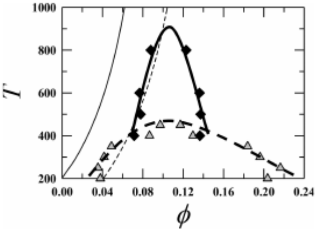
- Condensates made up of chain molecules, e.g. proteins, RNA.
- LLPS is sequence-dependent.
- Phase-separating proteins are often
  - multivalent.
  - intrinsically disordered.



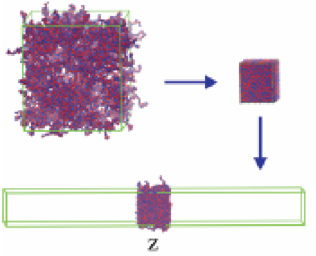
From Shin, Brangwynne, *Science* 2017

Previous studies

- Focused on drawing phase diagrams.
- Different calculational techniques
  - Random Phase Approximation.
  - Slab-method simulation.
  - Field-theoretic simulation.
- However, due to computational limitations, systems are always much smaller than real systems.



From Das, Eisen, Lin, Chan, *J. Phys. Chem. B* 2018



From Das, Amin, Lin, Chan, *Phys. Chem. Chem. Phys.* 2018

Finite-size scaling

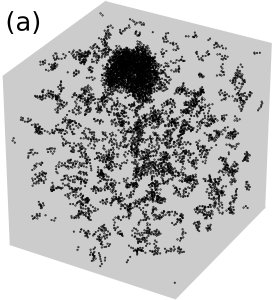
- Add δN particles to system with N particles in dilute phase.
- Added particles can be
  - absorbed in the dilute phase, $\Delta F_{\text{dilute}} \propto (\delta N)^2/N$.
  - form droplet of dense phase, $\Delta F_{\text{droplet}} \propto (\delta N)^{(d-1)/d}$.
- As system size increases, ΔF_{dilute} increases faster than $\Delta F_{\text{droplet}}$.
- Gives scaling relations, e.g.

$$T_{\text{b}}^{(N)}(\rho) - T_{\text{b}}(\rho) \sim N^{-1/(d+1)}$$

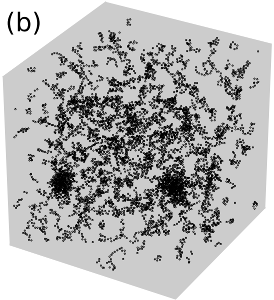
Two simulated sequences behave differently

- We simulate two hydrophobic-polar (HP) sequences, A (HPHPHPHPHP) and B (HHHHHPPPPP).
- Sequence A forms a single droplet, which grows as the system size increases.
- Sequence B droplets stop growing, but as temperature decreases, multiple droplets form.

(a)

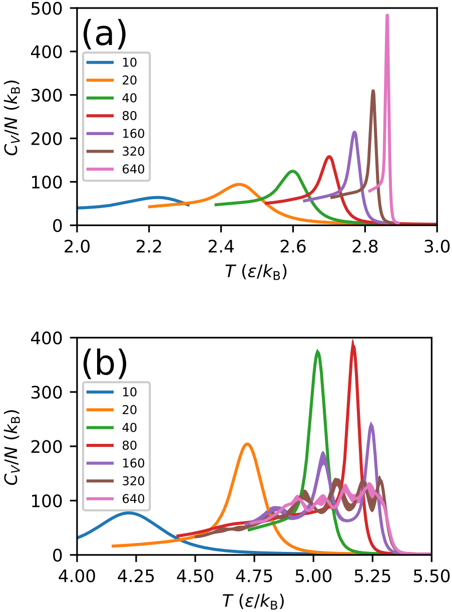


(b)



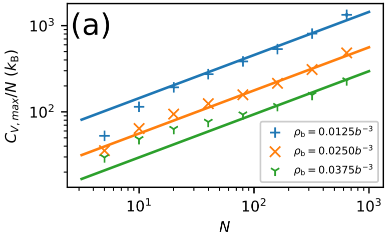
Only one of the sequences phase separates

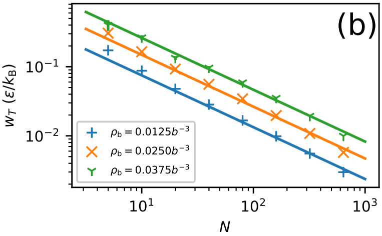
- For sequence A, the peak in heat capacity gets higher and narrower with system size - as expected from finite-size scaling.
- For sequence B, the C_V-peak stops growing and becomes multimodal for $N \gtrsim 80$.

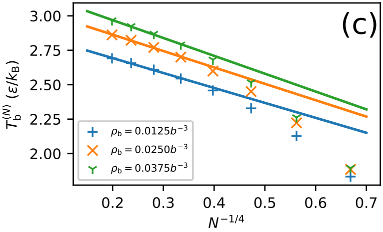


Simulations agree with predictions from finite-size scaling.

- (a) Peak in heat capacity, $C_{V,\mathrm{max}}/N \sim N^{1/2}$.
- (b) Smearing of the transition, $w_T \sim N^{-3/4}$.
- (c) Shift in transition temperature, $\Delta T_\mathrm{b} \sim N^{-1/4}$.

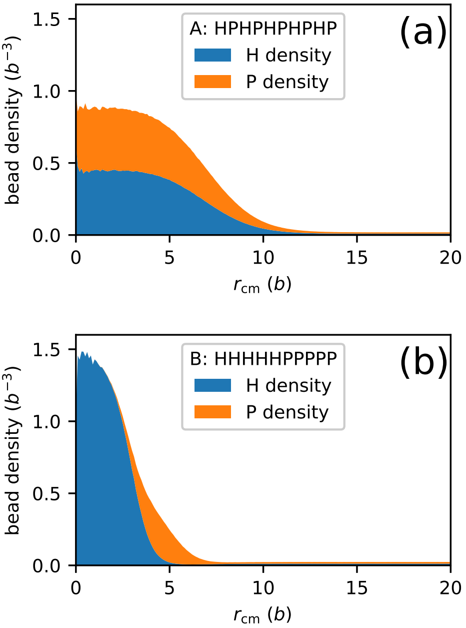






Why doesn't sequence B phase separate?

- Sequence A forms droplets with similar density profiles for H and P.
- Sequence B has a high-density core with only hydrophobic residues.
- At some point, the polar parts of the B sequence prevents further residues from moving into the core.



Summary

- We are able to simulate LLPS in a simple hydrophobic-polar protein model.
- Finite-size scaling analysis can be used to determine whether a phase transition happens or not.
- Of the two simulated sequences, one turned out to phase separate, but not the other.