EMBO | EMBL Symposia: Cellular Mechanisms Driven by Liquid Phase Separation
May 16, 2018

The Physics of Non-Equilibrium Phase separation: Implications for stress granules

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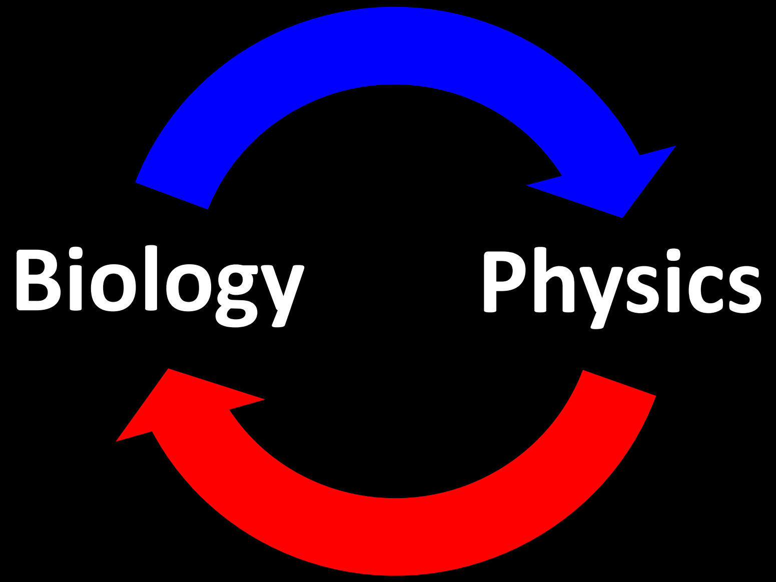
Biology inspires new physics



Physics allows us to do quantitative biology

Plan

1. Equilibrium (passive) phase separation
2. Non-equilibrium (active) phase separation
3. Implications for stress granule formation
4. Summary

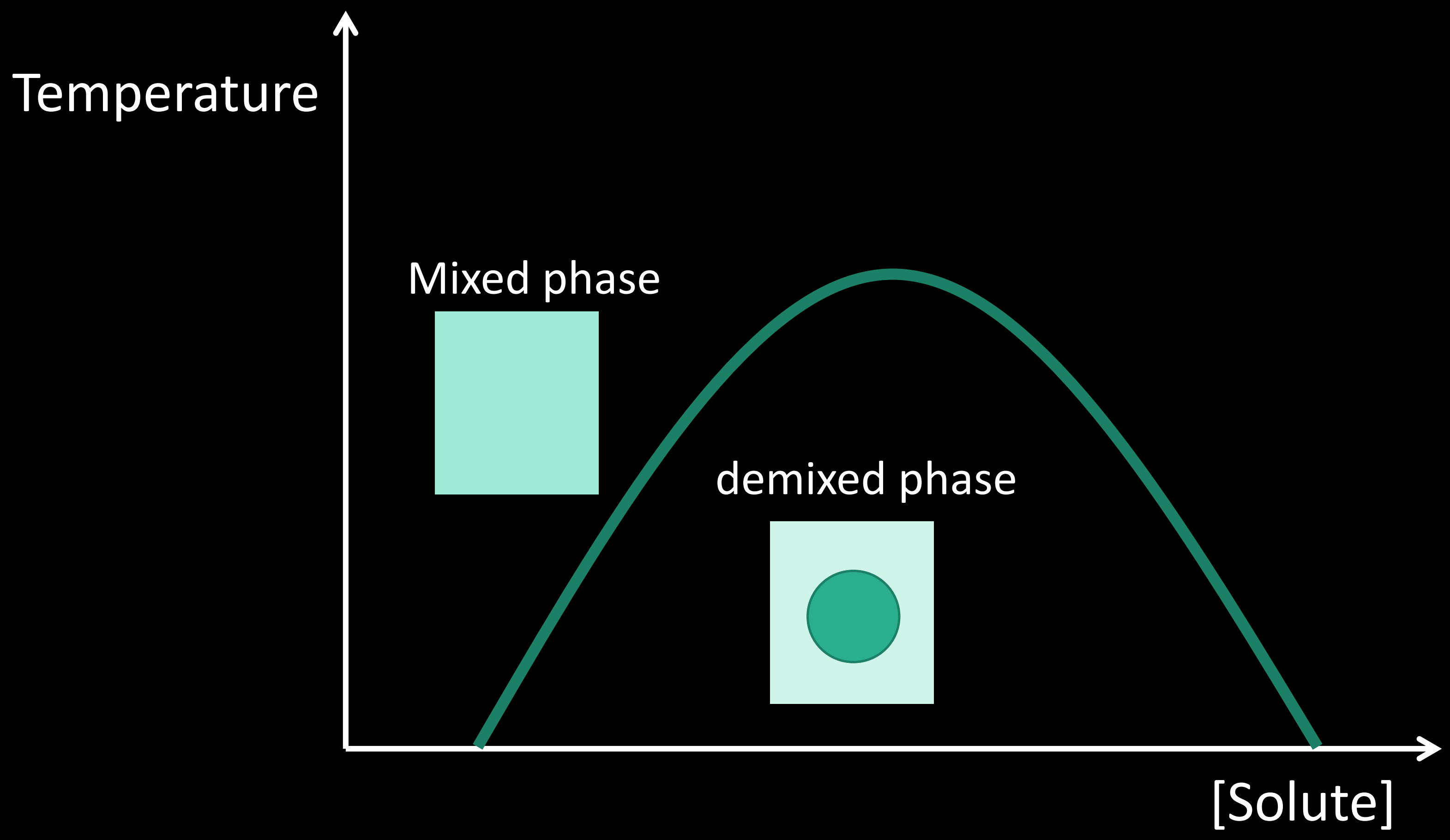
Biology

Physics

Biology

1. Equilibrium (passive) phase separation

Phase diagram

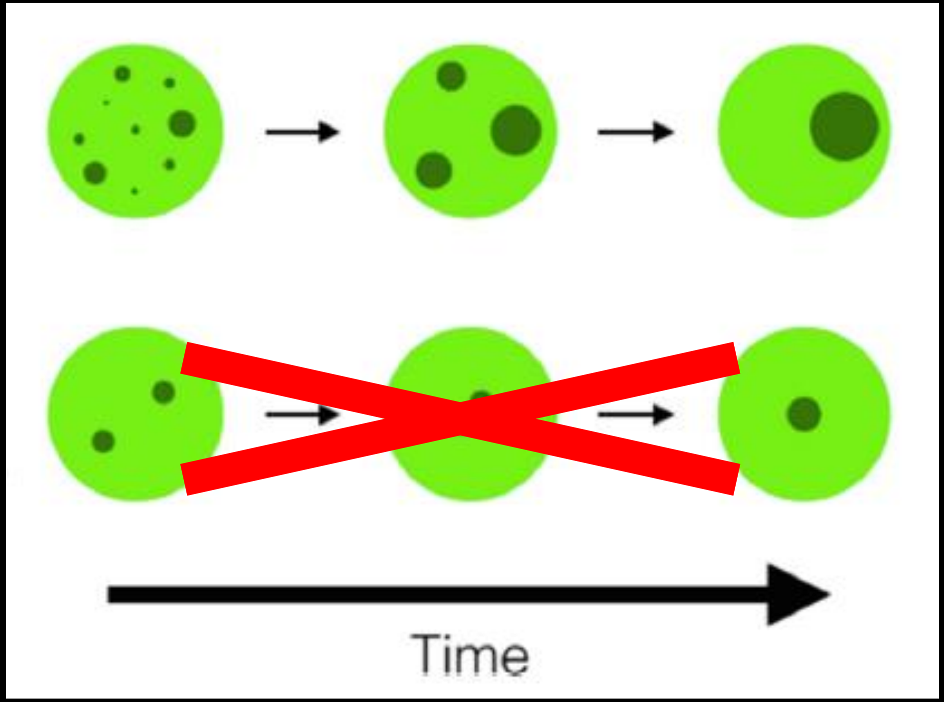


Coarsening

Two mechanisms:

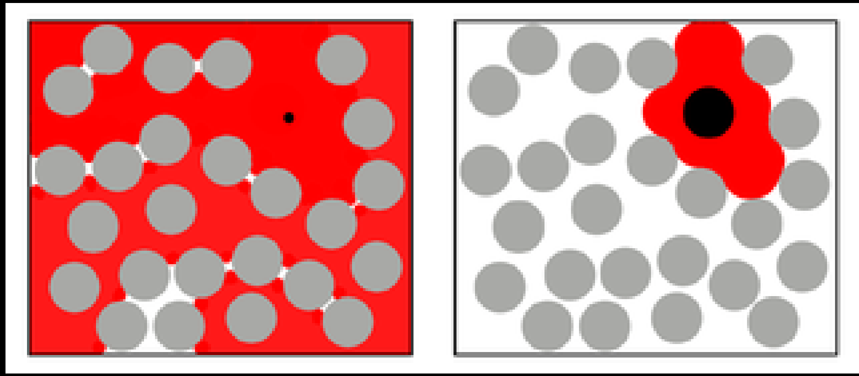
Ostwald ripening

Drop coalescence

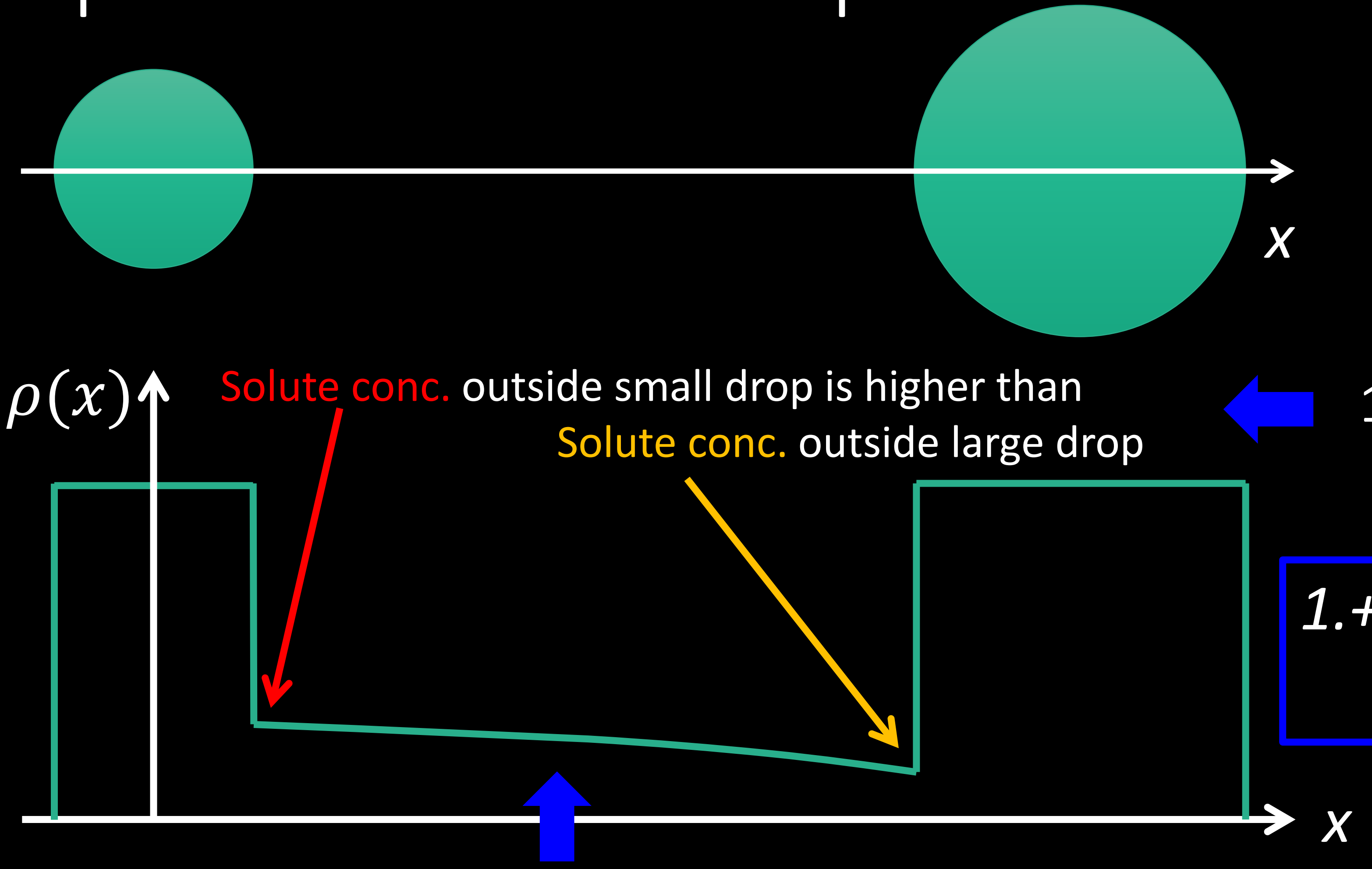


J Berry, C Brangwynne, MP Haataja (2018) Reports on Progress in Physics

Macromolecular crowding -> drops diffuse less as they grow



Ostwald ripening: big drops grow at the expense of small drops



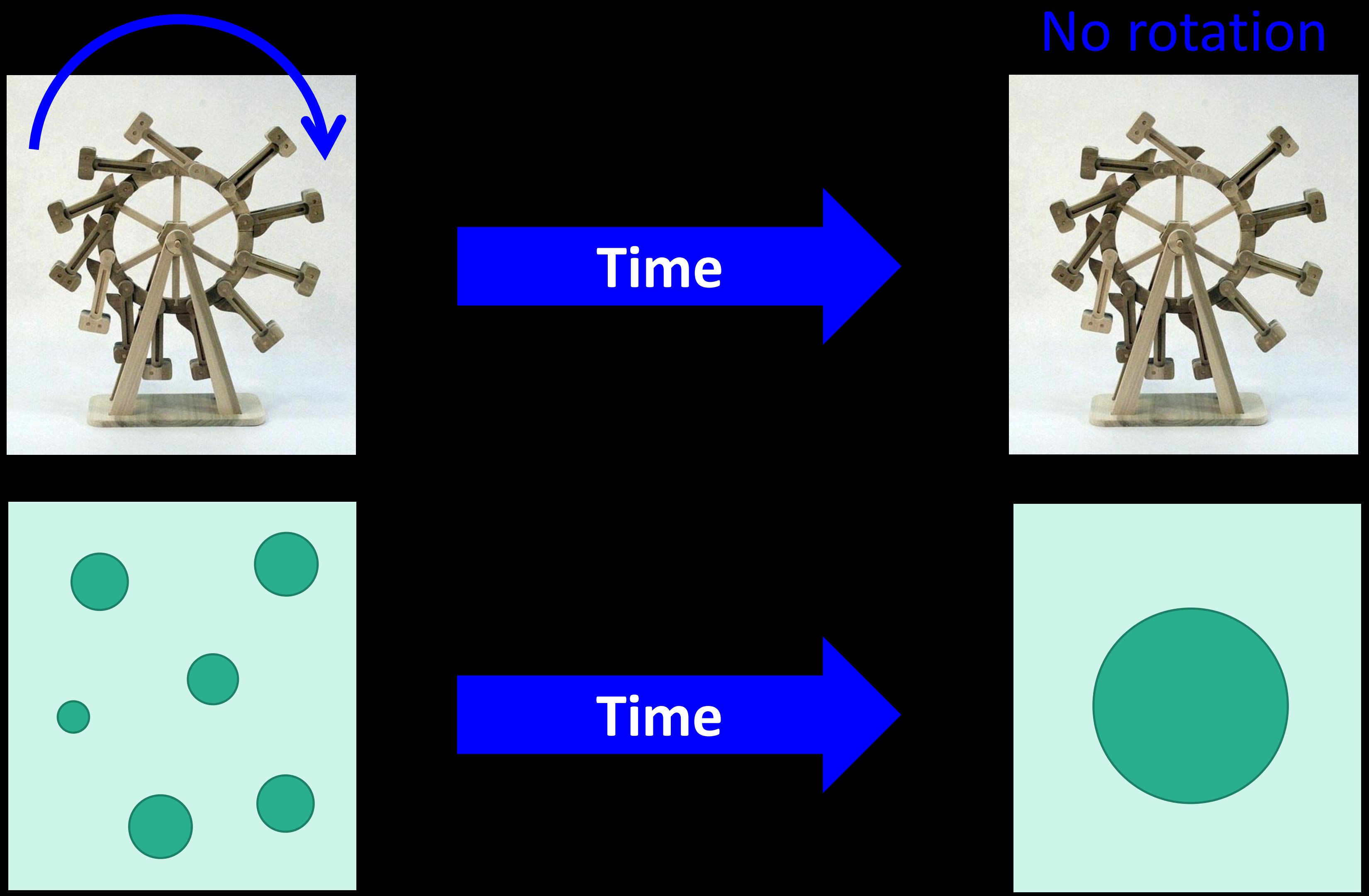
1. Gibbs-Thomson relation

2. Solute diffuses between drops

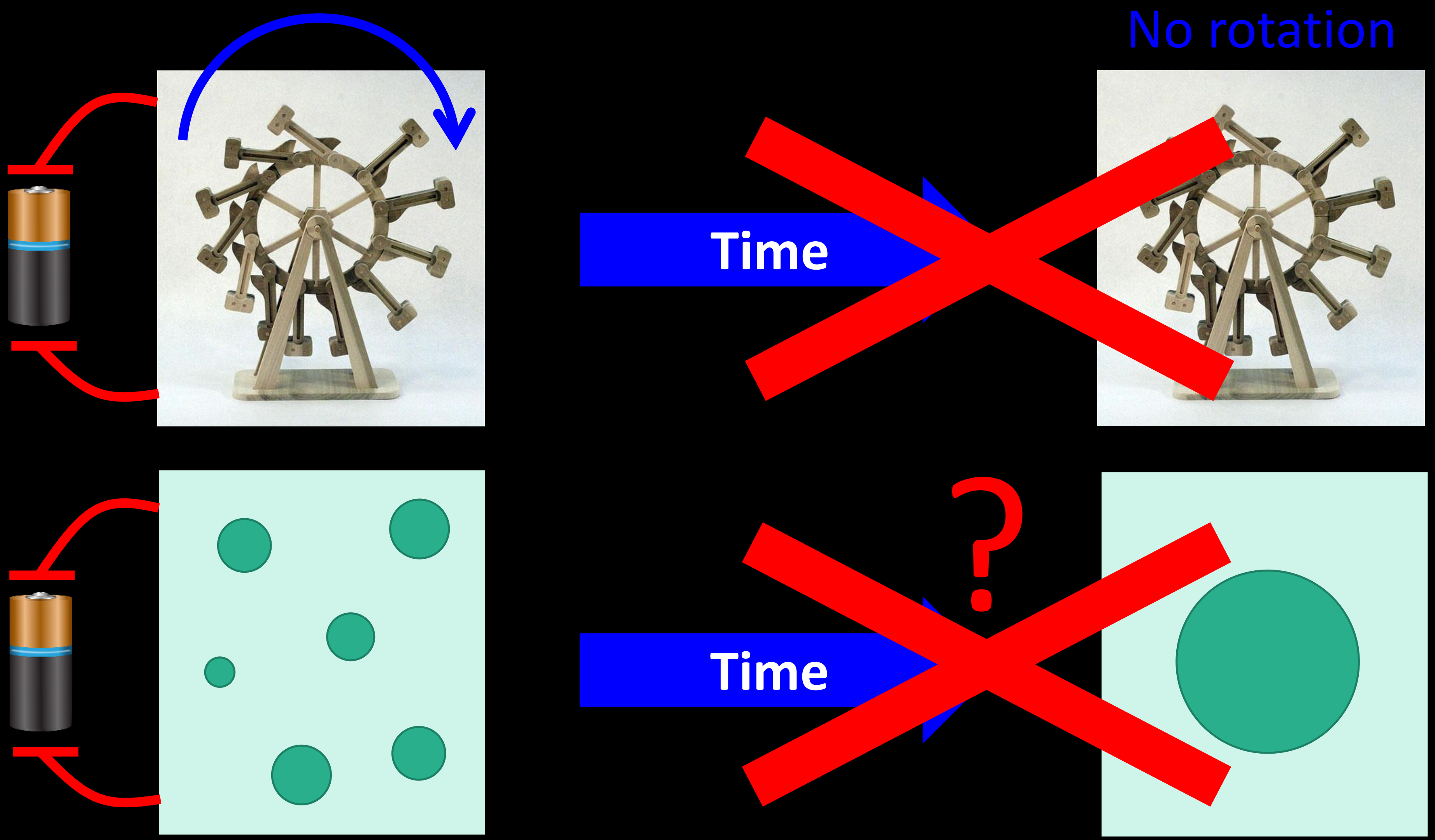
1.+2. -> Ostwald ripening

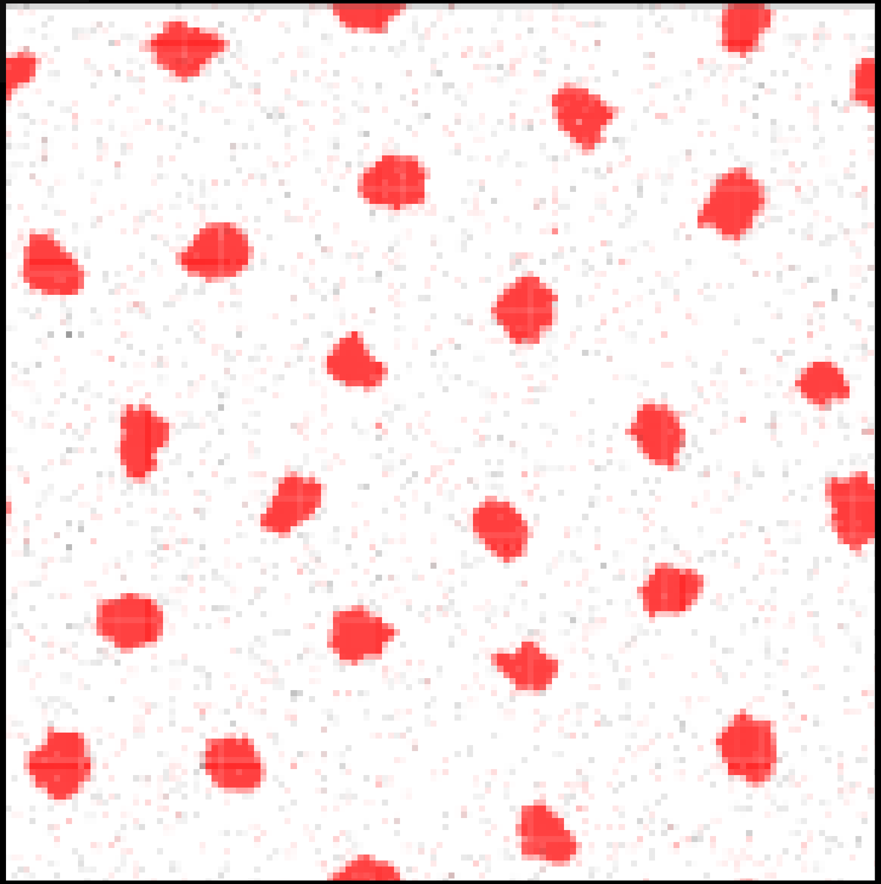
$$\langle R(t)\rangle \sim t^{1/3}$$

Second law of thermodynamics



~~Second law of thermodynamics~~





2. Non-equilibrium (active) phase separation

Two hallmarks of living matter

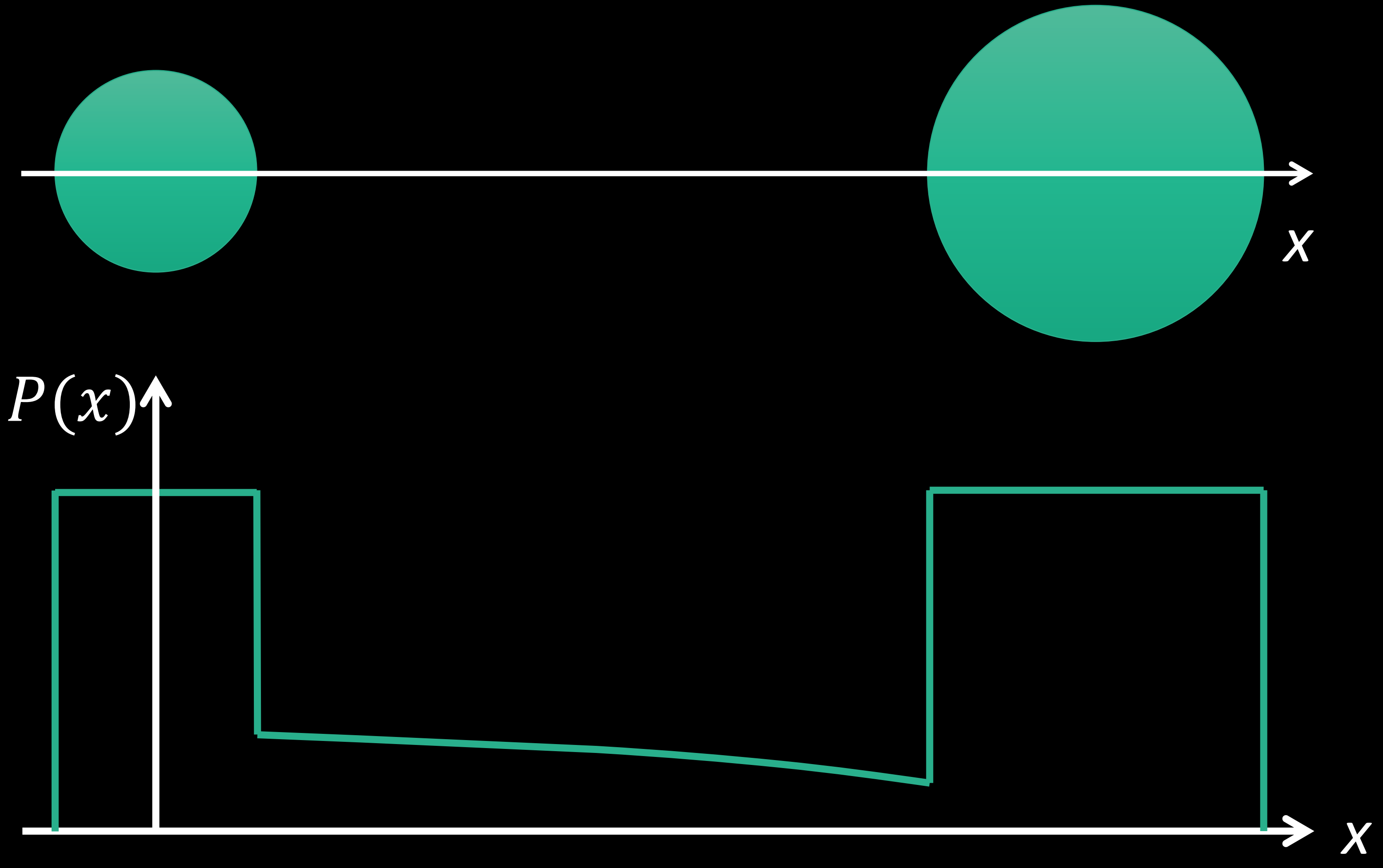
- Driven chemical reactions (e.g., metabolism, ATP-driven phosphorylation)

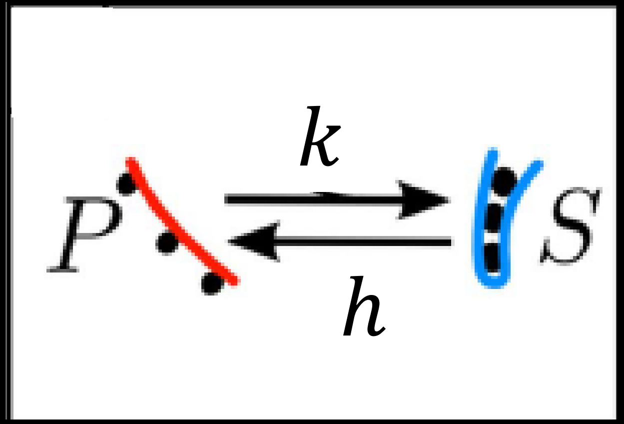
- Self-generated mechanical force (e.g., motility via ATP-driven molecular motors)
  - Motility alone can lead to phase separation

    [J Tailleur & ME Cates (2008) Phys. Rev. Lett.; Y Fily & MC Marchetti (2012) Phys. Rev. Lett.; GS Redner, MF Hagan & A Baskaran (2013) Phys. Rev. Lett.]
  - But the system coarsens as in passive phase separation

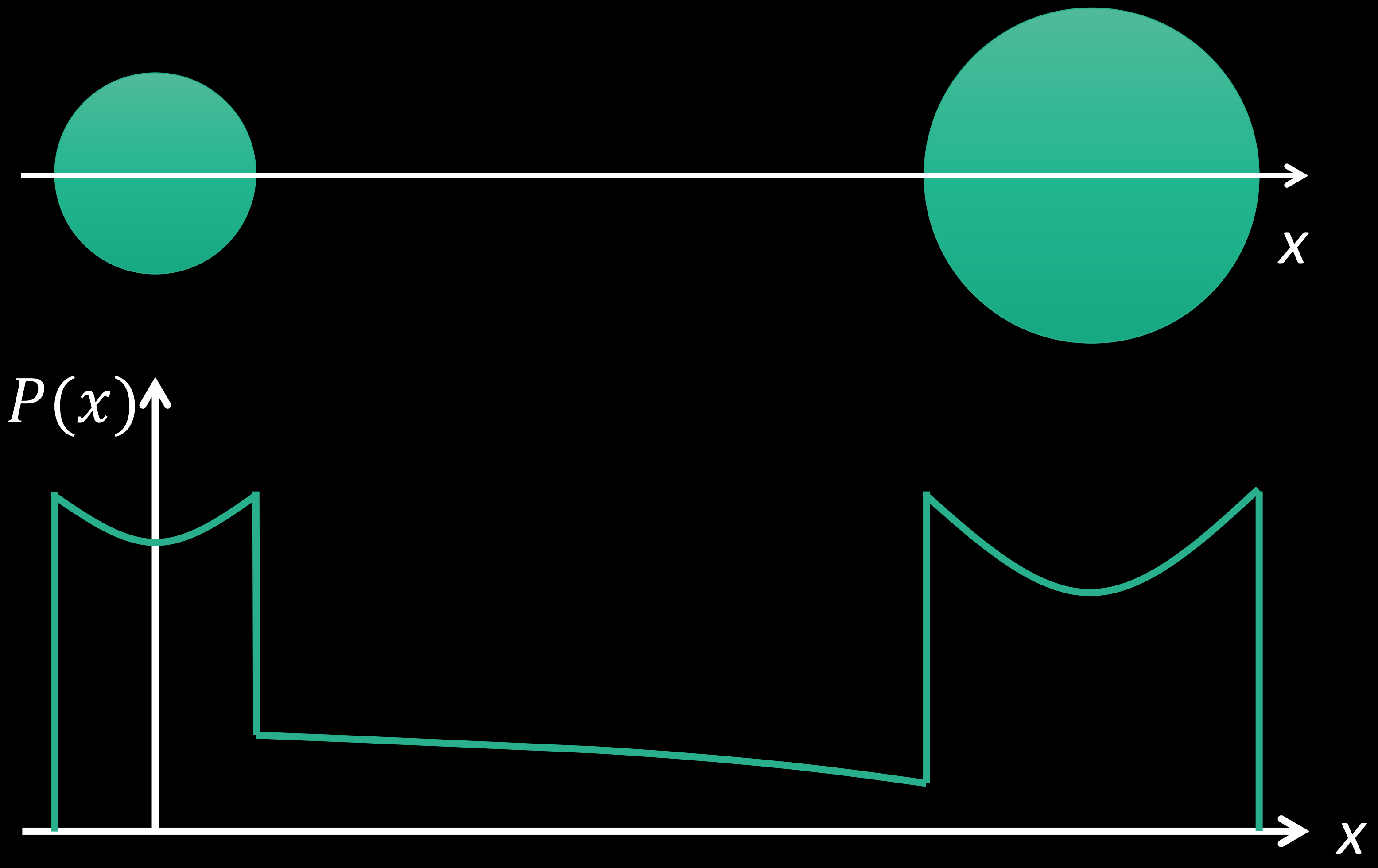
    [CFL (2018) Soft Matter]

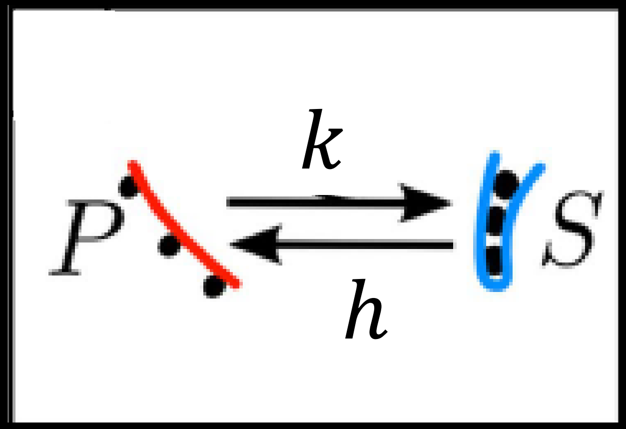
Phase separation with chemical reactions



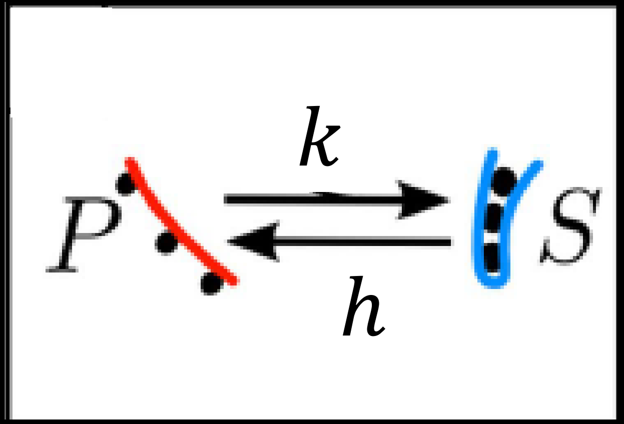


Phase separation with chemical reactions

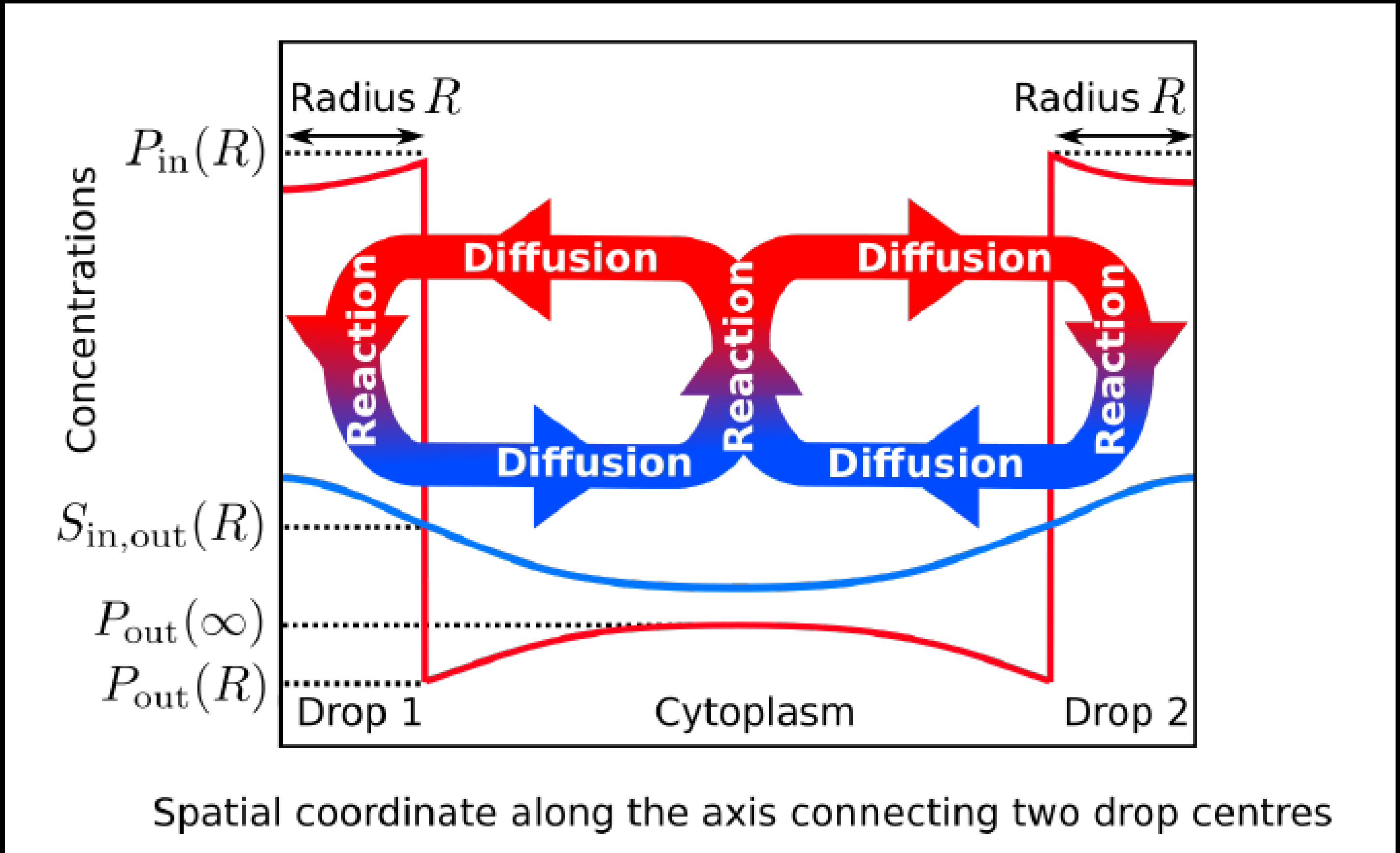




Phase separation with chemical reactions



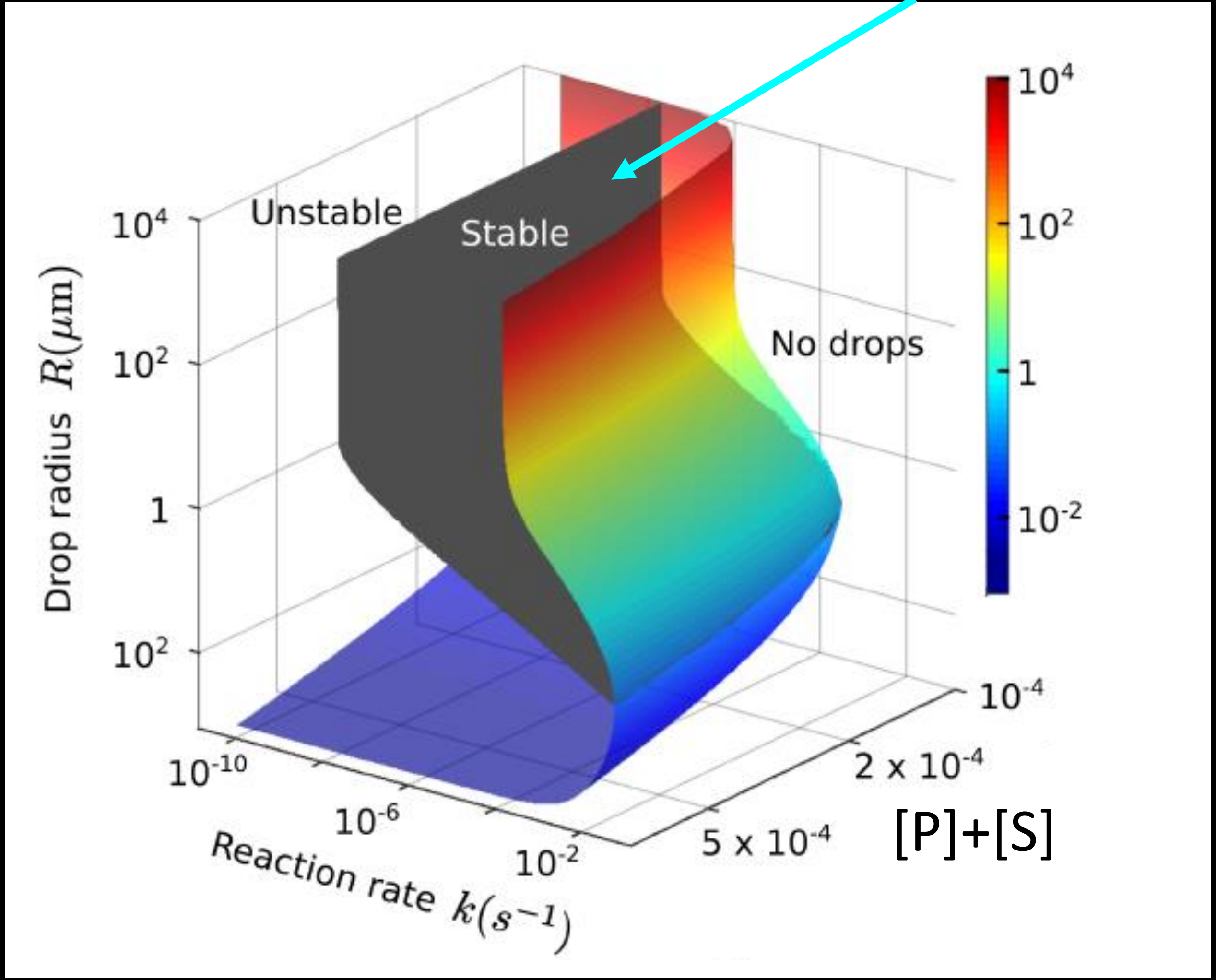
Chemical reaction can stop coarsening



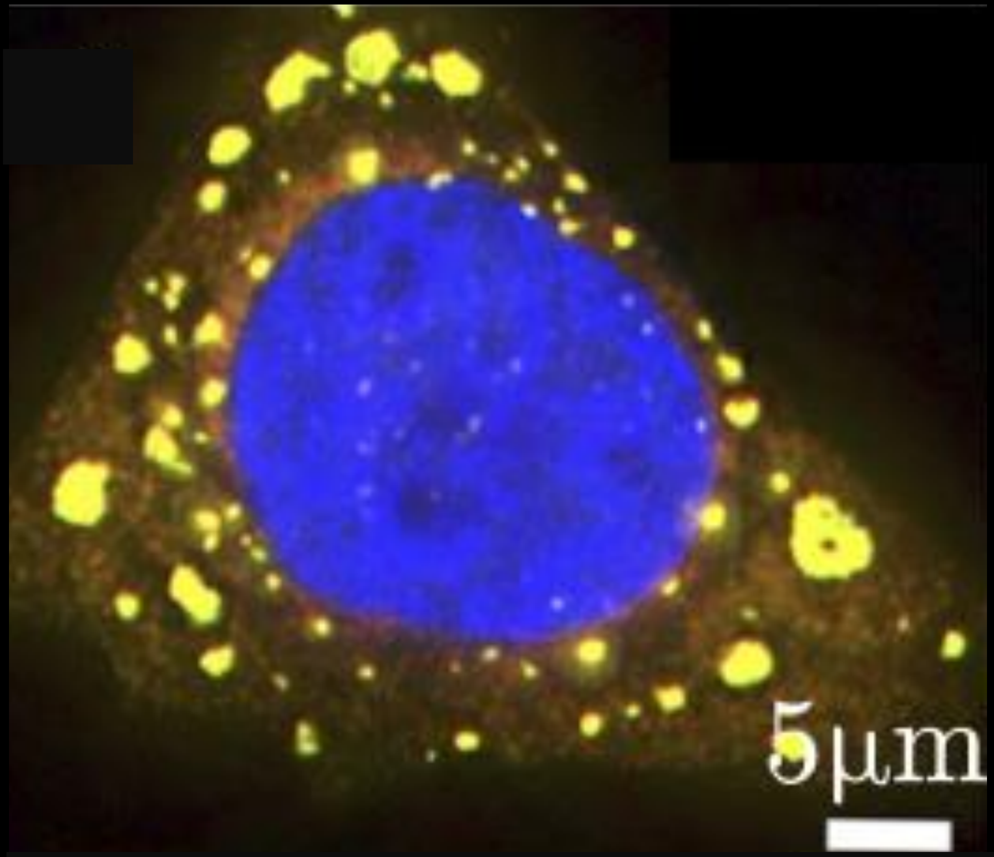
Binary fluids, high solute conc.: SC Glotzer, EA Di Marzio & M Muthukumar (1995) Phys. Rev. Lett.;
Binary fluids, multi-drop system: D Zwicker, AA Hyman & F Jülicher (2015) Phys. Rev. E
Ternay fluids, multi-drop system: JD Wurtz & CFL (2018) Phys. Rev. Lett.

Phase diagram

Stable, multi-drop system



JD Wurtz, CFL (2018) Phys. Rev. Lett.



JR Wheeler et al. (2018) eLife

Implications for stress granule formation

Stress granule formation and dissolution

Interactions Influencing Stress Granule Assembly

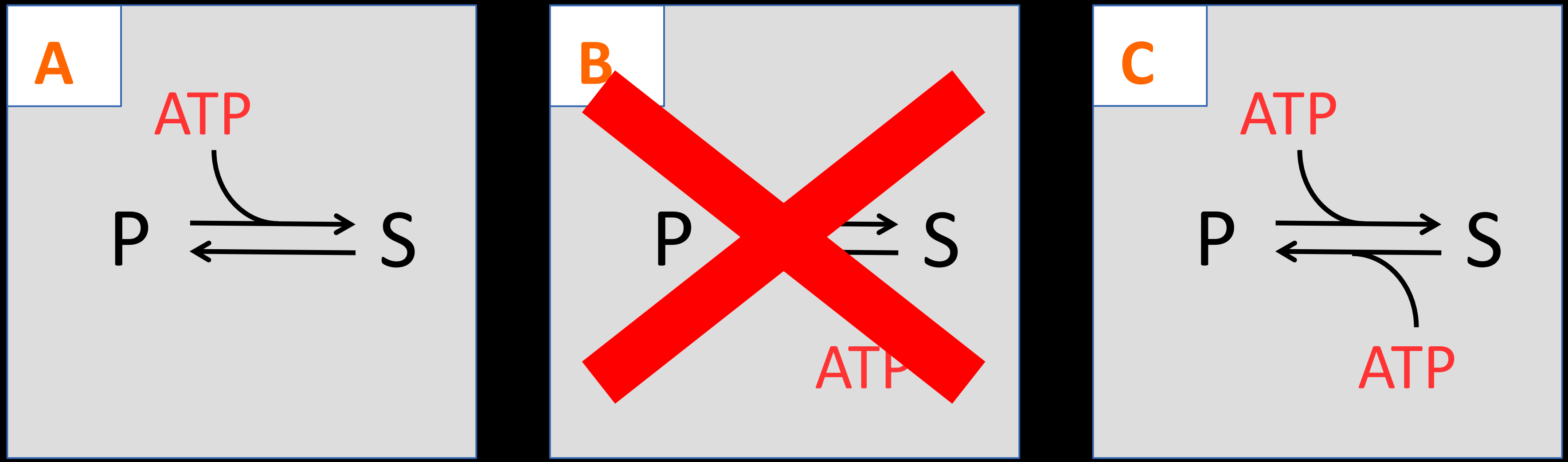
Stress granules assemble when untranslating mRNPs interact through protein–protein interactions between mRNA-binding proteins (Figure 2A). Analyses of the proteomes of yeast and mammalian stress granule cores identified a dense network of protein–protein interactions between stress granule components that could contribute in a redundant manner to stress granule formation [7]. For example, in both mammals and yeast, Atx2/Pbp1 or TIA1/Pub1 proteins promote but are not absolutely required for stress granule assembly [9,27]. The redundancy of interactions suggests that stress granule formation under different conditions can occur by different interactions. For example, the paralogs G3BP1 and G3BP2 play important roles in stress granule formation in mammalian cells in oxidative stress, both by self-interaction [28] and by interaction with the caprin RNA-binding protein [29]. However, during osmotic stress G3BP1/2 and caprin are not required for stress granule formation [30]. Similarly, in yeast Gtr1, Rps1b, and Hgh1 promote stress granule formation during glucose starvation but suppress stress granule formation during heat shock [31]. Therefore, granule assembly is highly redundant and the mechanism of assembly can be context specific. This suggests that granules can assemble differently in response to specific cellular conditions and that stress granules may have different functions for different stresses.

DSW Protter & R Parker (2016)
Trends in Cell Biology

ATP depletion-triggered stress granule formation

Two assumptions

1. ATP-driven conversion(s) between phase separating form (P) and soluble form (S)
2. No SG at normal [ATP], but SG form at 50% [ATP]



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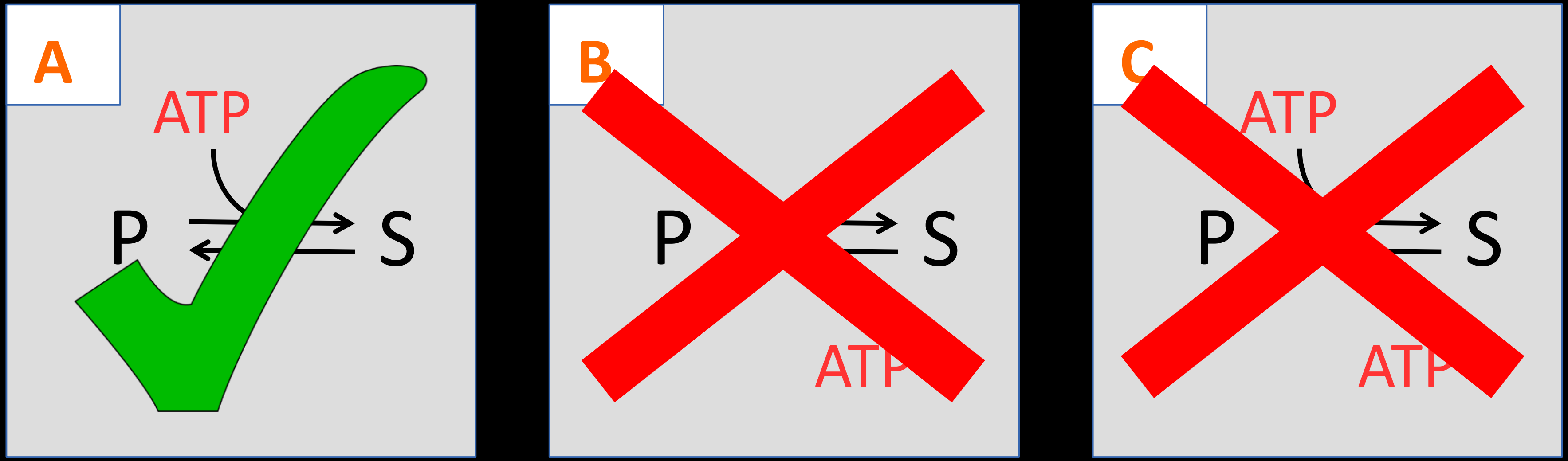
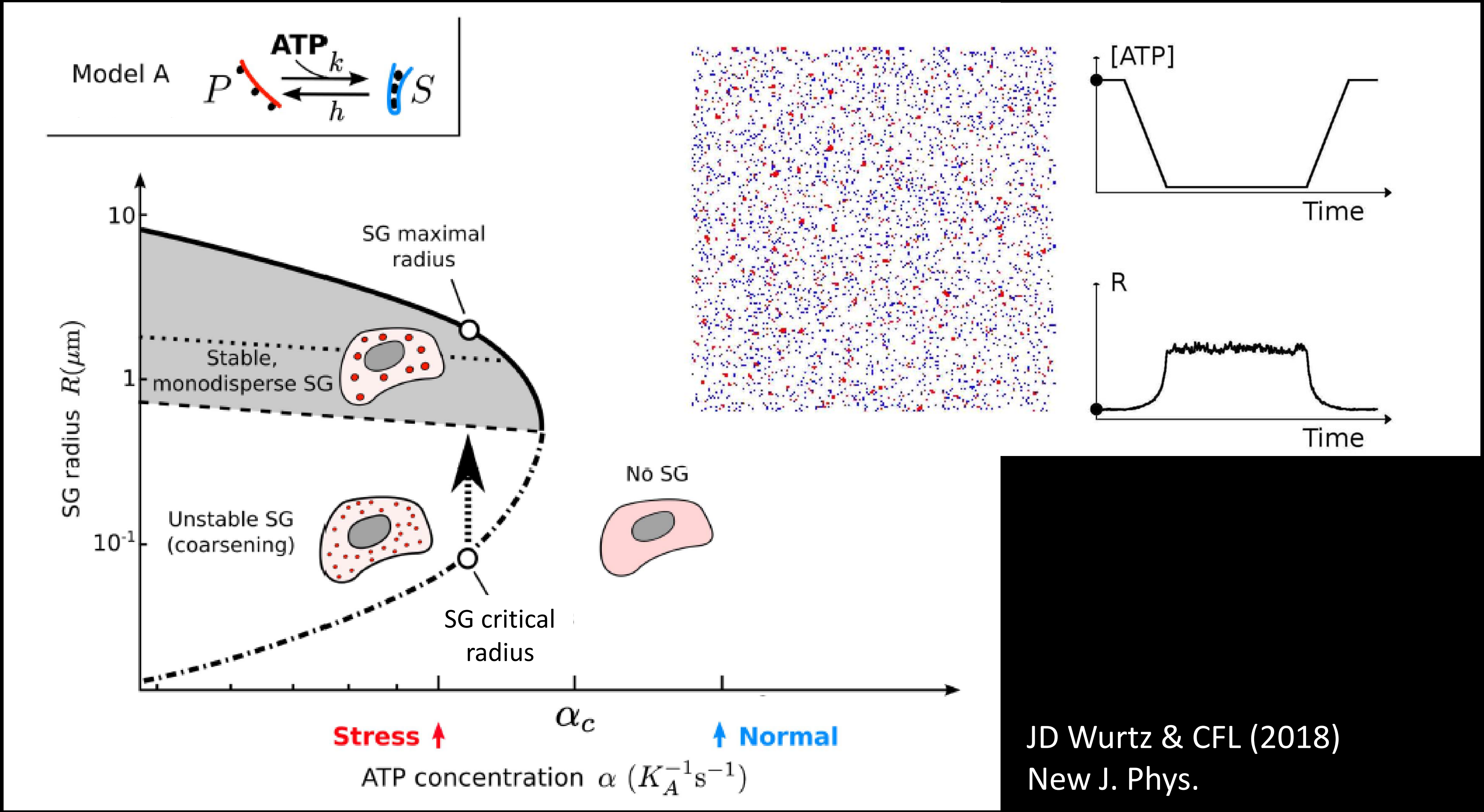


Model C: A 50% drop in [ATP] -> SGs with < 140nm in size

[JD Wurtz & CFL (2018) New J. Phys.]

Poster 162: Stress granule formation via ATP-dependent phase separation



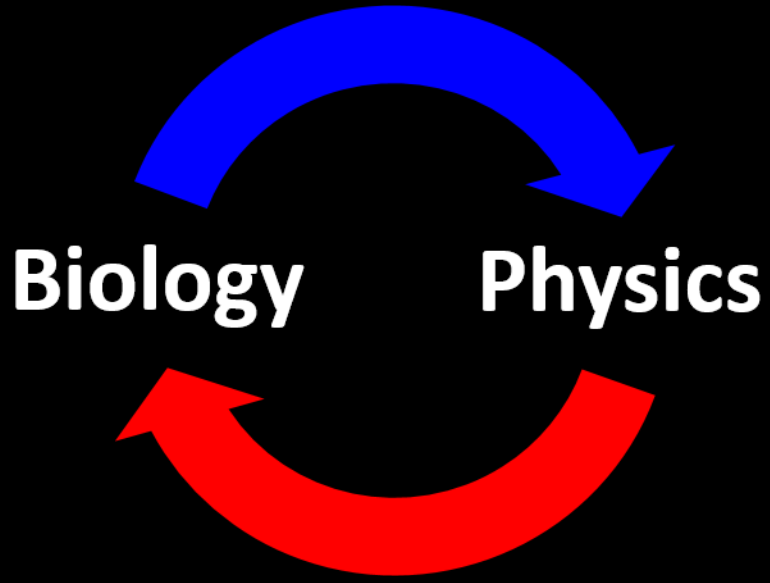
JD Wurtz & CFL (2018)
New J. Phys.

Insurance mechanism

	Cell	**Car**
Normal conditions	ATP consumption	Monthly payment
Stress conditions / Accident	SG formation for free	Insurance coverage

Insurance scheme: SG are tied to unpredictable environment

Summary



- Driven phase separation
  - Chemical reaction can lead to a stable, multidrop system
- ATP depletion-triggered stress granule formation
  - ATP promotes solubility of SG constituents
  - Regulation by crossing phase boundary

Imperial College London

Universality in biology group

Ben Partridge | Jean David Wurtz | David Nesbitt | Andrea Cairoli | Alice Spenlauhauer

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Frank Jülicher (MPI-PKS)
Tony Hyman (MPI-CBG)

Thank you for your attention!

Poster 162: Stress granule formation via ATP-dependent phase separation