Imperial College London

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Oct 16, 2013

Phase transitions in cell biology

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A cell

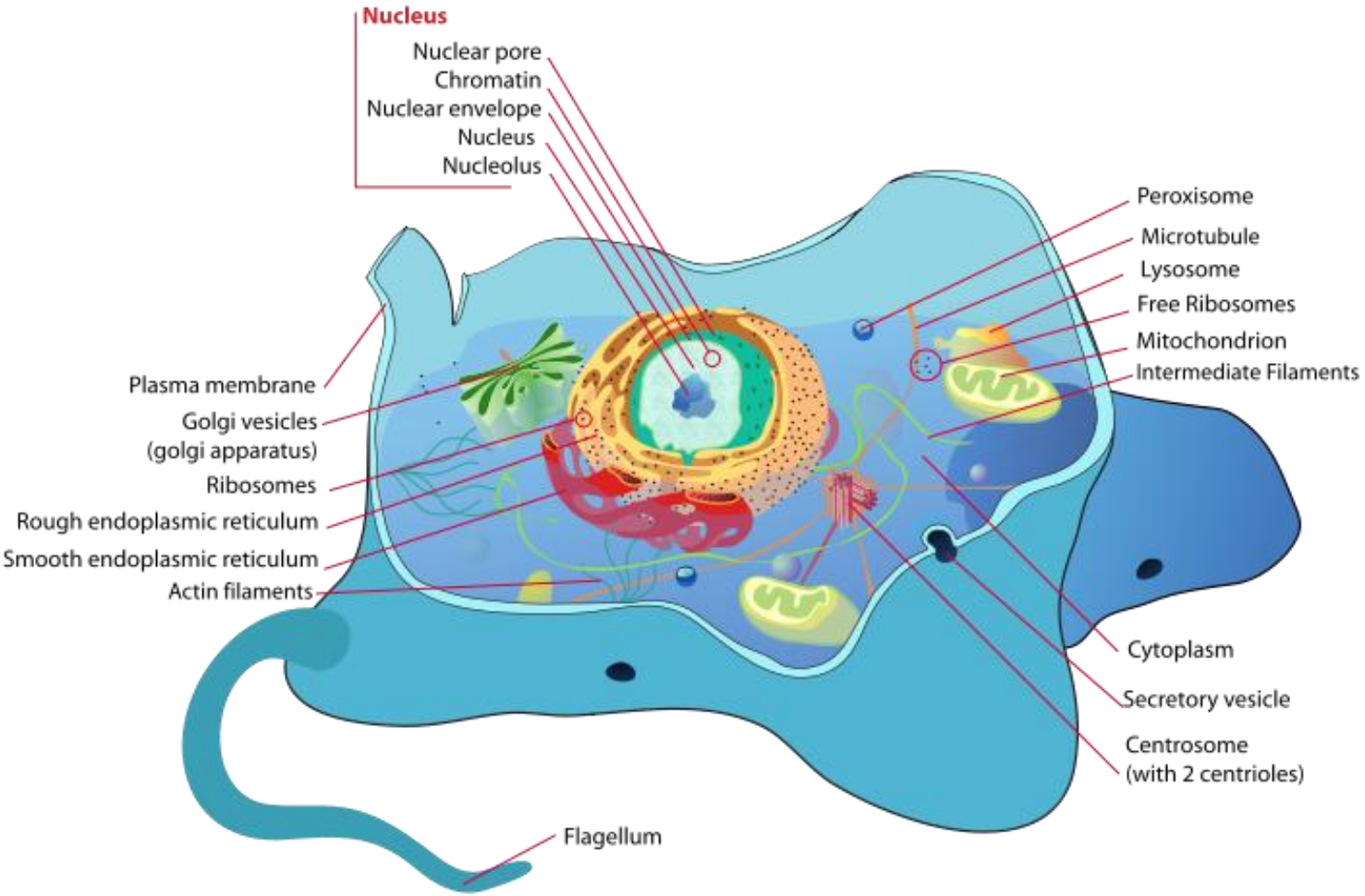


Figure from Wikipedia

Nonmembrane bound organelles

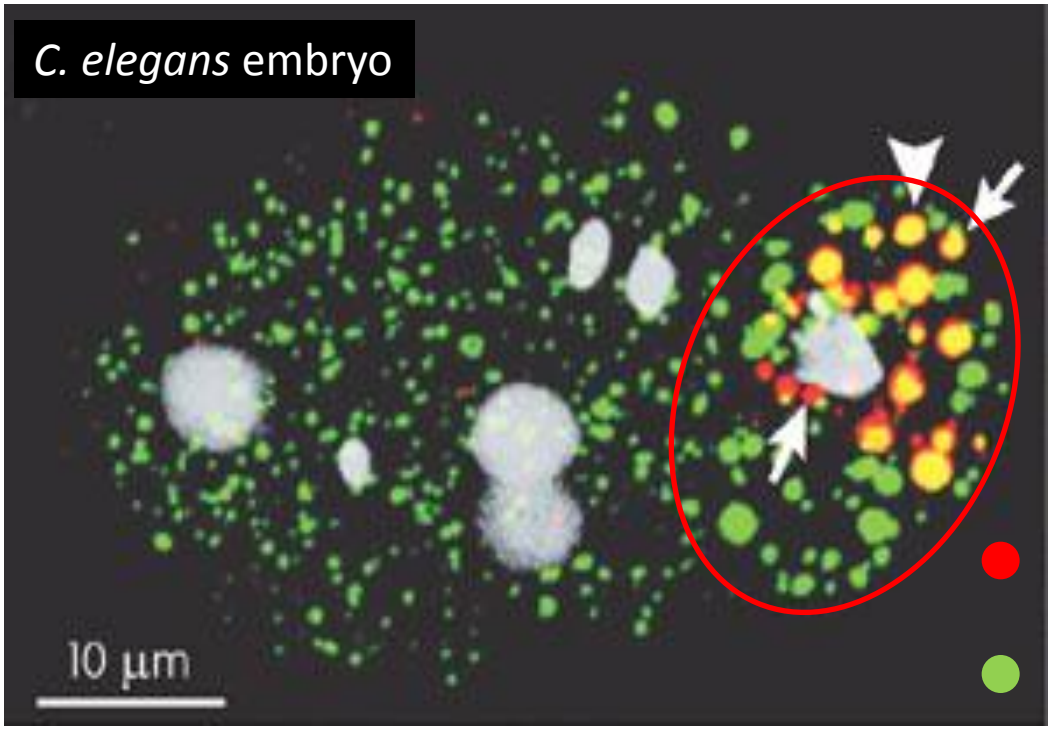


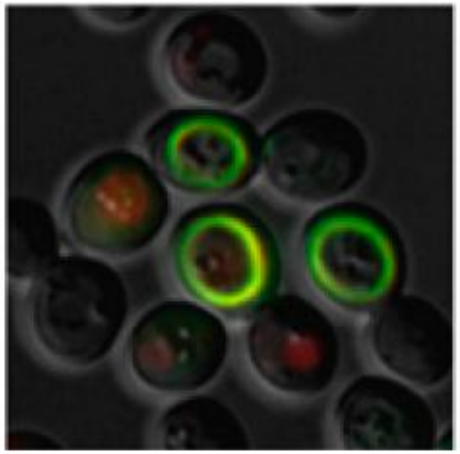
Fig. adapted from Anderson & Kedersha (2009) *Nature Rev. Mol. Cell Biol.*

Self-assembly *via* phase transitions?

[Sear (2008) Faradays Discussions; Brangwynne *et al.* (2009) Science]

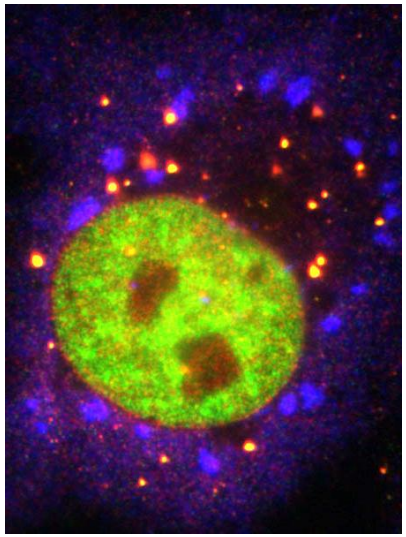
Structure formations by phase transitions

Prion in yeast



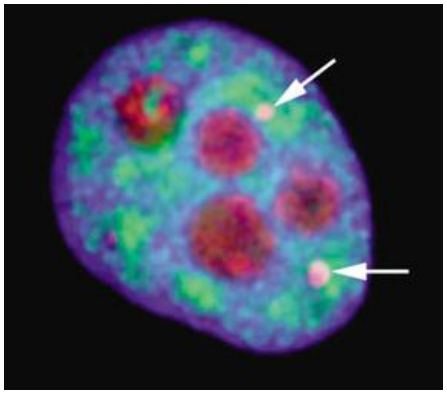
Saibil et al. (2012) PNAS

Stress Granules



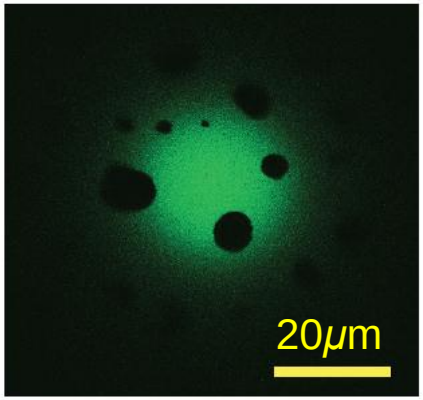
Stoecklin Lab (Heidelberg)

Cajal Bodies



Swedlow and Lamond (2001) *Genome Biol.*

Membrane raft formation



Ehrig, Petrov & Schwille (2011) New J. Phys.

Plan

- Physics of phase transitions

- Self-organised cellular structures via phase transitions
  - [1D] Amyloid self-assembly
  - [2D] Two-component lipid membrane phase separation
  - [3D] Nonmembrane-bound organelle formation and localisation – Germ granules

- Fundamental limitations on phase transitions
  - And how nature finds a way around it

Physics of phase transitions

A system will minimise its free energy

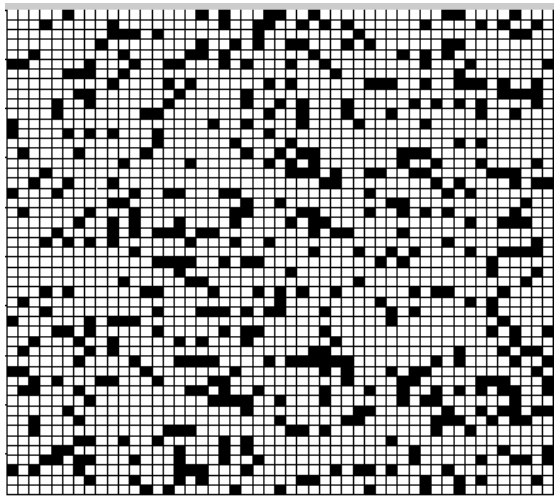
Free energy: $F = -TS + E$

Entropy: $S = k_B \log \Omega$

Bonding energy

Boltzmann constant

Number of different configurations



Consider a square lattice with N sites that are filled with N_1 particles of type A (■)and N_2 particles of type B (□)

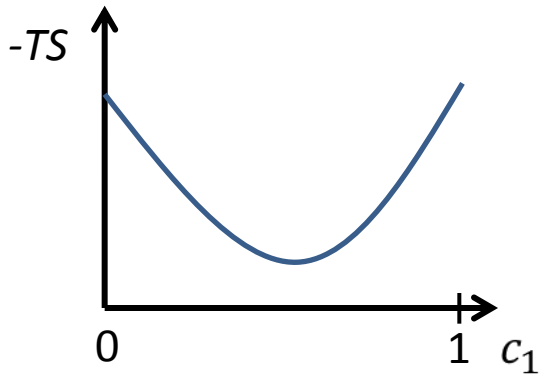
$$\Omega = \binom{N}{N_1} = \frac{N!}{N_1!\,(N-N_1)!} \xrightarrow{\text{Stirling's formula}} N\left[\left(\frac{N_1}{N}\right) log\left(\frac{N_1}{N}\right) + \left(\frac{N_2}{N}\right) log\left(\frac{N_2}{N}\right)\right]$$

c_1

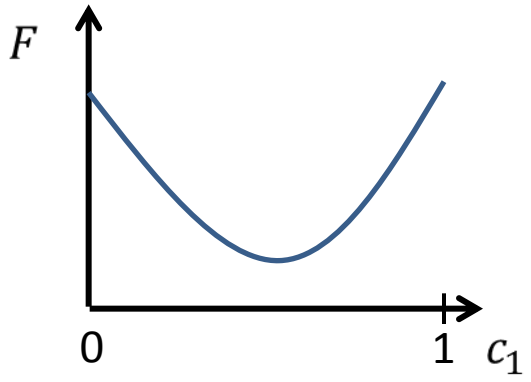
$c_2 = 1 - c_1$

A system will minimise its free energy

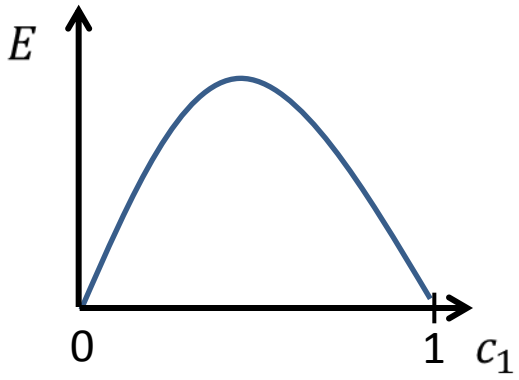
Free energy: $F = -TS + E$

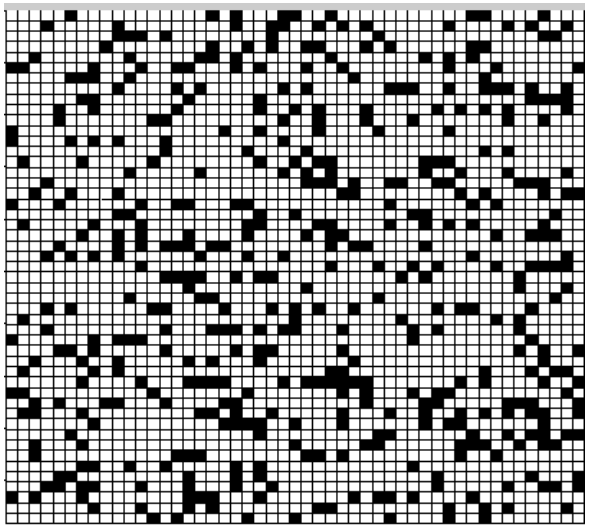


High *T*, low *g* -> mixing



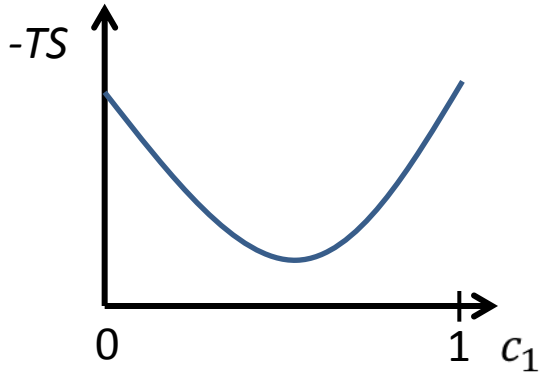
What if the particles A & B dislike each other? $E = gc_1c_2 = gc_1(1 - c_1)$



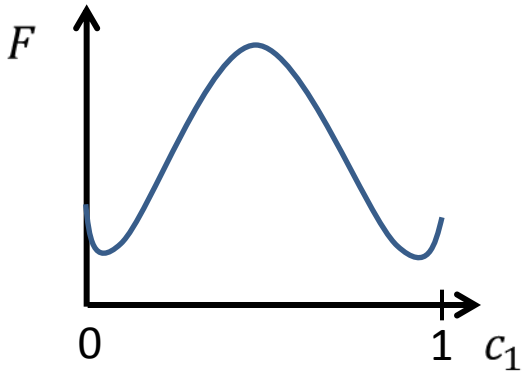


A system will minimise its free energy

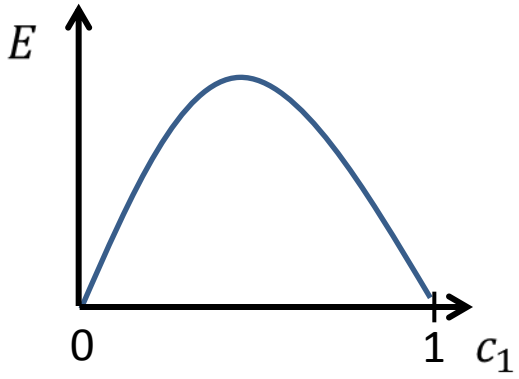
Free energy: $F = -TS + E$

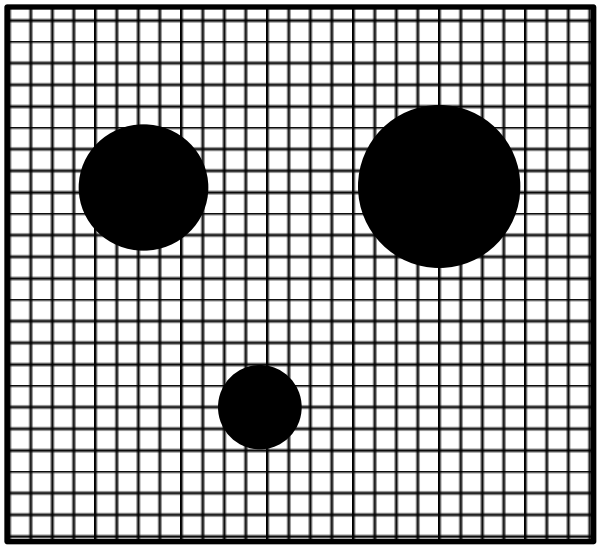


Low *T*, high *g* -> **de**mixing

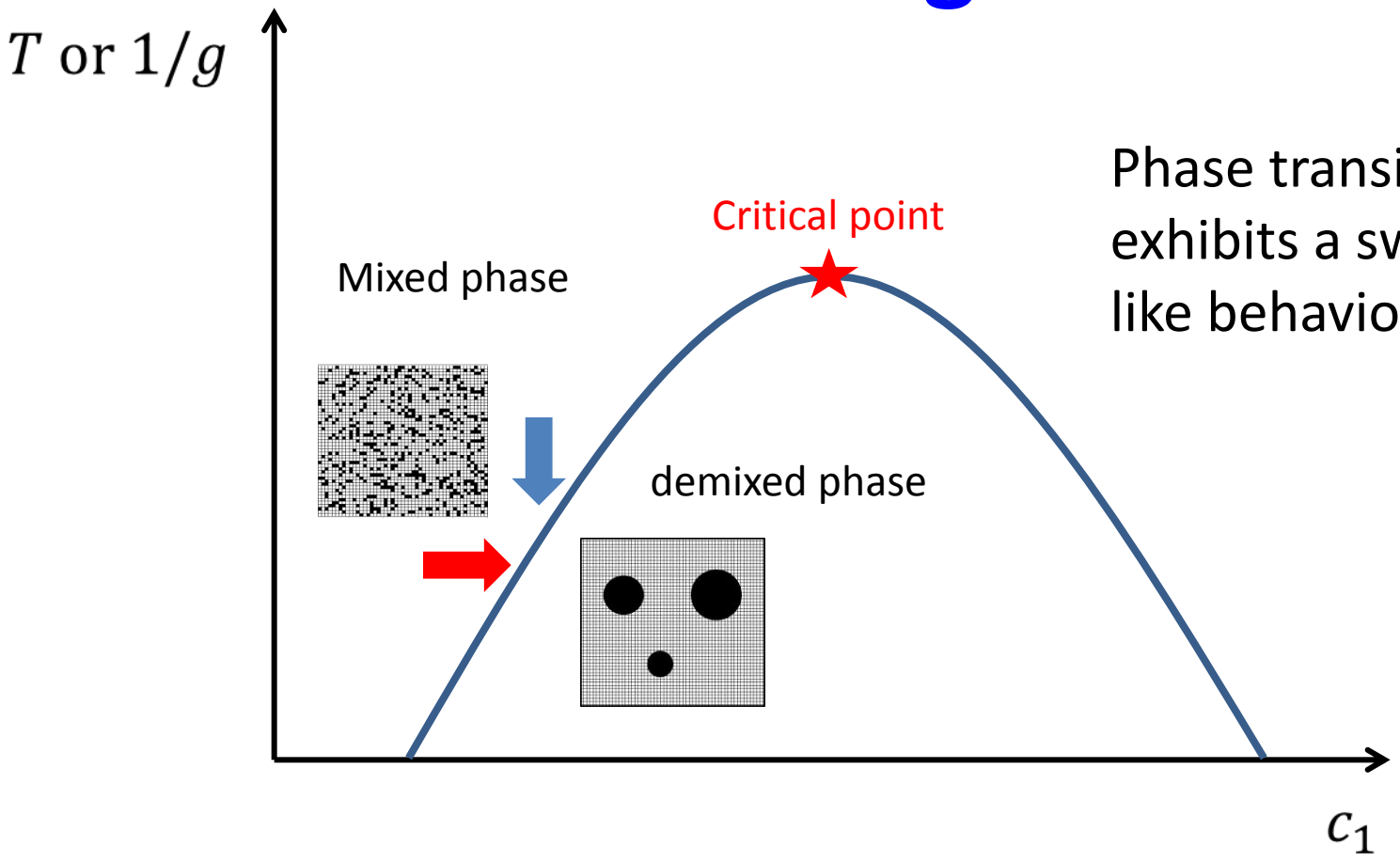


What if the particles A & B dislike each other? $E = gc_1c_2 = gc_1(1 - c_1)$





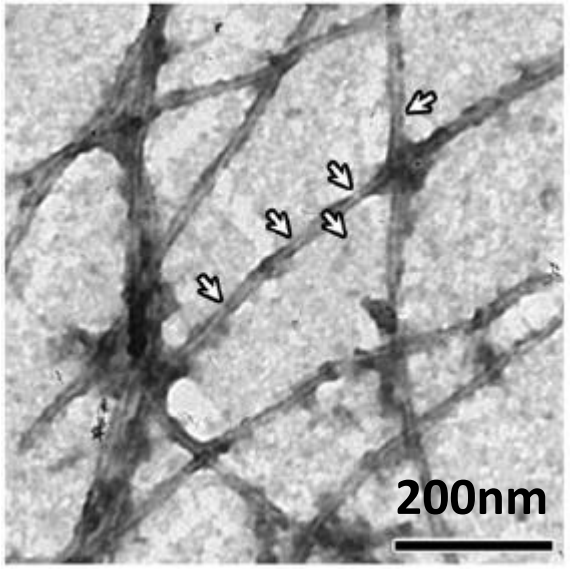
Phase diagram



Phase transition exhibits a switch-like behaviour

Phase transitions can be induced by increasing g (or decreasing T) ⬇
or by increasing c_1 ➡

Abeta



Lee, Bird, Shaw, Jean and Vaux (2012) J. Biol. Chem.

One-dimensional aggregate: Amyloid fibril self-assembly

Amyloid fibrils

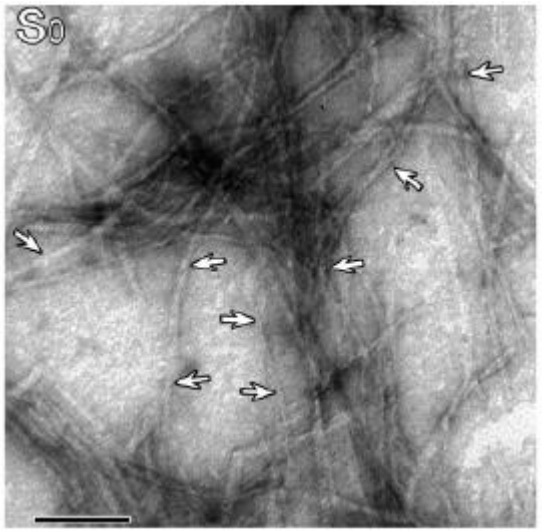
Amyloid fibrils are linear aggregates of proteins

Many proteins form amyloids

Many amyloid related diseases, e.g., Alzheimer's, Parkinson, Type II diabetes

Amyloid fibrils form easily *in vitro*

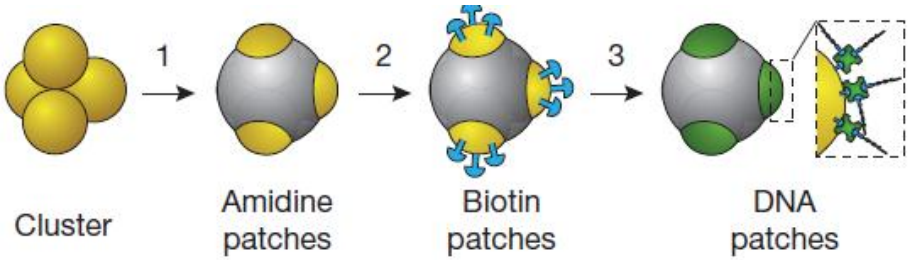
IAPP

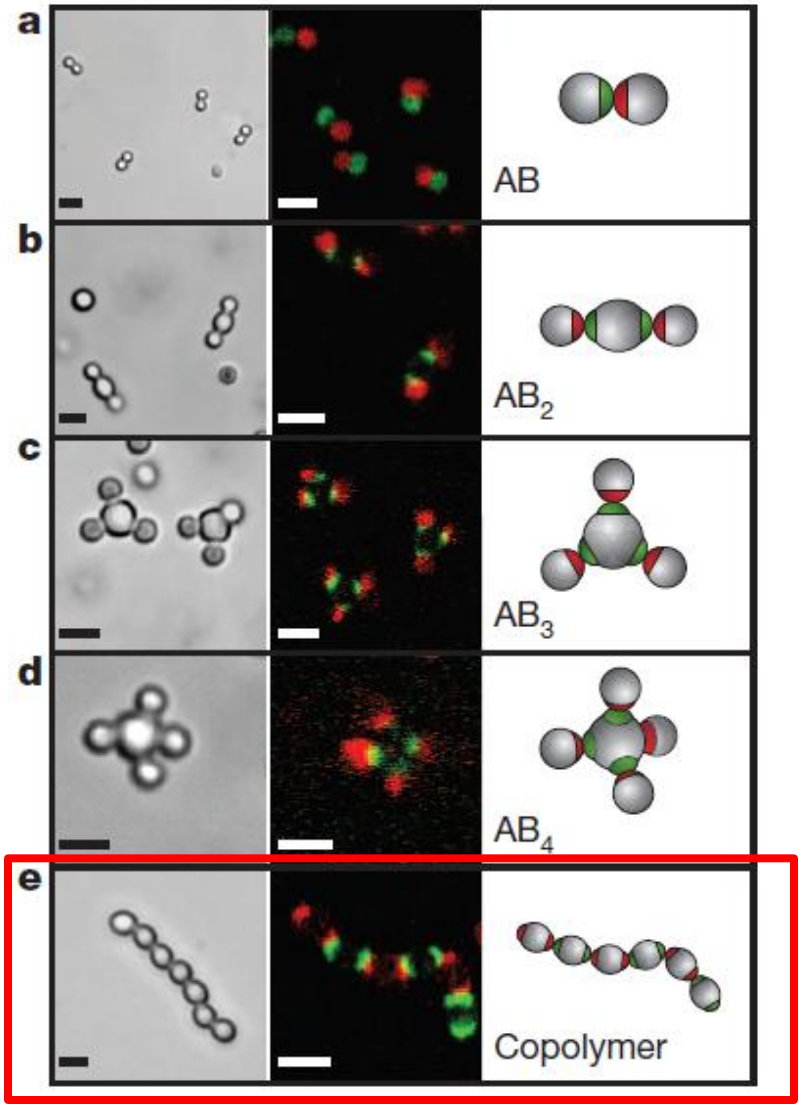


100nm

Trigg, Lee, Vaux and Jean (2013) Biochem. J

A colloidal analogue



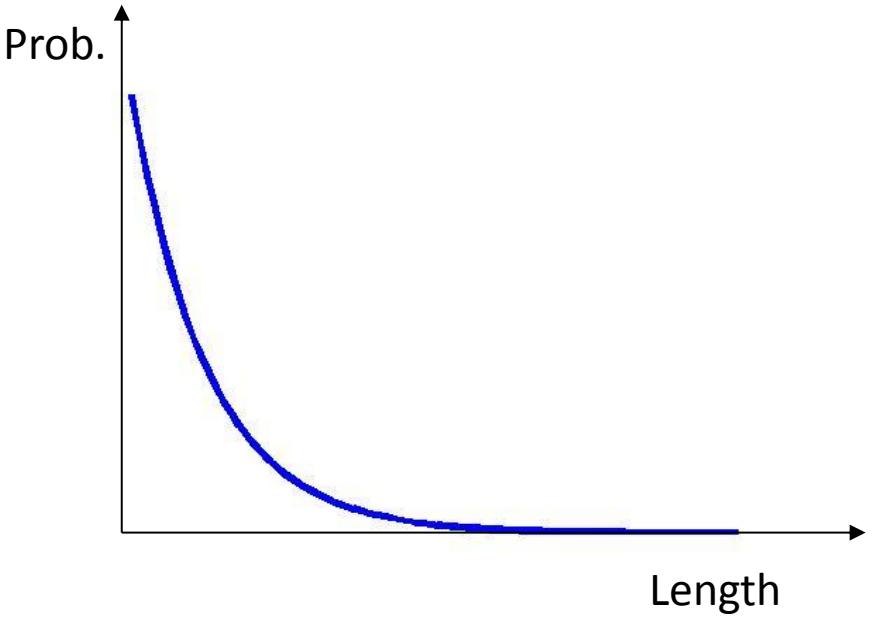


Wang et al. (2012) Nature 491, 51

Universal patterns of amyloid fibril formation

- Existence of a critical concentration

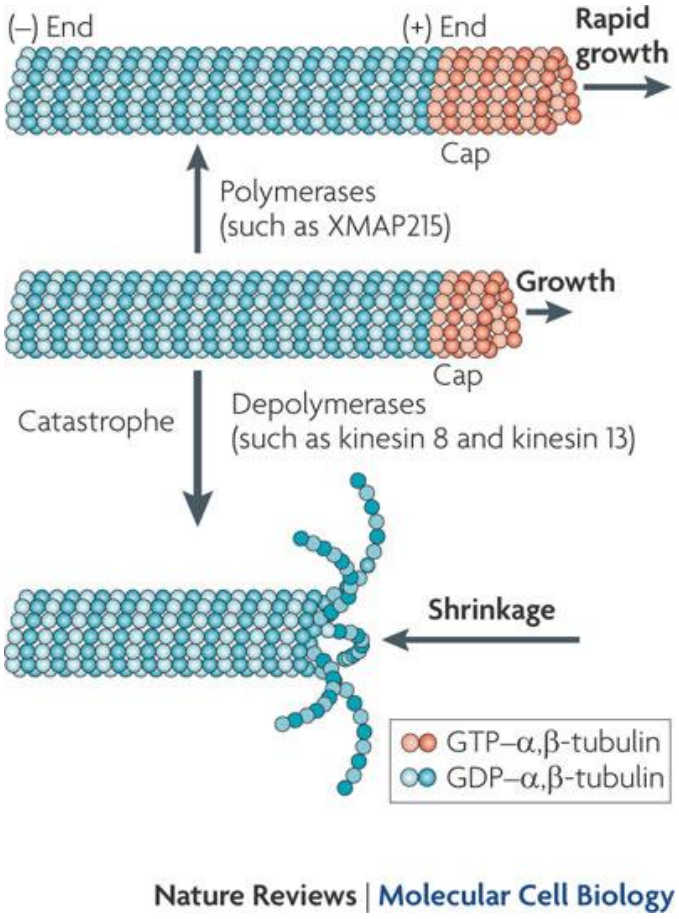
- At equilibrium, length distribution is exponential
  - No precise length control



Lee (2009) Physics Review E 80, 031902
Lee (2012) J. of Phys.: Condensed Matter 24, 415101

Dynamic length control

Micotubules



Howard & Hyman (2009) *Nature Rev. Mol. Cell Biol.*

Actin filaments

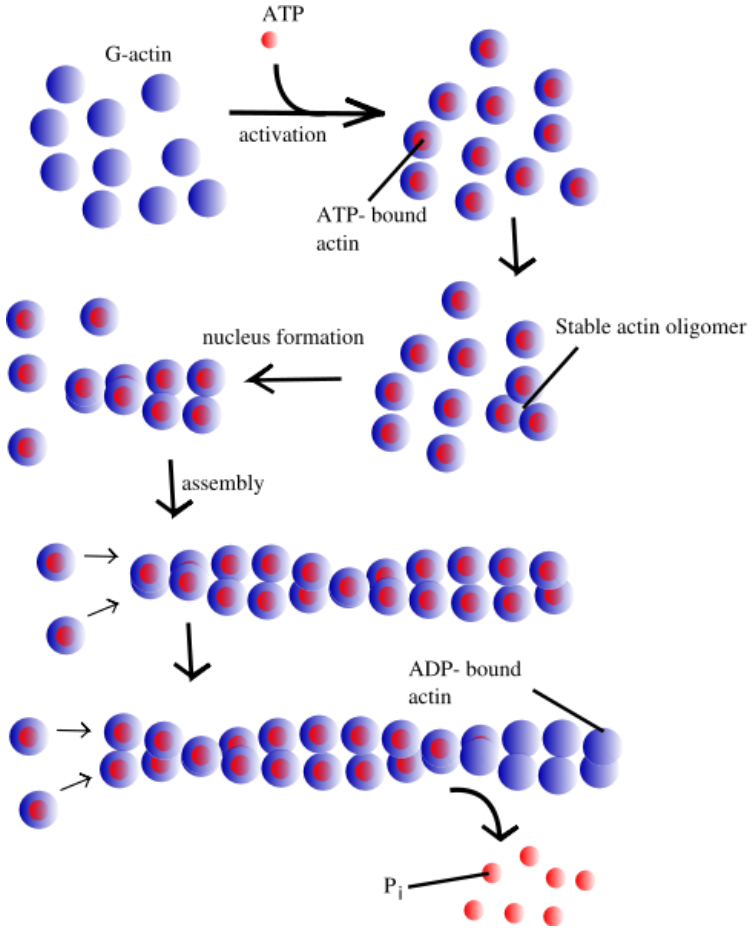


Fig. from Wikipedia

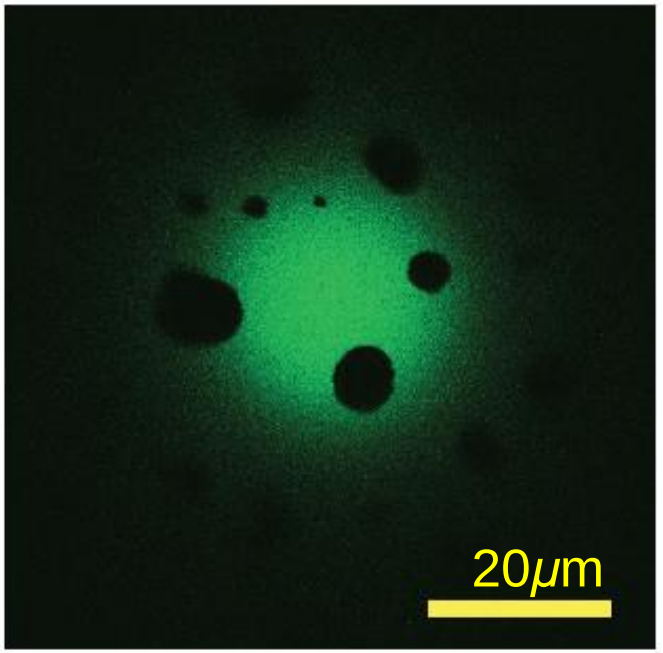
Limitation

- Lack of biopolymer length control

Nature's solution

- Two-state monomers with active enzymatic control

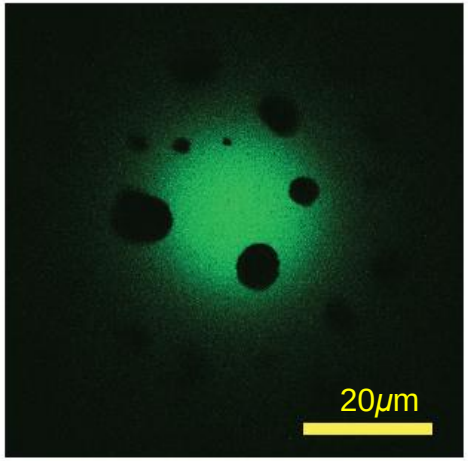
Ehrig, Petrov & Schwille (2011) New J. Phys.



Phase transition in two dimensions: Two-component lipid membrane

Why study phase separation in lipid membranes?

- Cell membranes consist of different types of lipids, and proteins
- The lipid membrane may undergo phase transition and partition itself into different domains
- Relevant to lipid raft formation
  - key to proper cell functioning

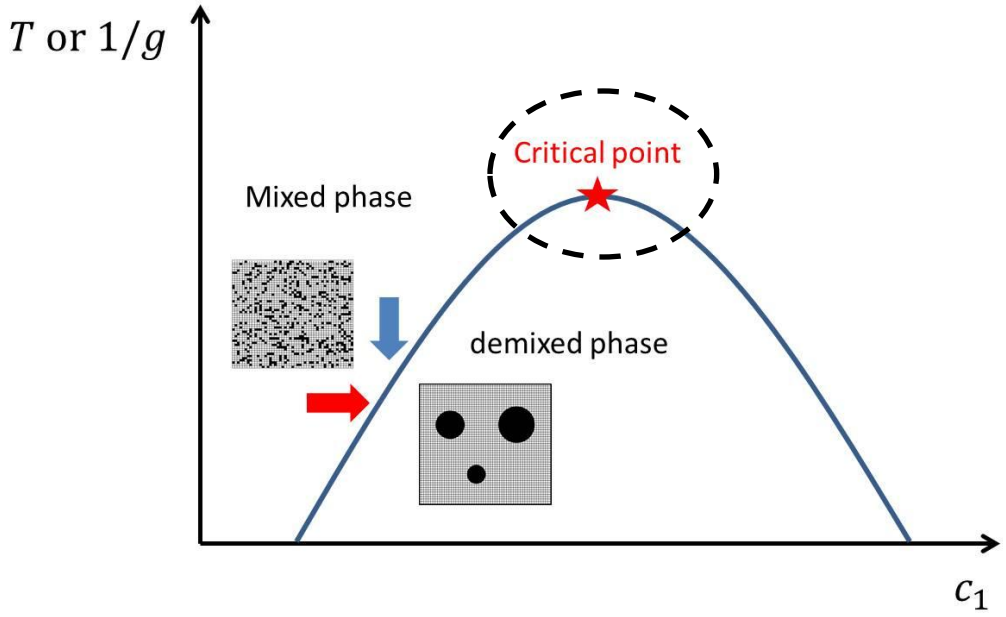


Ehrig, Petrov & Schwille (2011) New J. Phys.

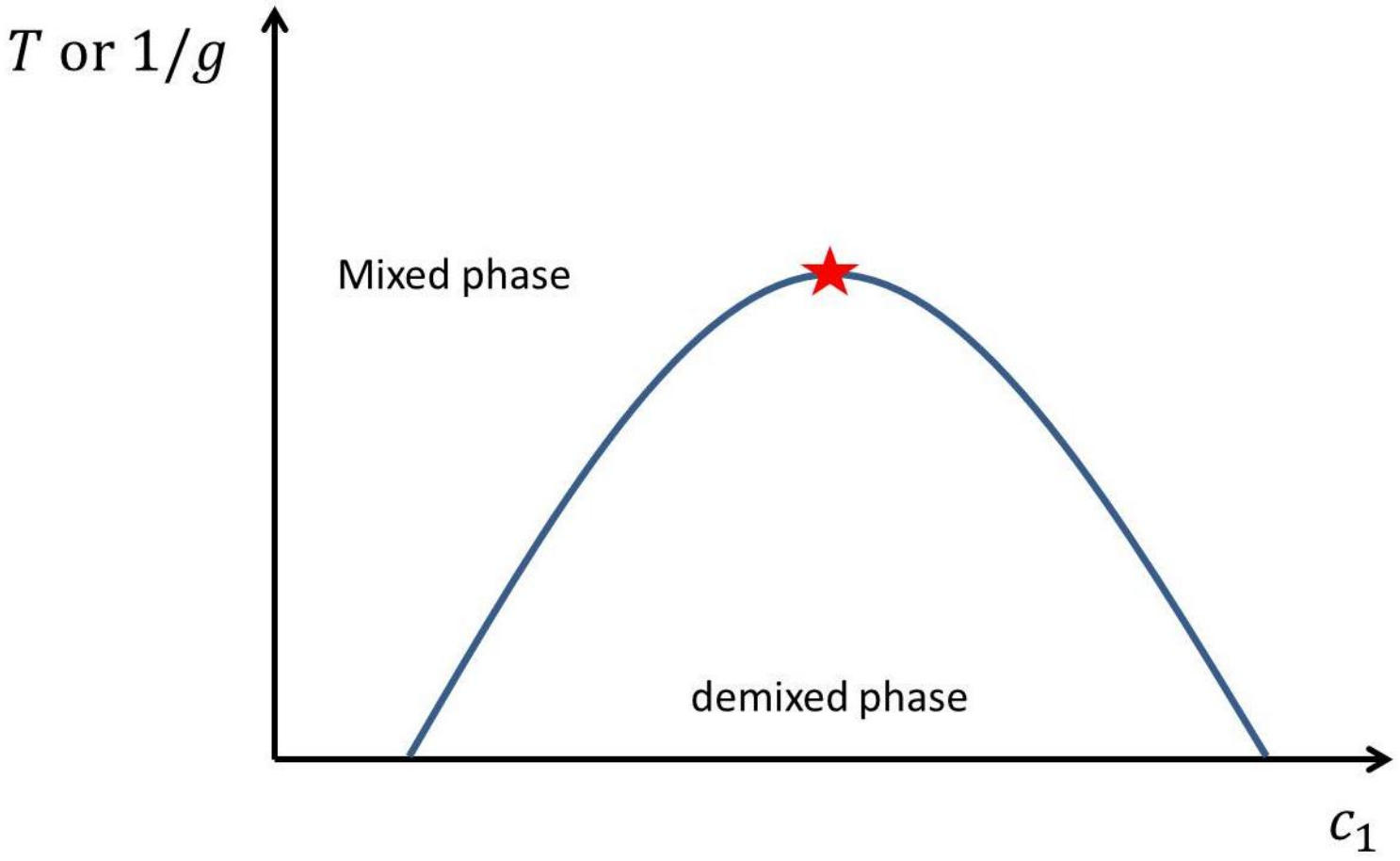
Domain size distribution?

- Again, there is the problem with size control – the domains tend to merge

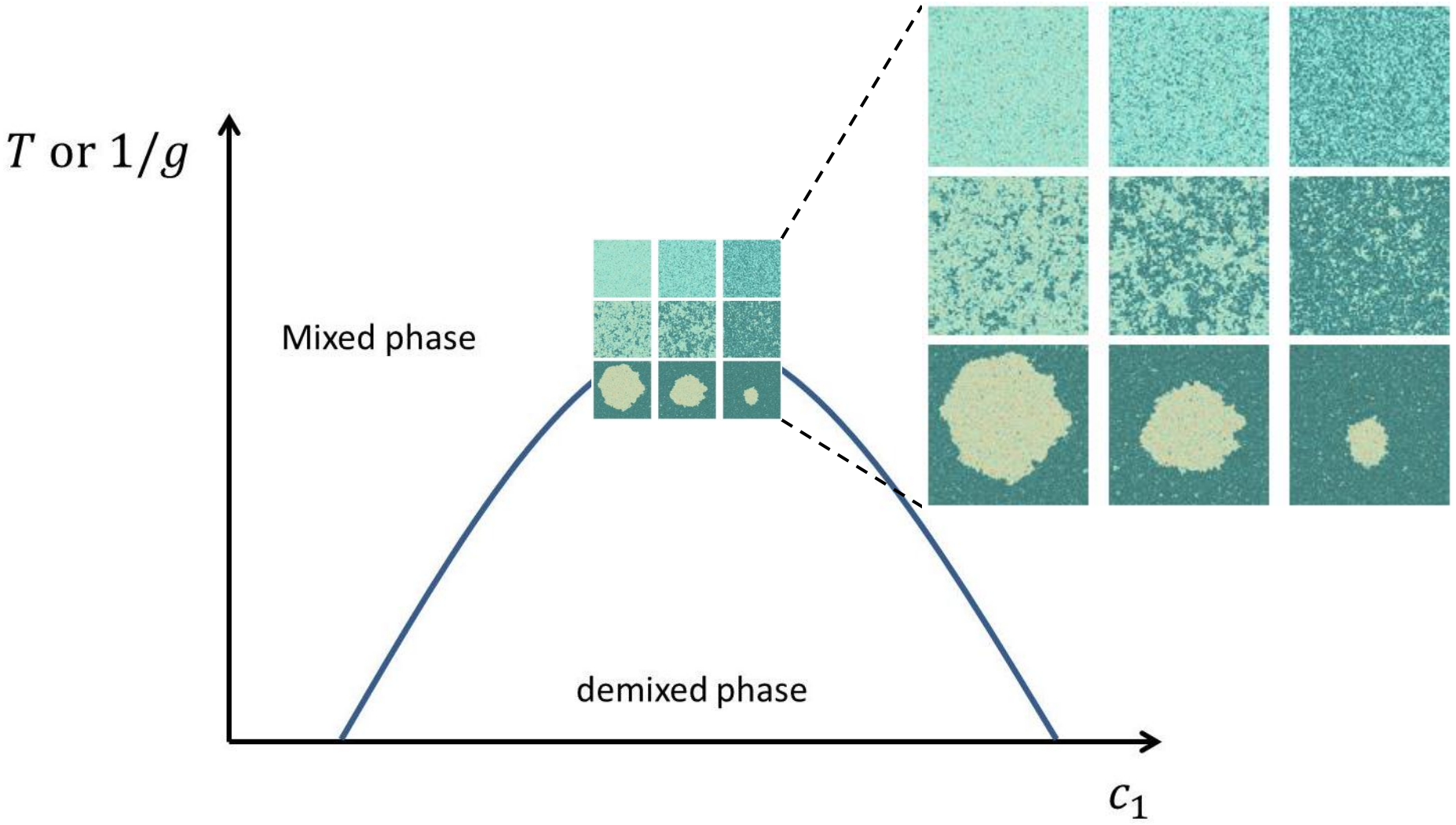
- Except close to the critical point



Domain size control



Compartment size control



Figures adapted from Ehrig, Petrov & Schwille (2011) New J. Phys.

Criticality-induce size control?

- In two-component lipid membrane close to the critical point, domains occurs at all length scales

- Equivalent to 2D Ising universality class [Lee, Petrov, Ehrig & Schwille, *in preparation*]

- Some biological membranes are close to criticality [Heimburg (2007) Thermal Biophysics of Membranes]
  - Bovine lung surfactant
  - *E. coli* membranes
  - *Bacillus subtilis* membranes

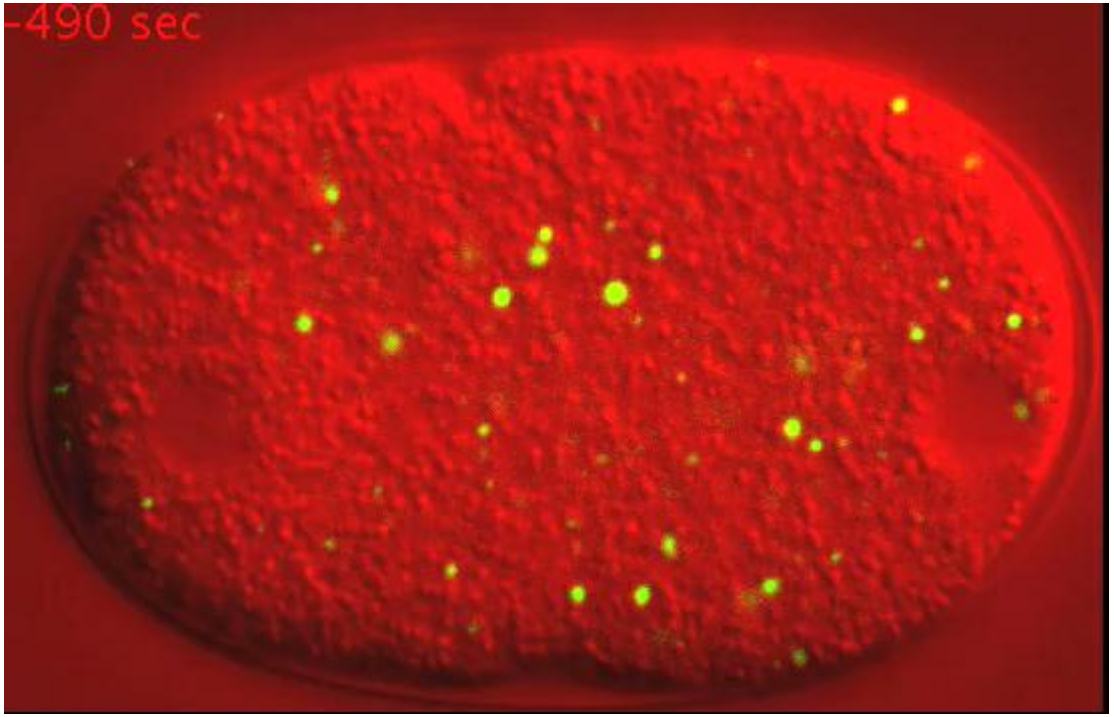
Limitation

- Rafts coarsen with time – lack of size control

Nature's solution

- Tuning membrane composition to be close to criticality

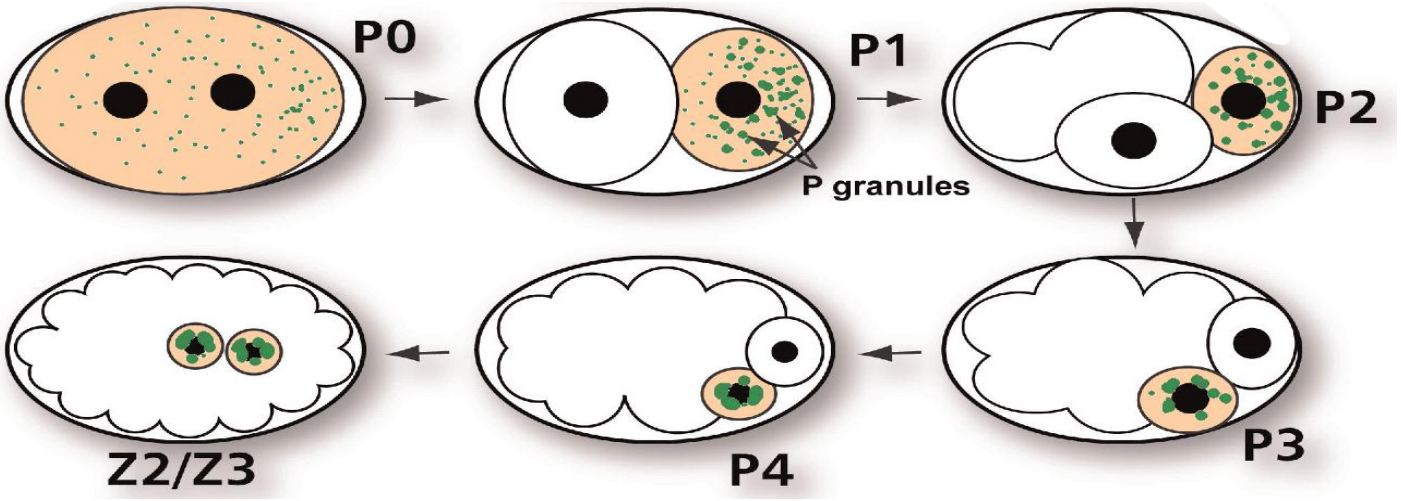
Cliff Brangwynne (Hyman Lab, MPI-CBG)



Phase transition in three dimensions: Germ granule formation

P Granules in *C. elegans* embryo

- P granules consist of mRNA and proteins that are important for germ cell specification
- Coined “nuage” by André and Rouiller in 1957

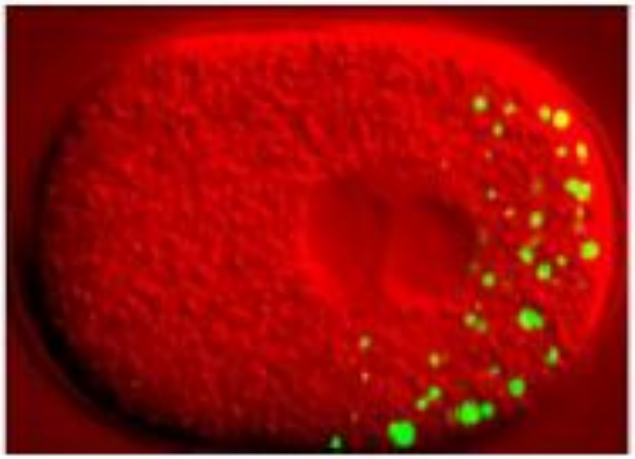


Updike and Strome (2010) *J. Andrology* **31**, 53

How do P granules form and get localised?

- Formation?
  - Phase transition!

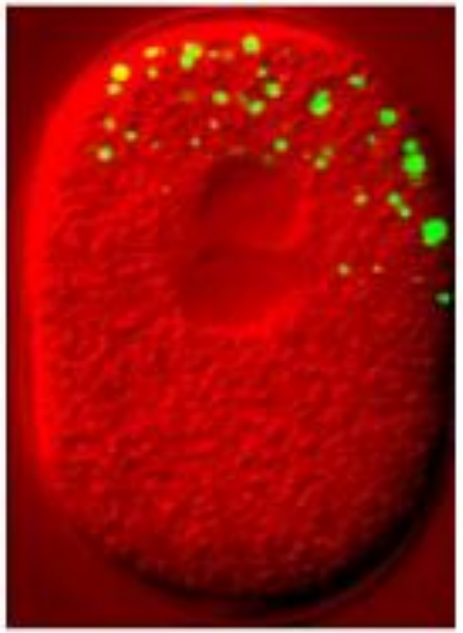
- Localisation?



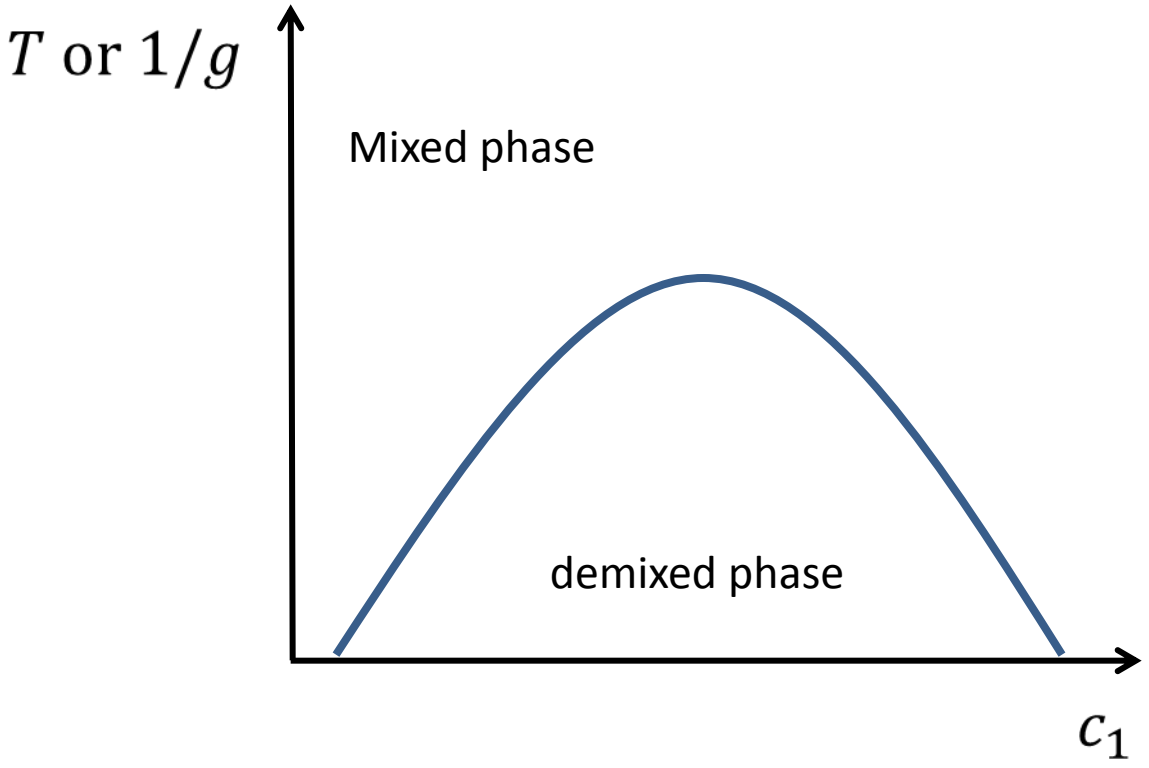
How do P granules form and get localised?

- Formation?
  - Phase transition!
- Localisation?

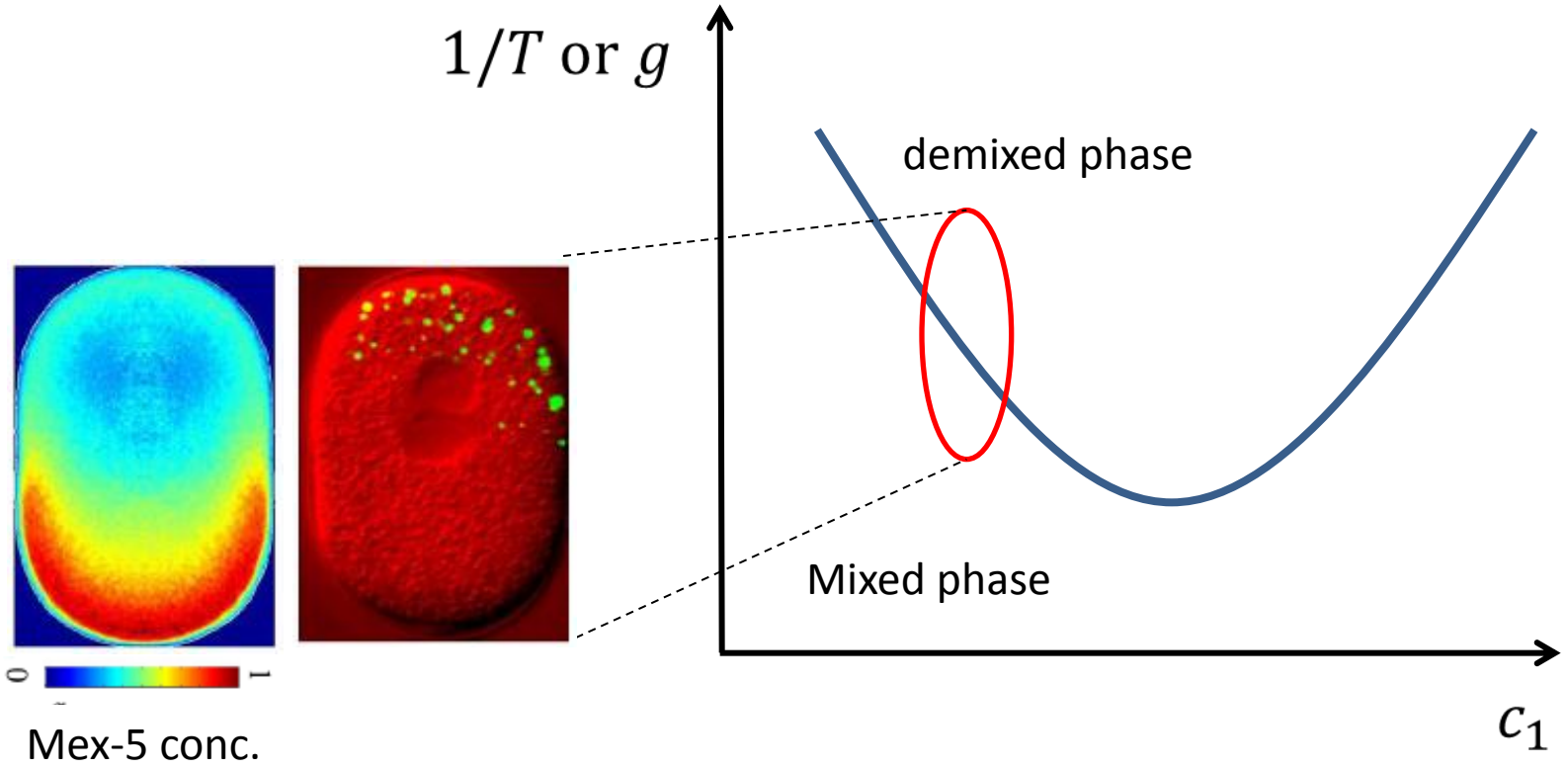
Picture from
National Weather Service, FL



Protein gradient controlled localisation



Protein gradient controlled localisation



Lee, Brangwynne, Gharakhani, Hyman, Jülicher (2013)
Physical Review Letters 111, 088101

Limitation

- Formation of granules is isotropic in space

Nature's solution

- Use the concentration of another protein to guide the position-dependent phase transition

Conclusion

- Phase transitions are everywhere in nature, it may also be true in cell biology
- Phase transition is switch-like – suitable for assembling structures on the go
- Specific examples
  - [1D] Amyloid self-assembly
  - [2D] Two-component lipid membrane phase separation
  - [3D] Germ granule formation and localisation
- Fundamental limits and nature's solutions

- What are the fundamental limits of exploiting phase transitions as a mechanism for cellular organisation?
- Can we do better than nature in bypassing these limits?

Acknowledgement

Amyloids (1D)

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Létitia Jean
Sarah Bird
Michael Shaw
Catherine Davison
Chongsoo Lee
David Vaux

Lipid membrane (2D)

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Eugene Petrov
Jens Ehrig
Petra Schwille

Germ granules (3D)

Princeton University

Cliff Brangwynne

Max Planck Institute of Cell Biology and Genetics, Dresden

Anthony Hyman

Max Planck Institute for the Physics of Complex Systems, Dresden

Jöbin Gharakhani
Frank Jülicher

Thank you!