Active Phase Separation in Biology

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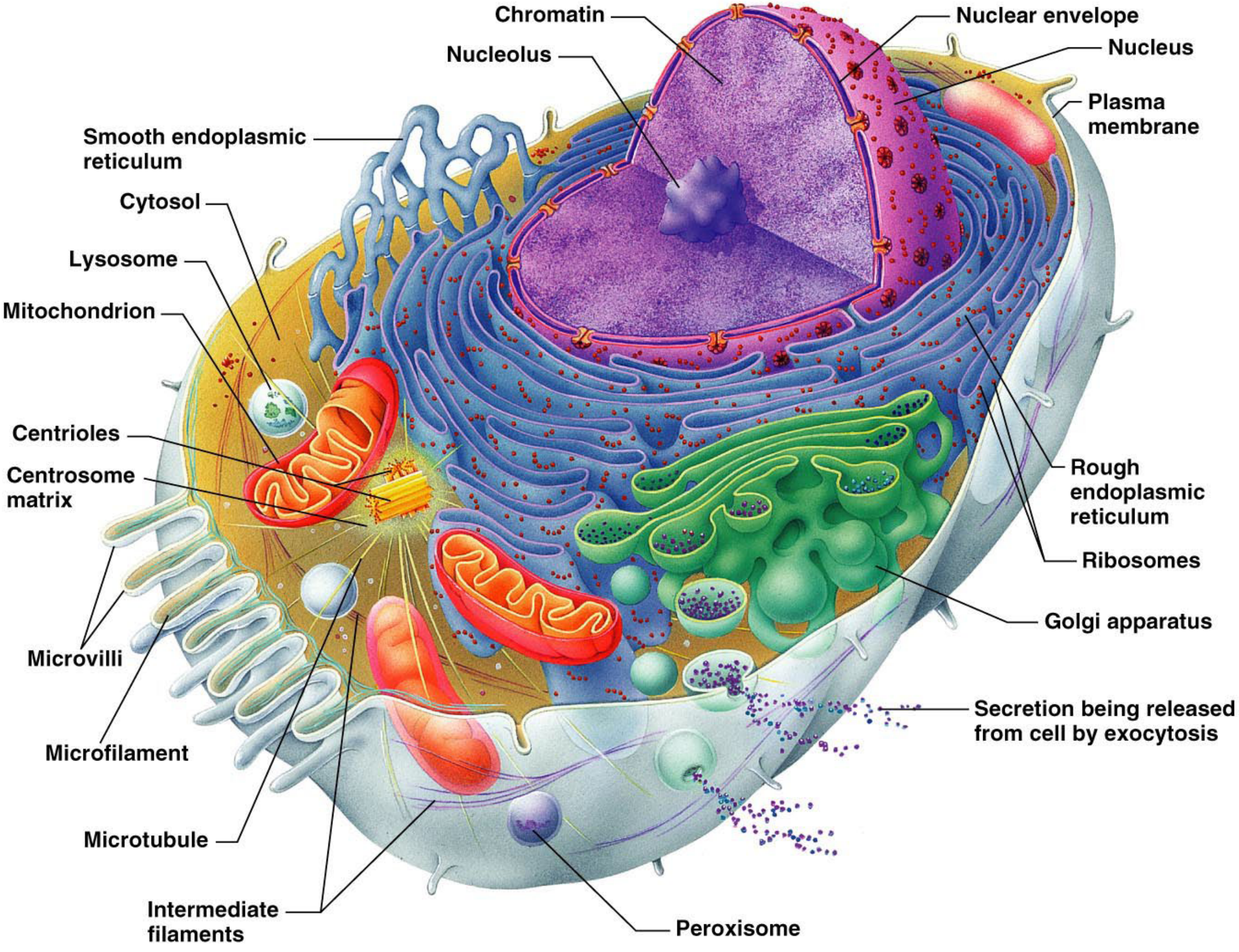
Zwicker Group
Theory of Biological Fluids

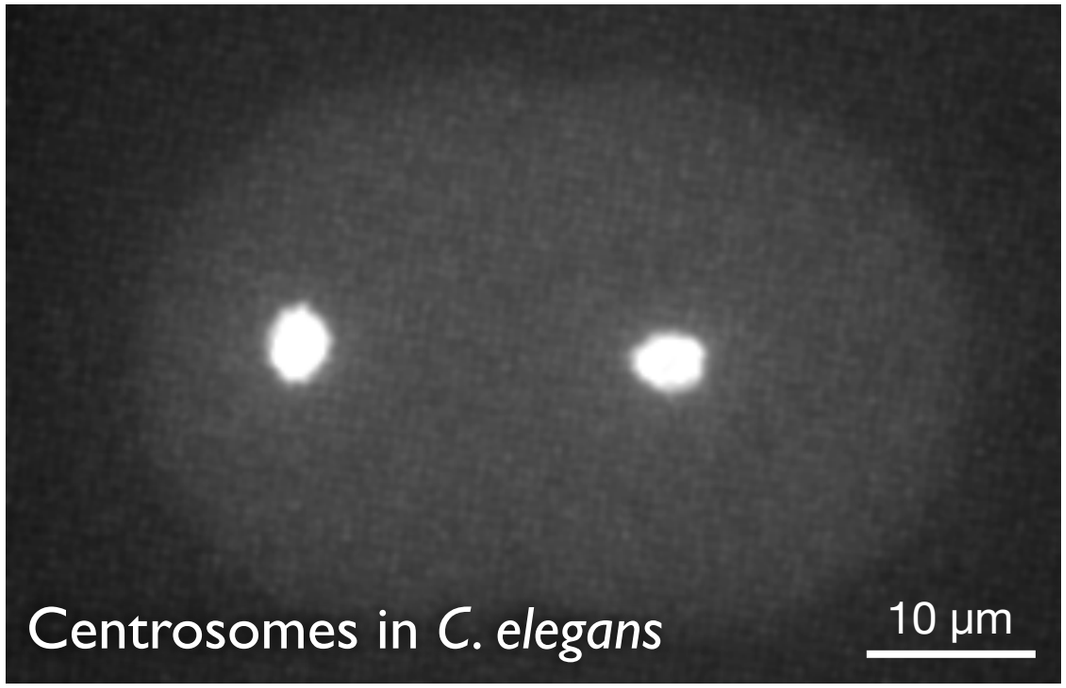
Max Planck Institute for Dynamics and Self-Organization

MAX-PLANCK-GESELLSCHAFT



Pearson Education, Inc., Upper Saddle River, NJ

Membrane-less organelles are biomolecular condensates



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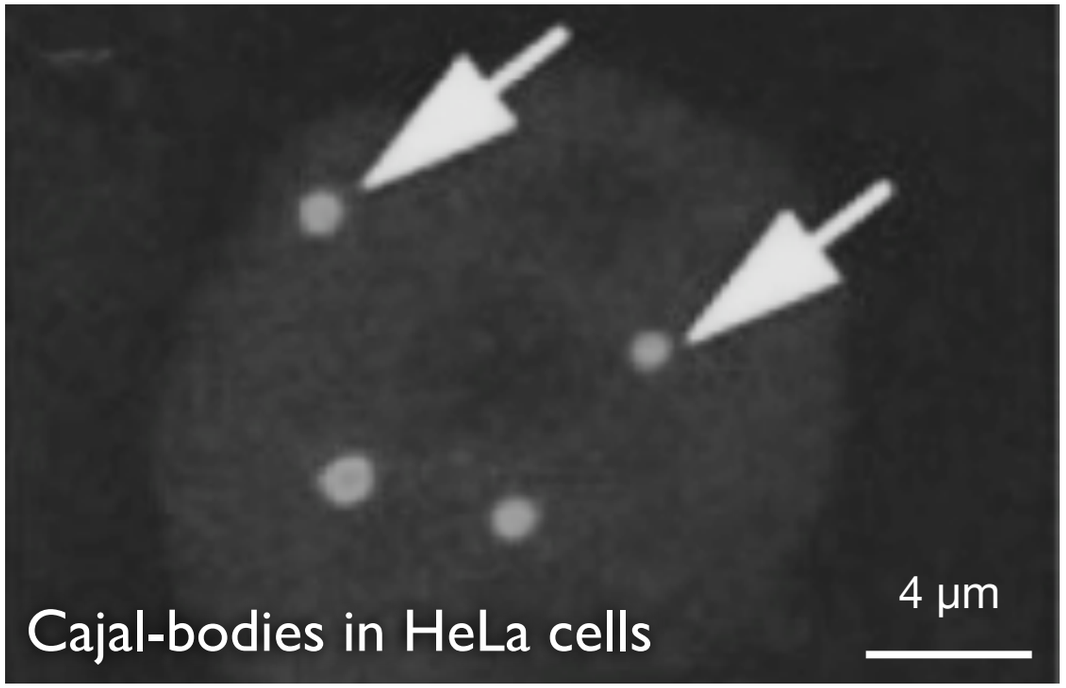

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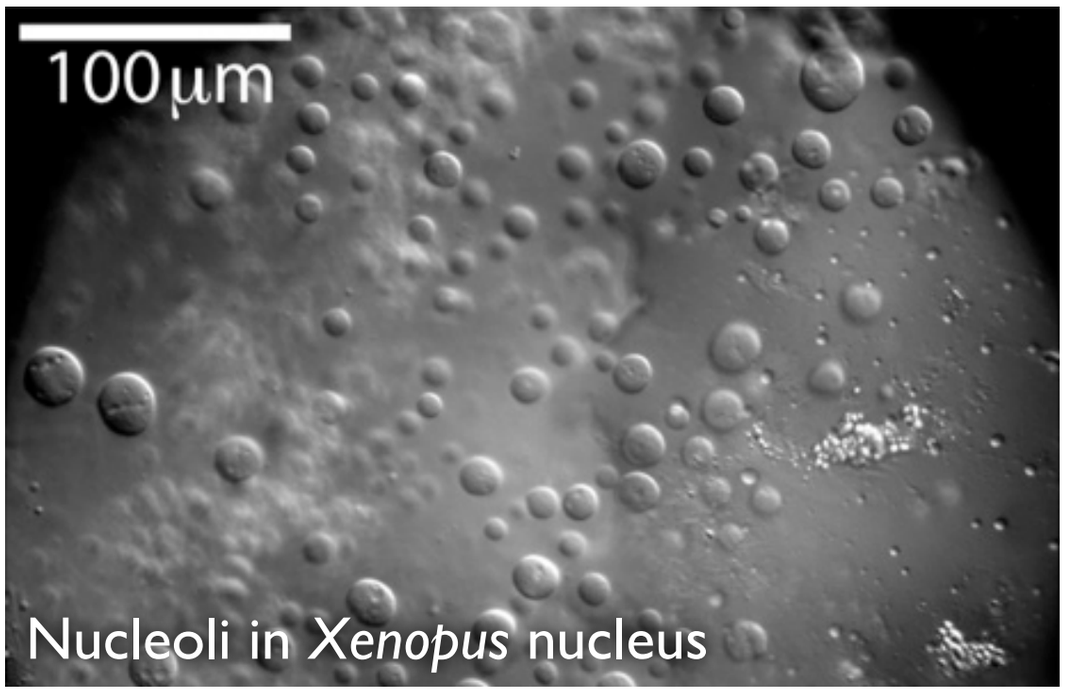

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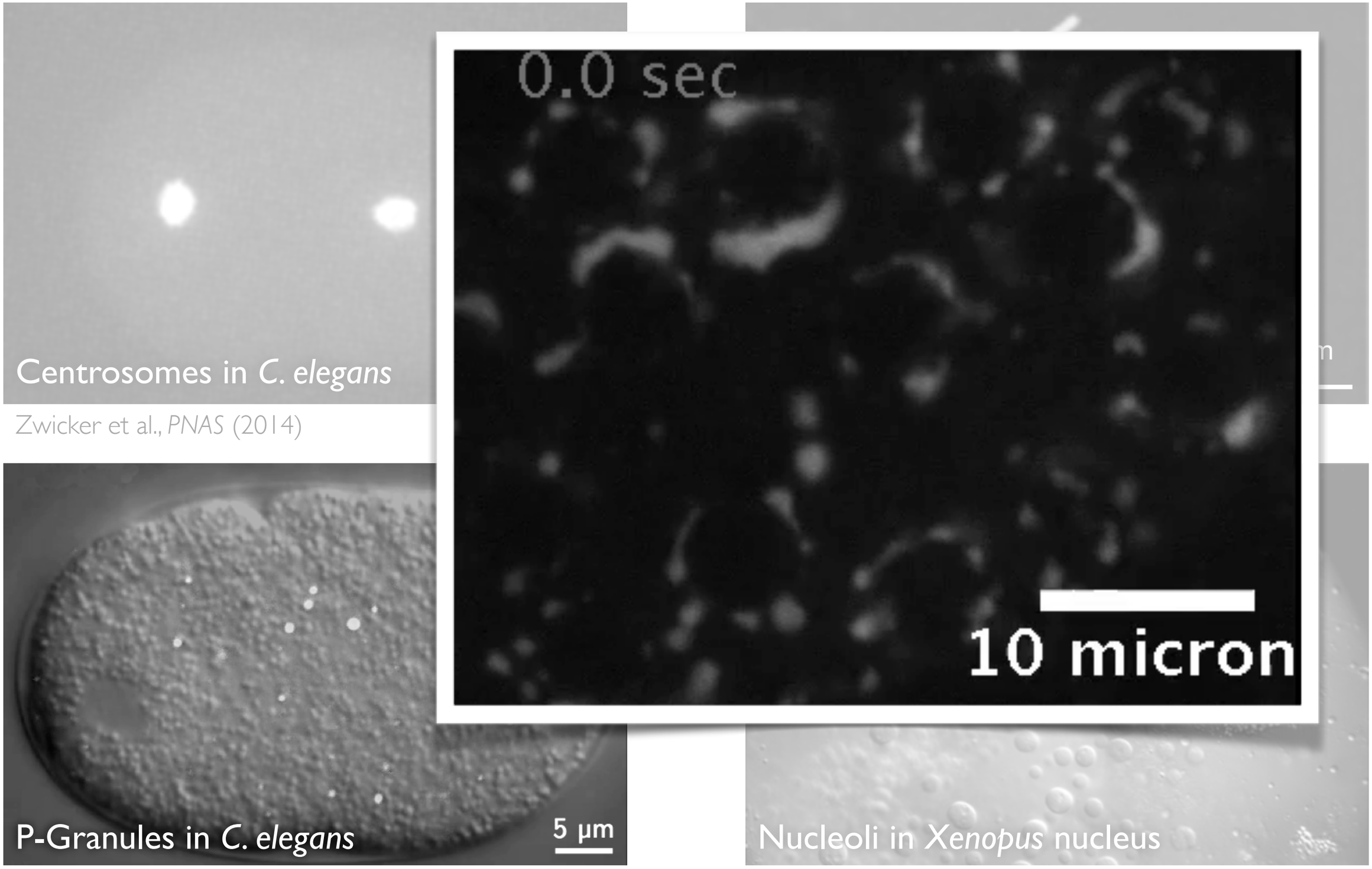

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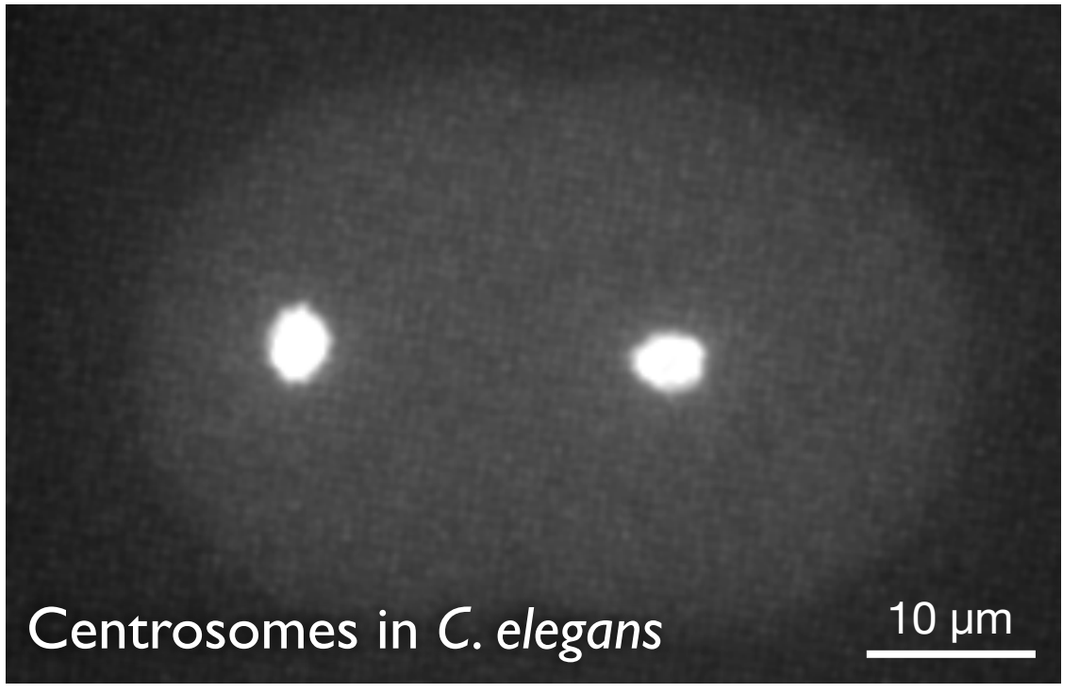

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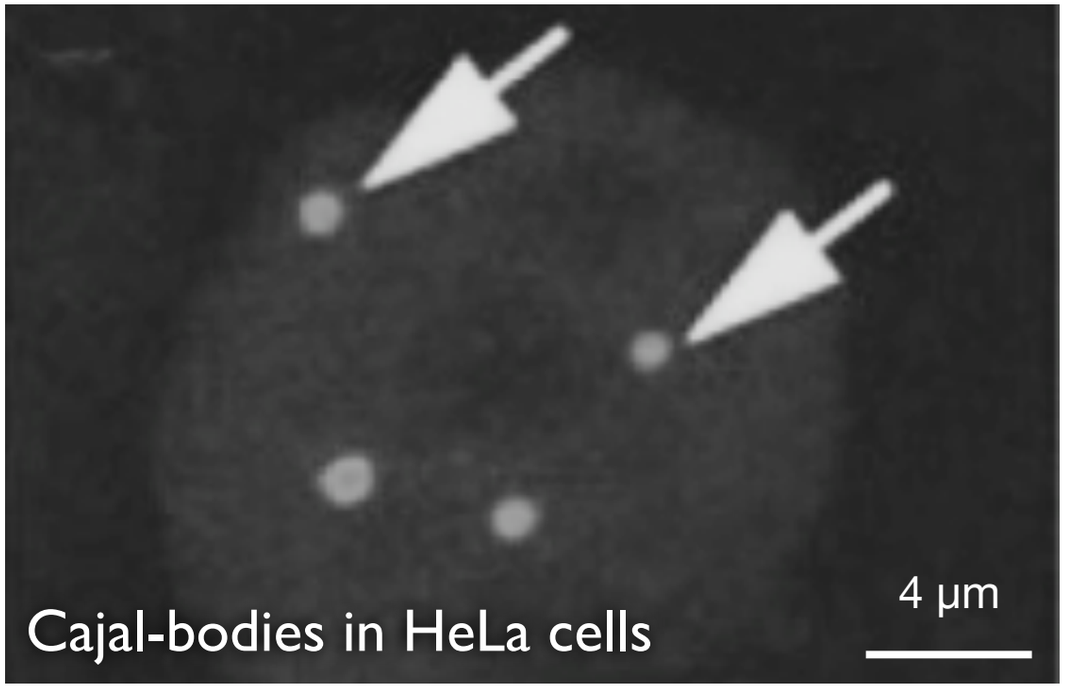

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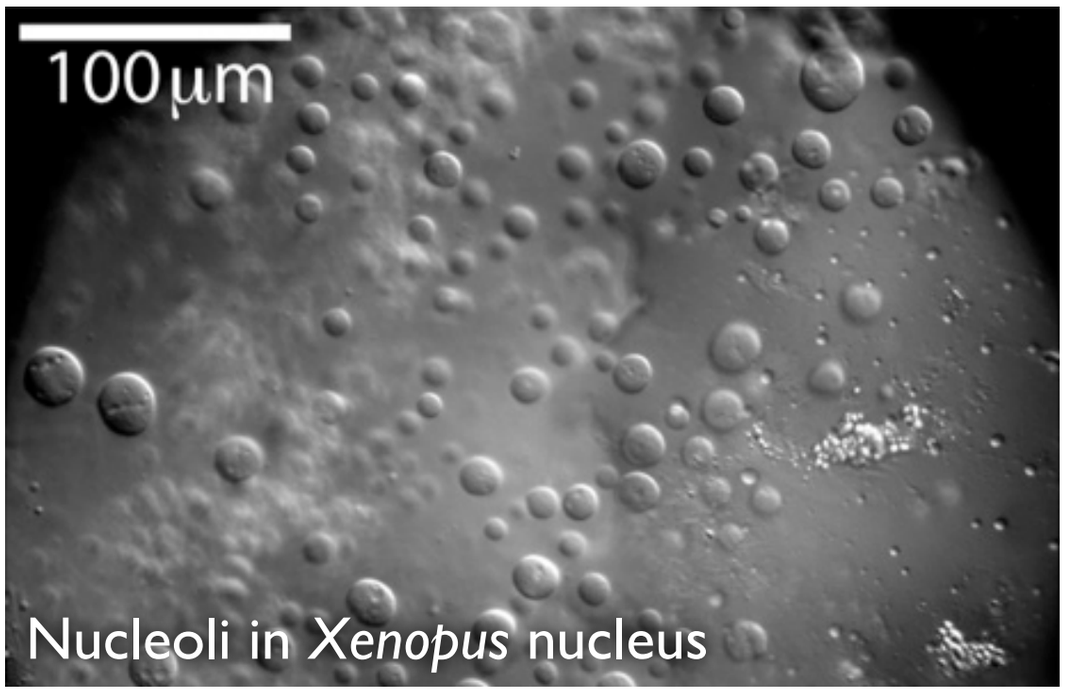

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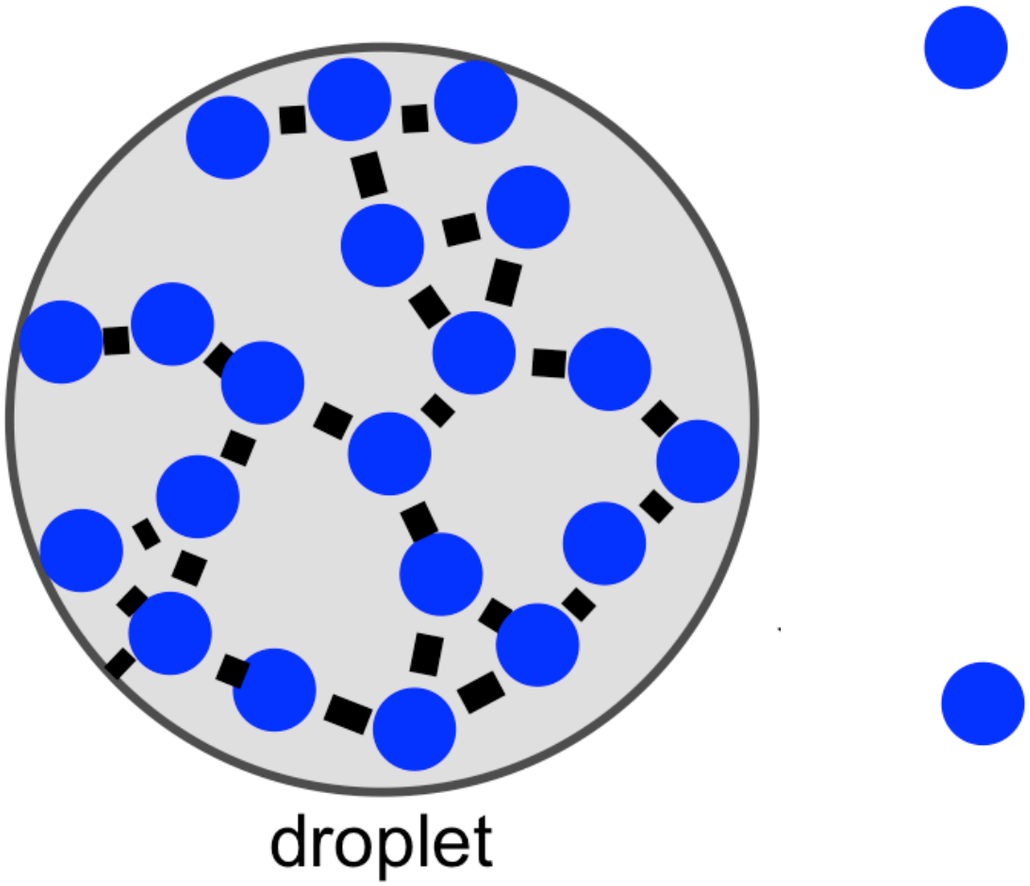
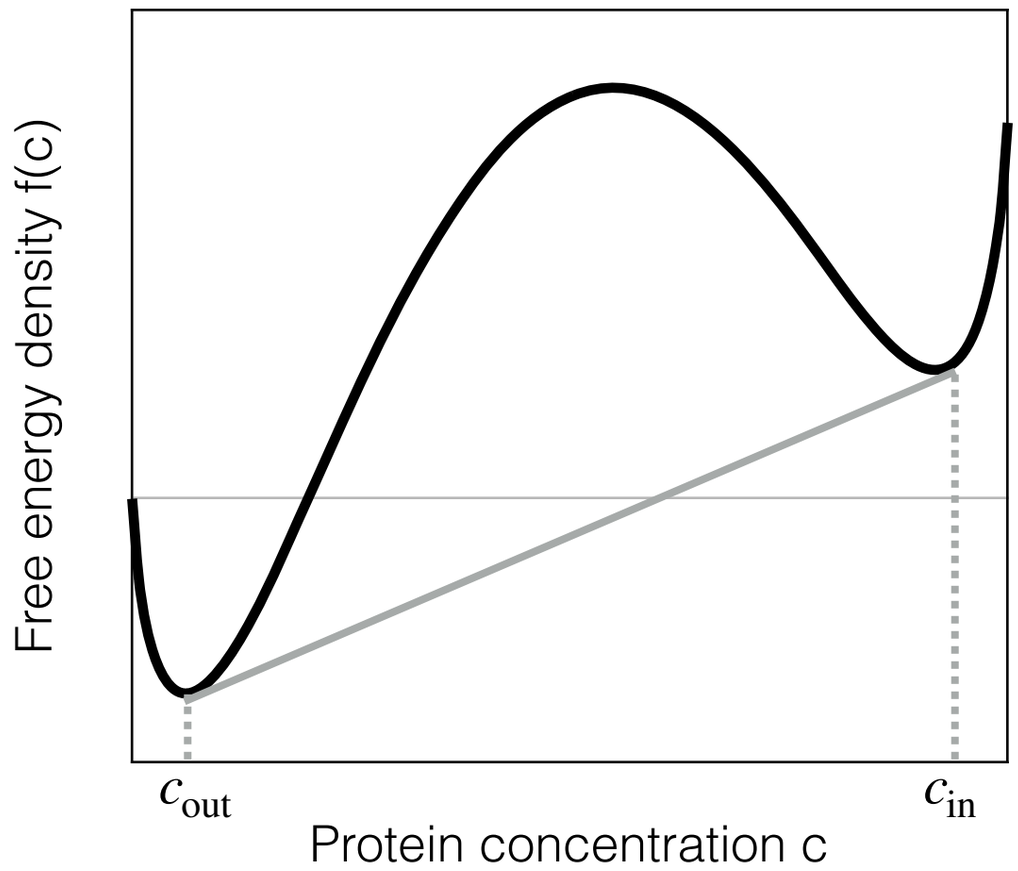
Surface tension implies round droplets



protein

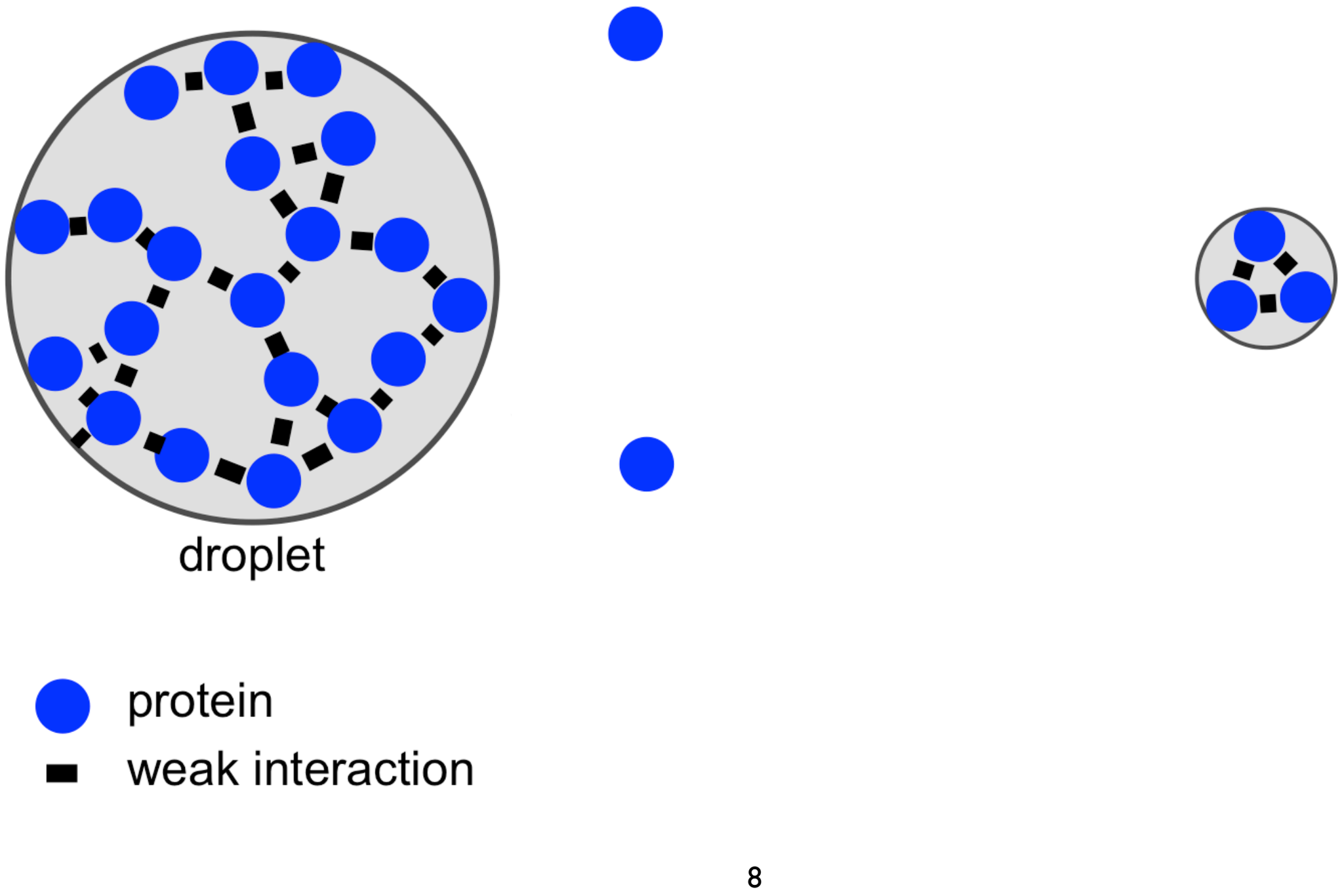
weak interaction



Free energy of the system:

$$F = Vf(c_{\text{in}}) + (V_{\text{sys}} - V)f(c_{\text{out}}) + \gamma A$$

Surface tension drives fluxes between droplets



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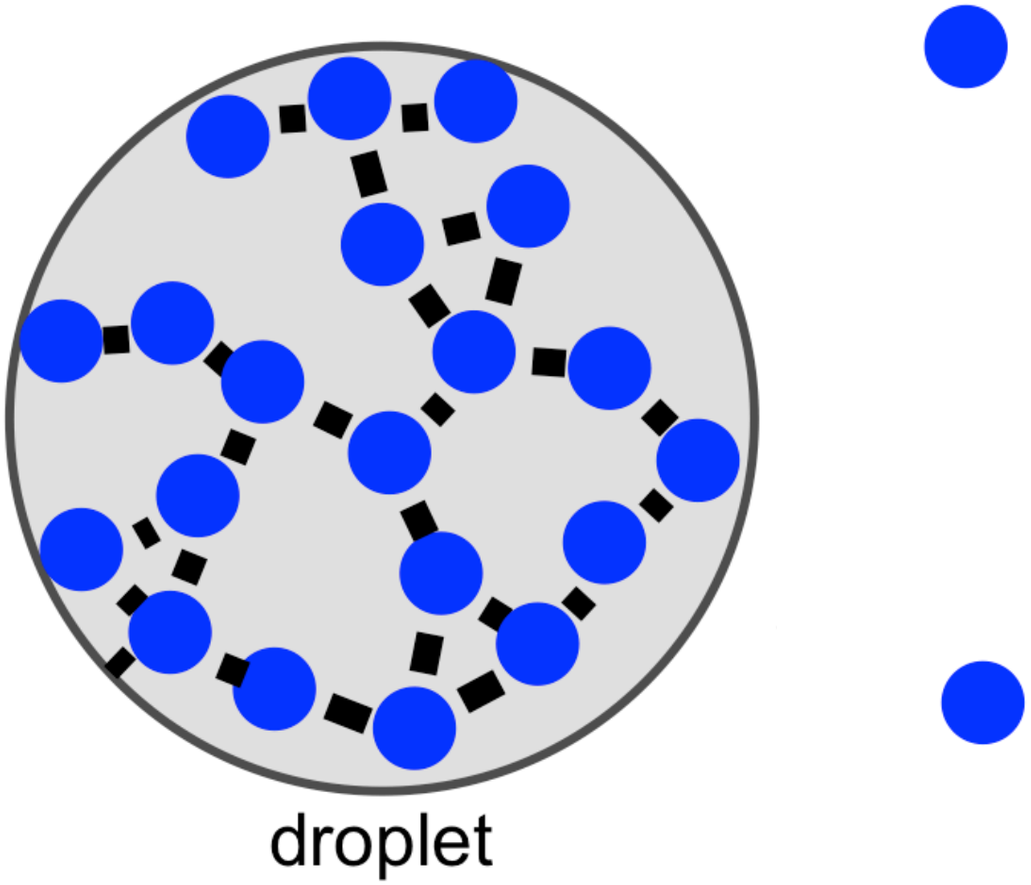


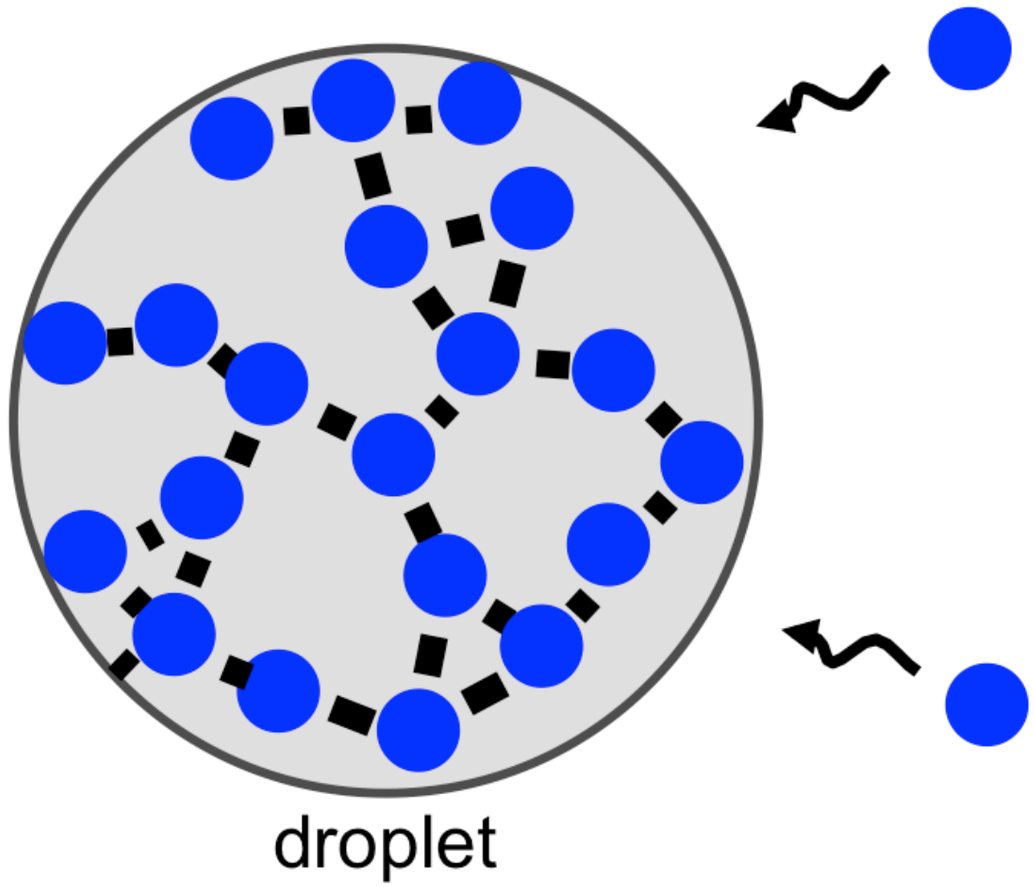
$$c_{\mathrm{out}}^{\mathrm{eq}} = c_{\mathrm{out}}^{(0)}\left(1 + \frac{\ell_c}{R}\right)$$

ℓ_c … Capillary length

protein

weak interaction

Surface tension drives fluxes between droplets



$$c_{\text{out}}^{\text{eq}} = c_{\text{out}}^{(0)}\left(1 + \frac{\ell_c}{R}\right)$$

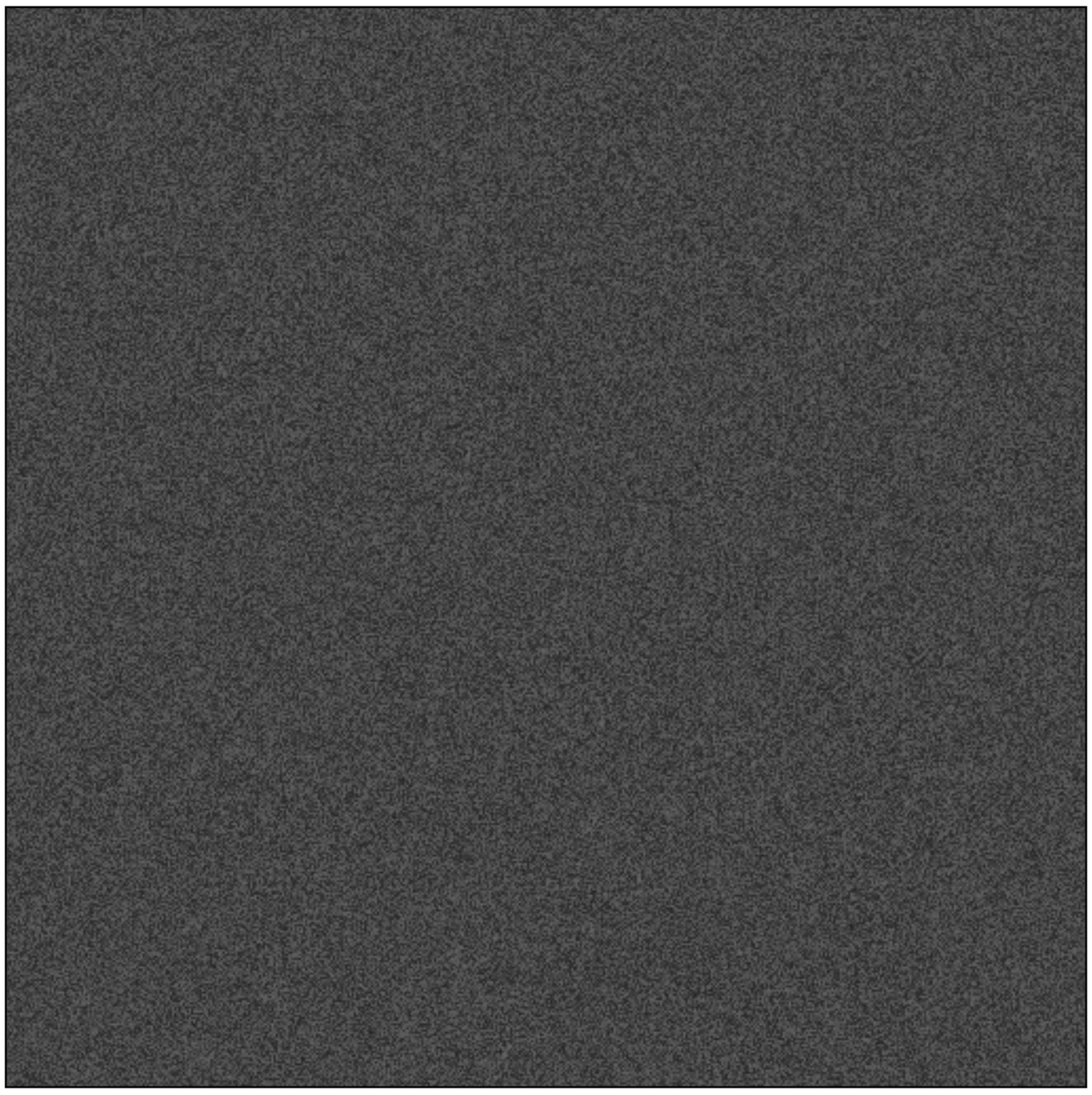
ℓ_c … Capillary length

protein

weak interaction

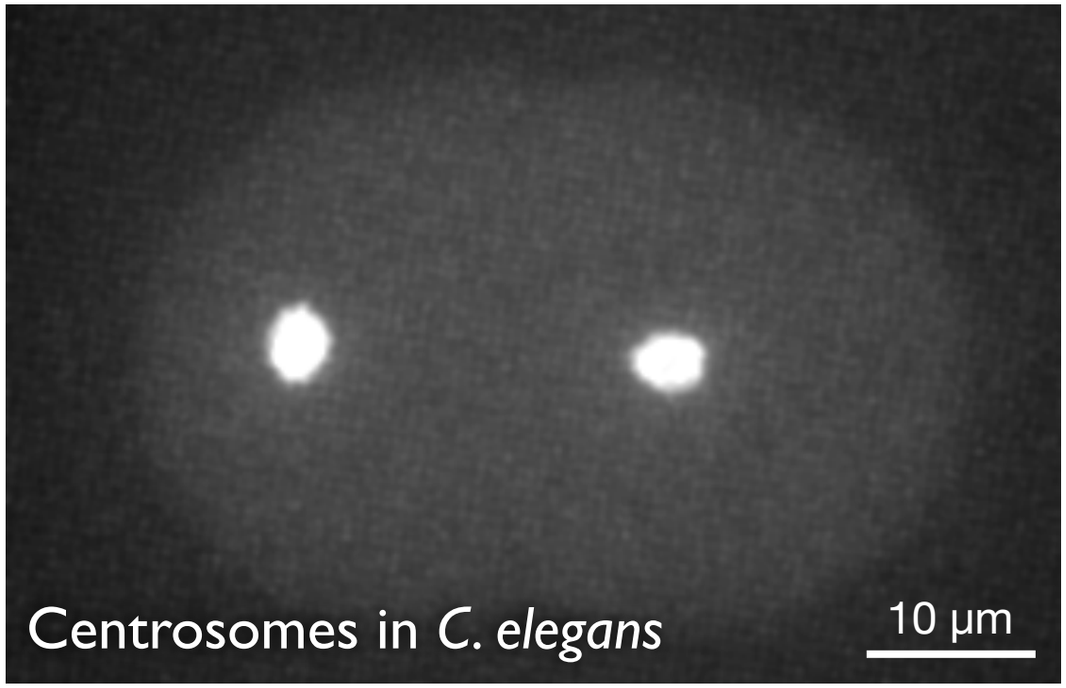
diffusive net flux

Classical droplets exhibit coarsening



Numerical simulation of Cahn-Hilliard equation in 2D

Membrane-less organelles are biomolecular condensates



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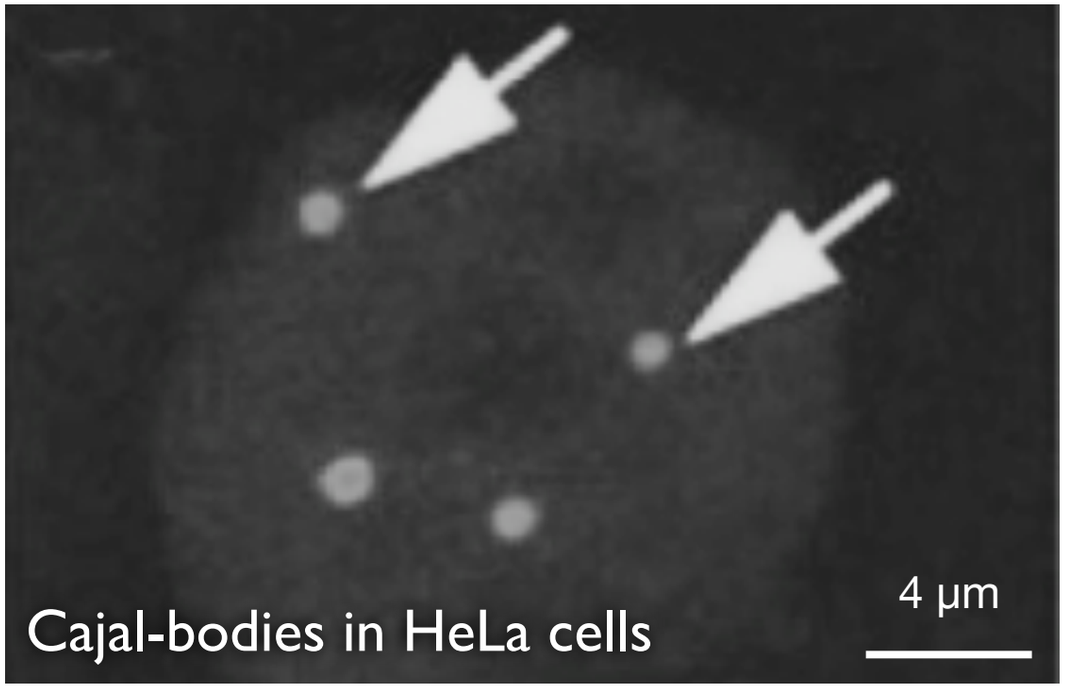

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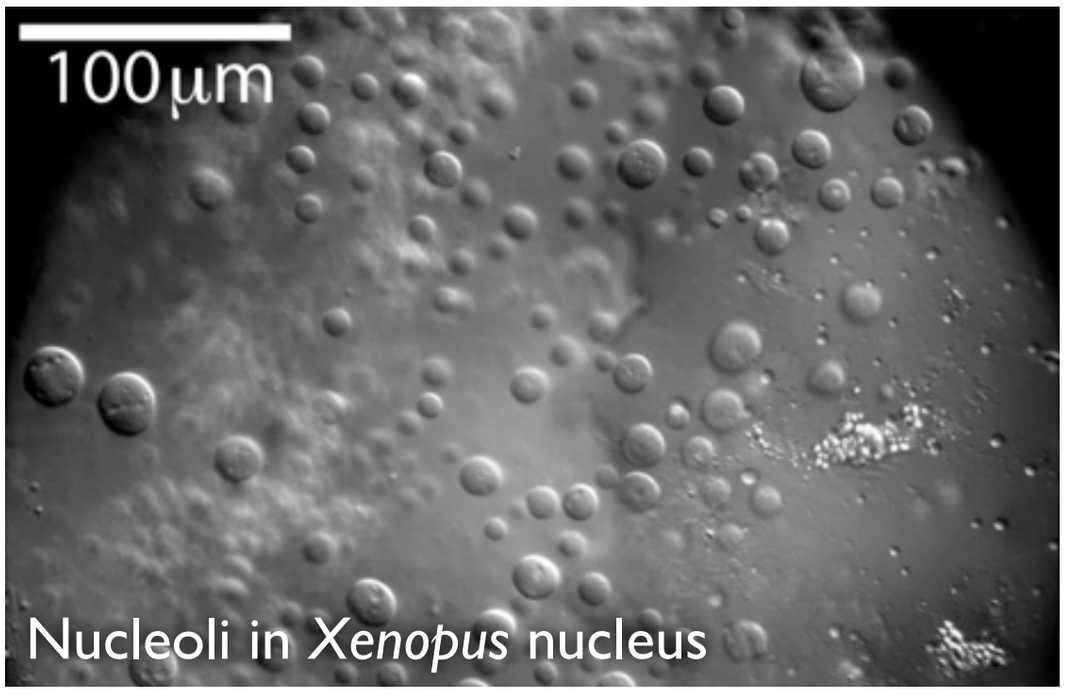

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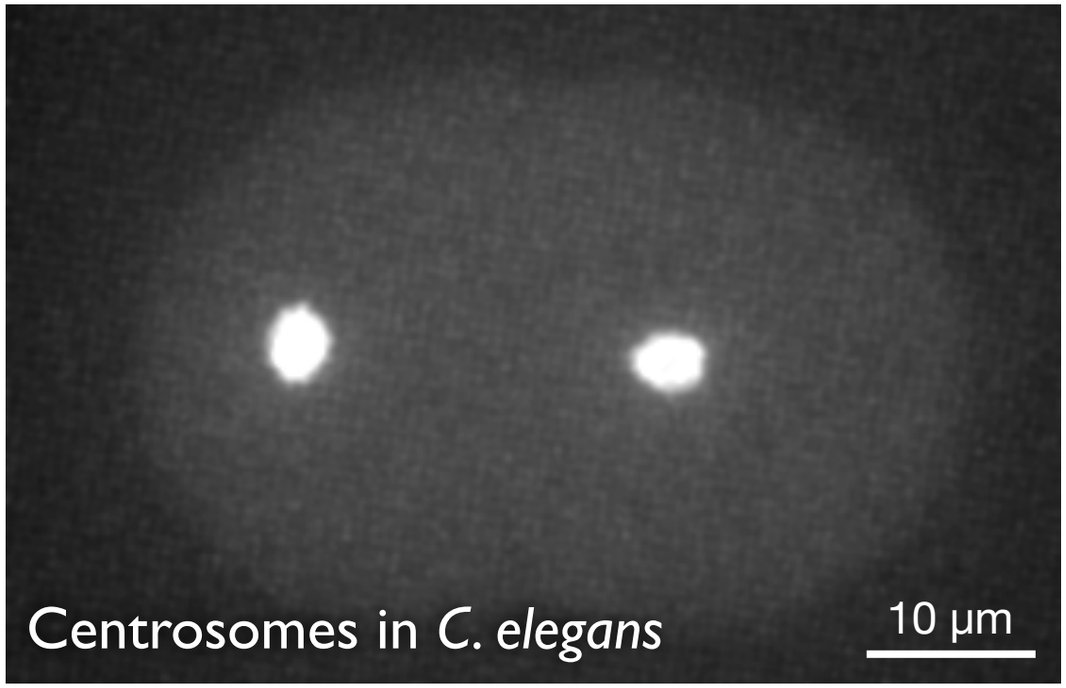

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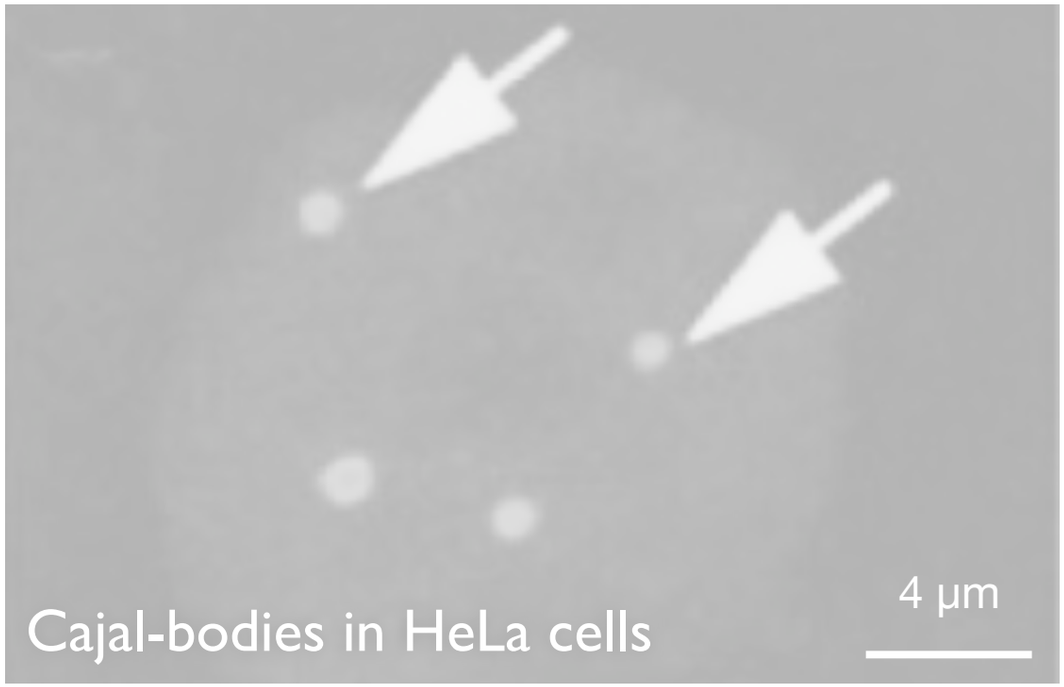

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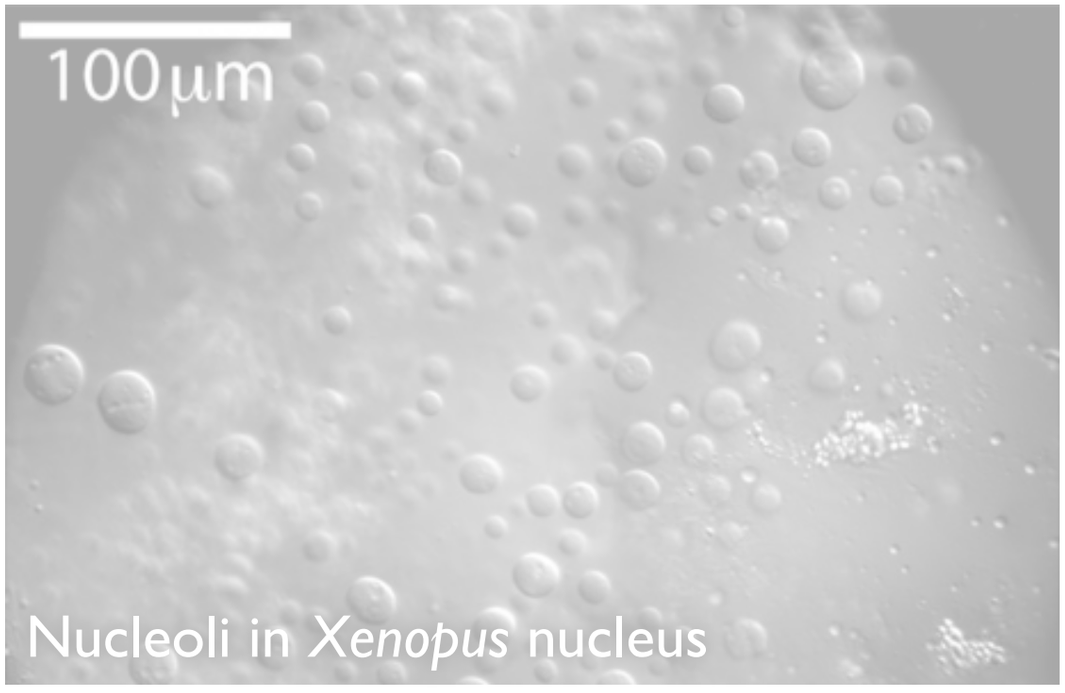


Brangwynne et al., *PNAS* (2011)

C. elegans embryo, GFP::SPD-5 Maximum projection, recorded by B. Gomes, Hyman lab, MPI-CBG

3 min

How can cells control droplet formation?

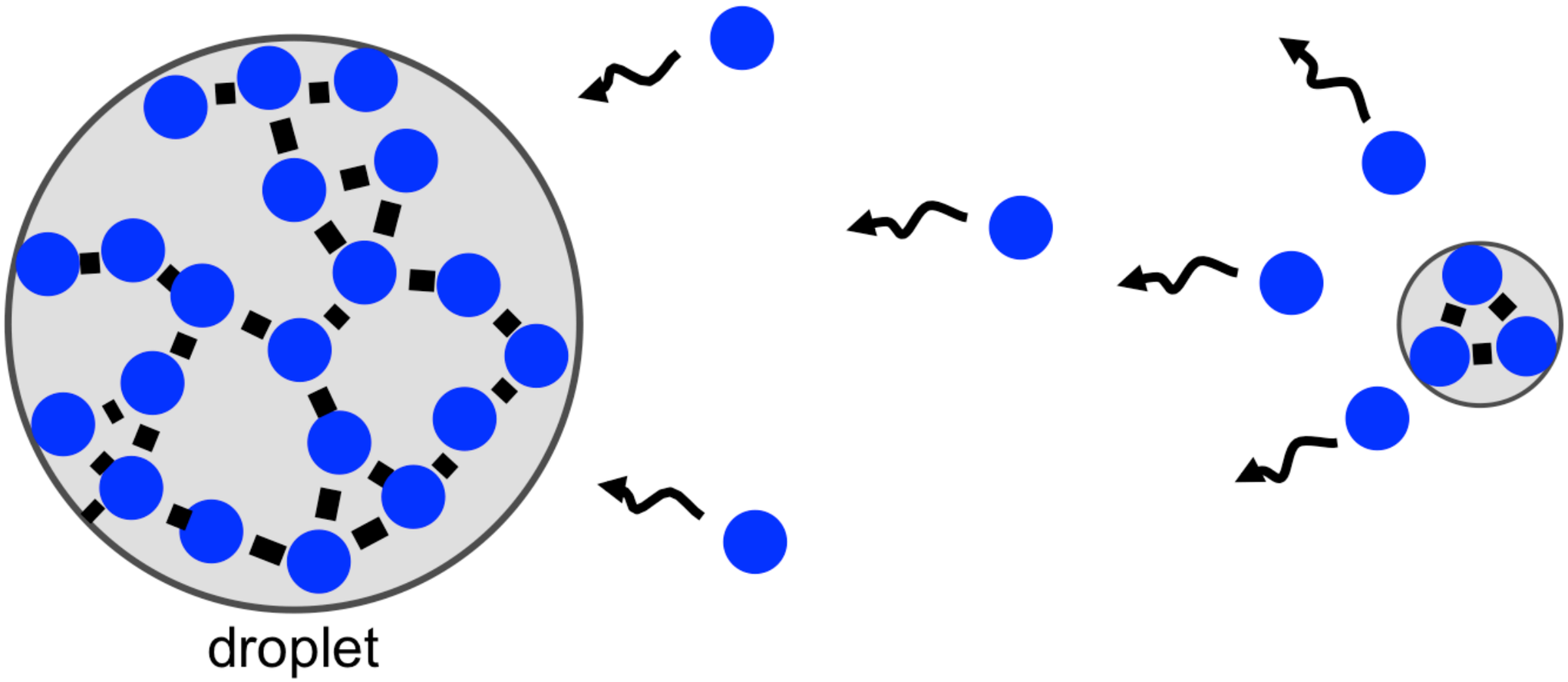
5 µm

C. elegans embryo, SPD-5::YFP, Maximum projection, recorded by M. Decker, Hymanlab, MPI-CBG

How can cells control droplet formation?

Alternative 1:
Take material from large droplets

Alternative 2:
Add material to small droplets



Söding et al, bioRxiv/694406

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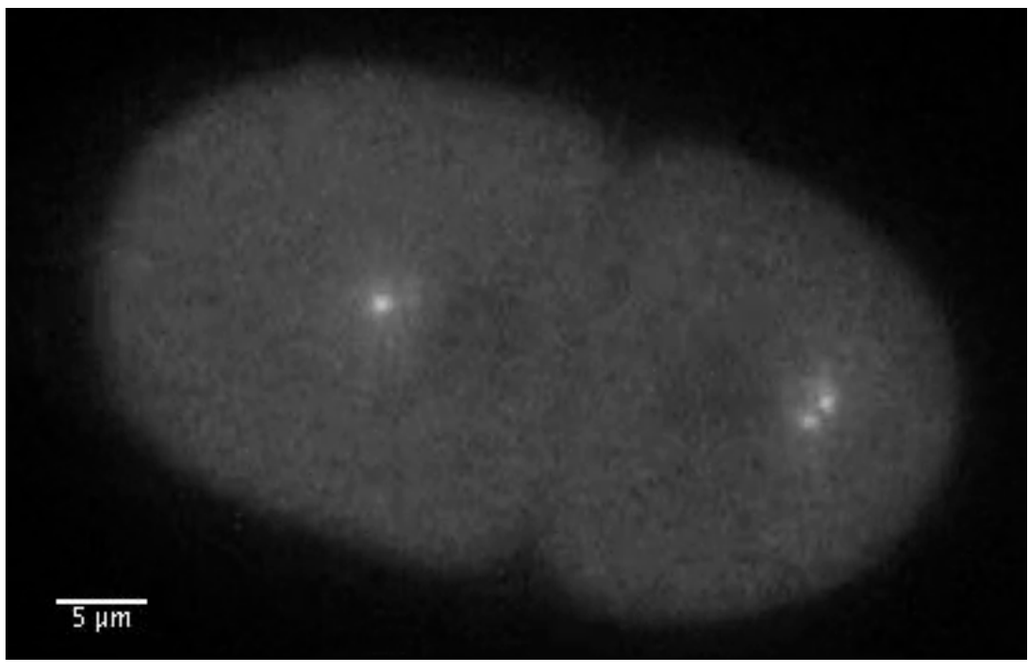
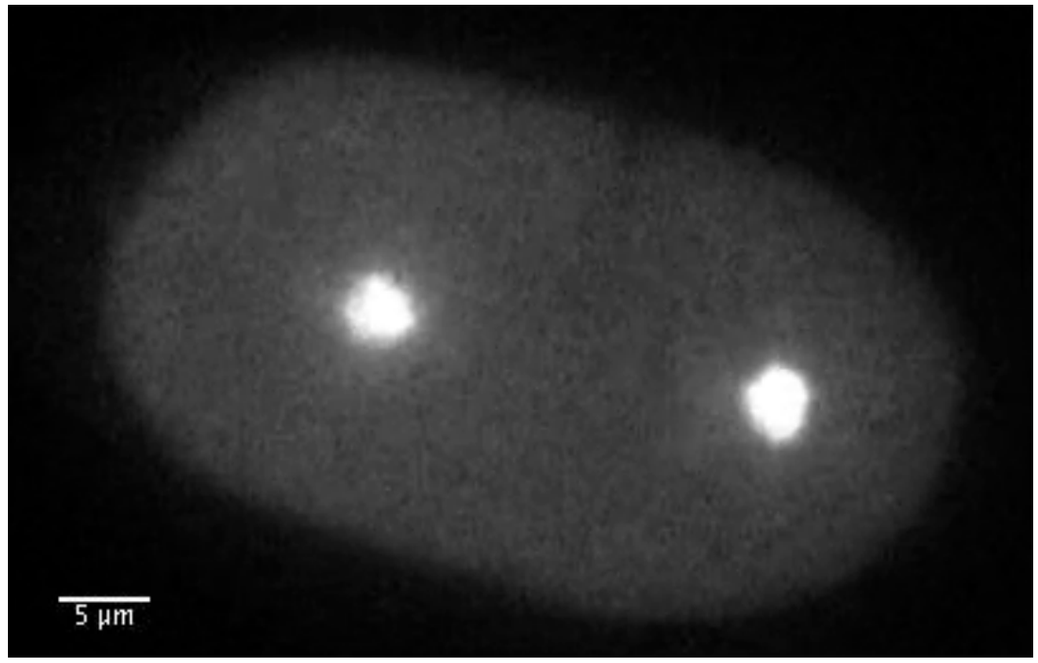
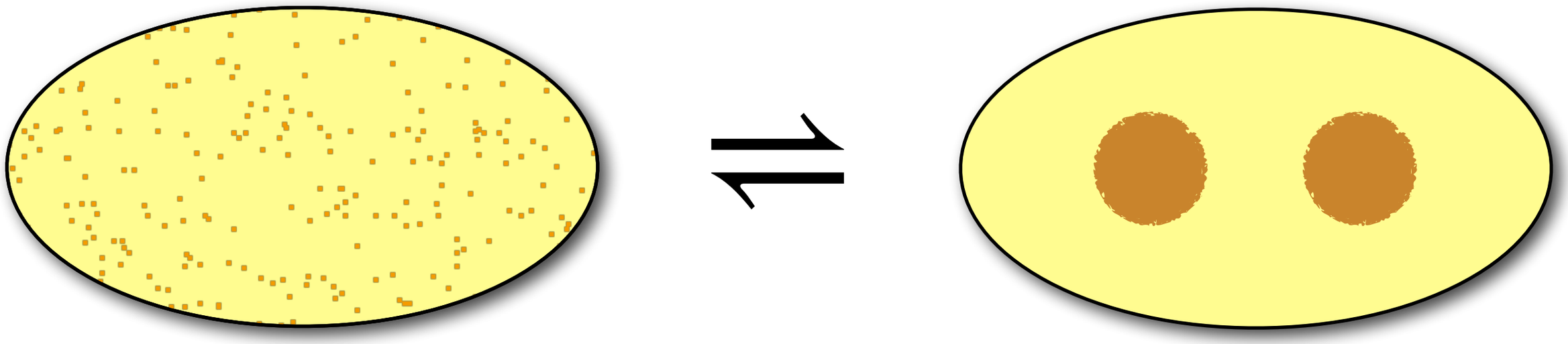


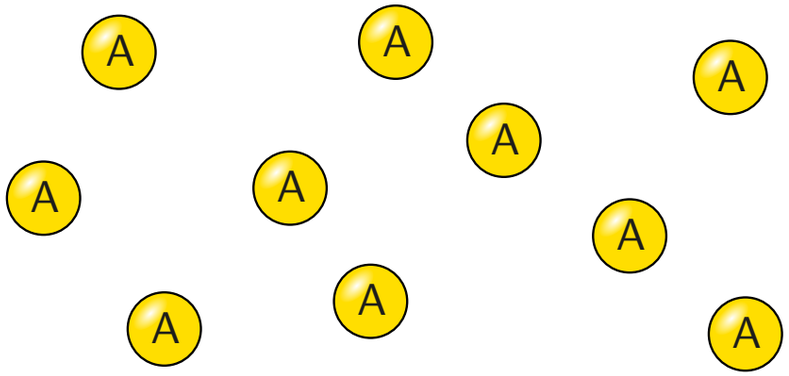


- No time for making new proteins
- Chemical modifications are crucial

How can cells control droplet formation?

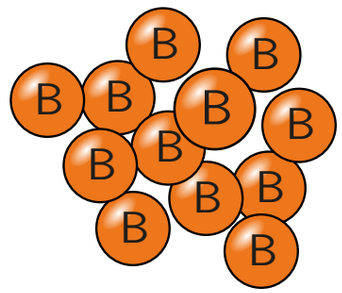


A form is soluble in cytosol



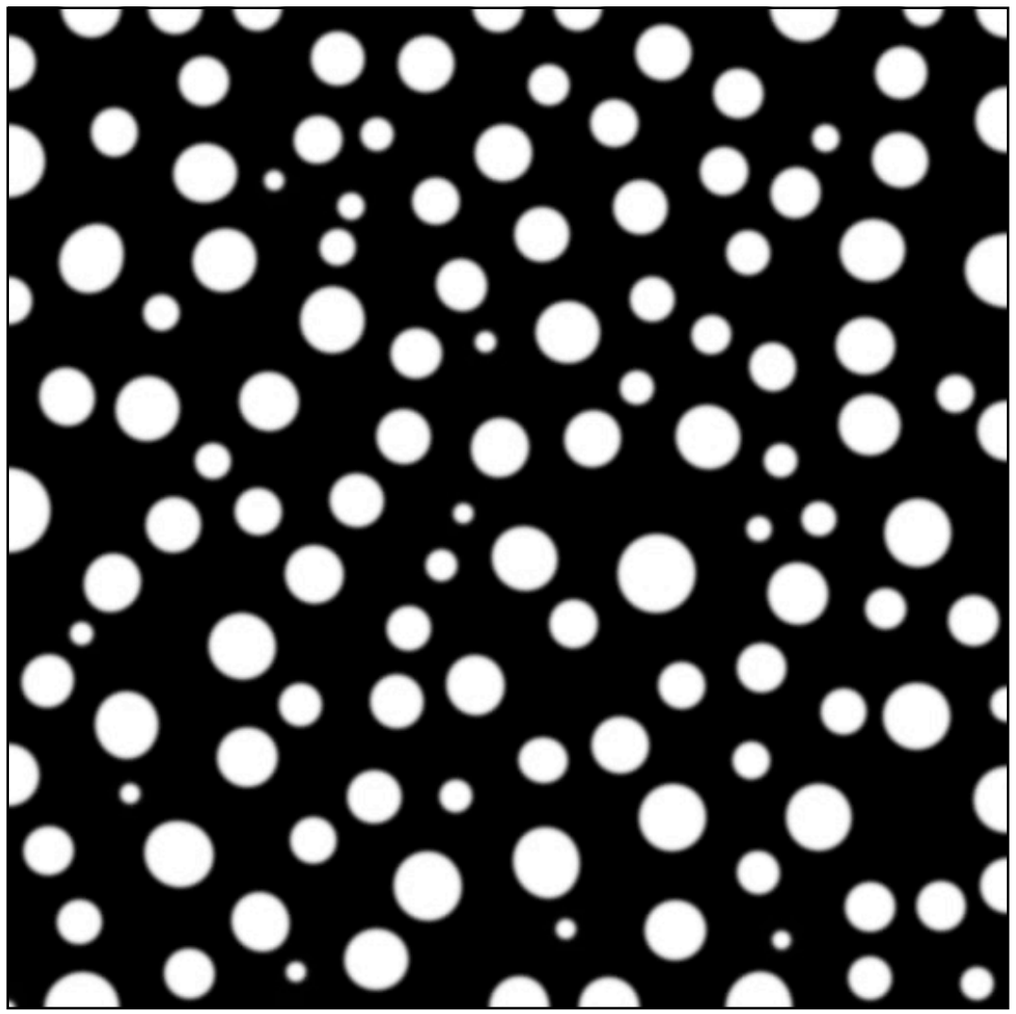
$$A \rightleftharpoons B$$

B form phase separates



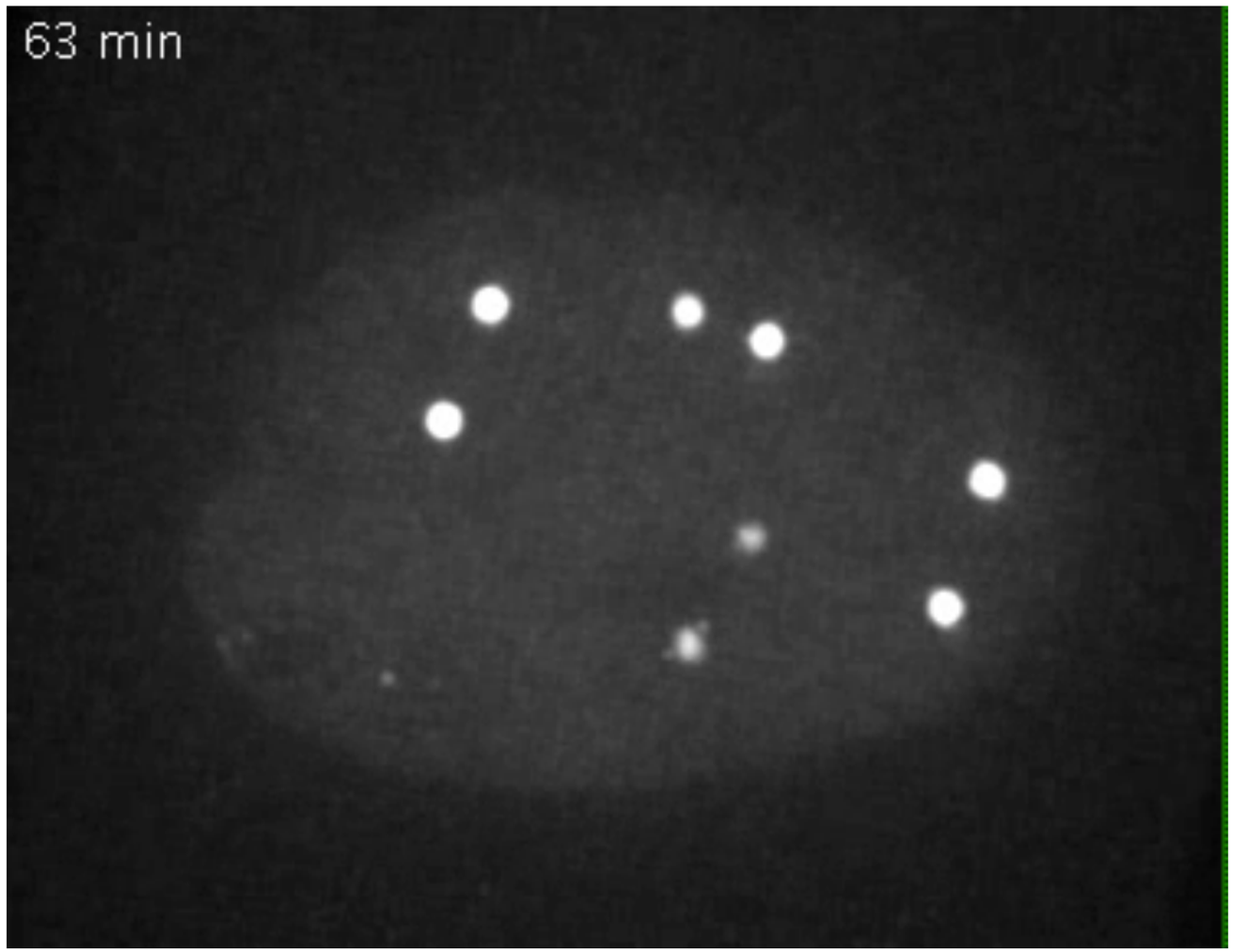
Biomolecular condensates are not in equilibrium

Passive droplets



No chemical reaction

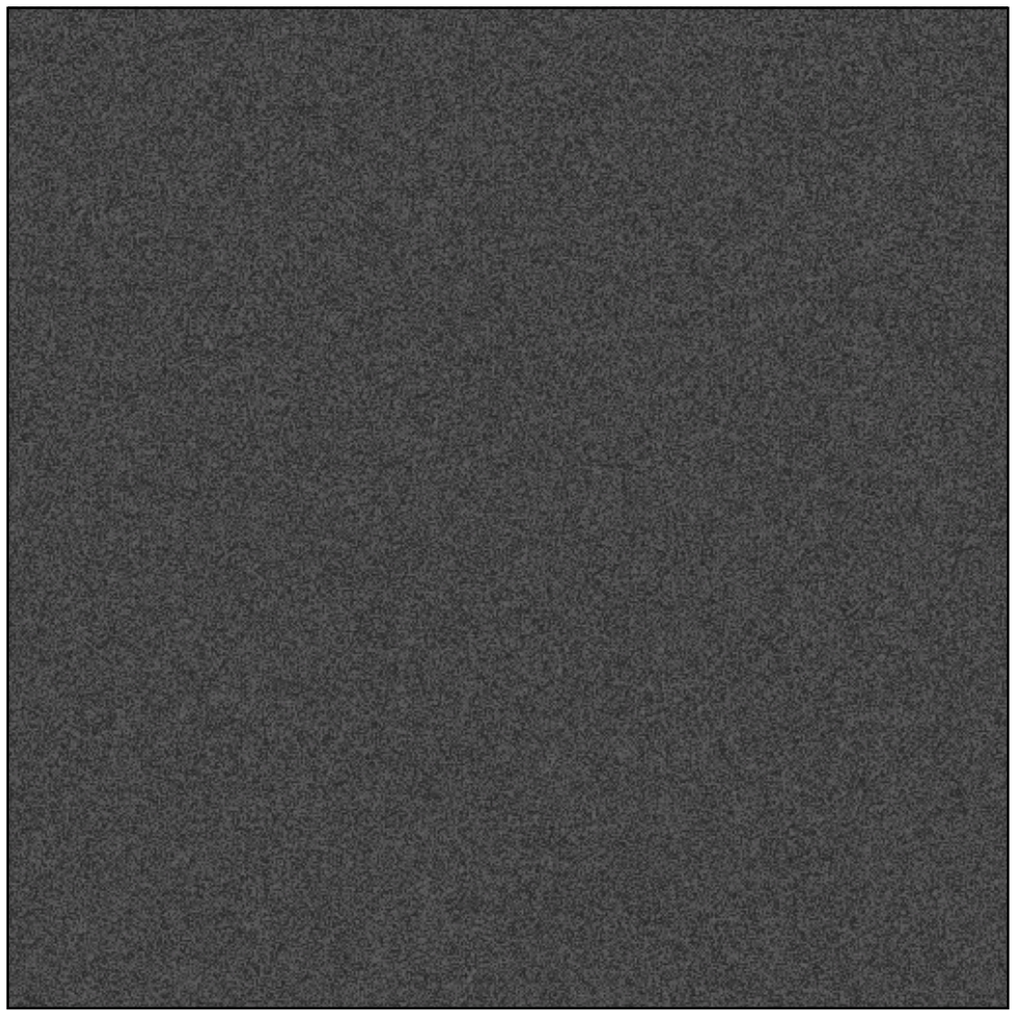
Droplets in cells



$$A \underset{k}{\overset{q}{\rightleftharpoons}} B$$

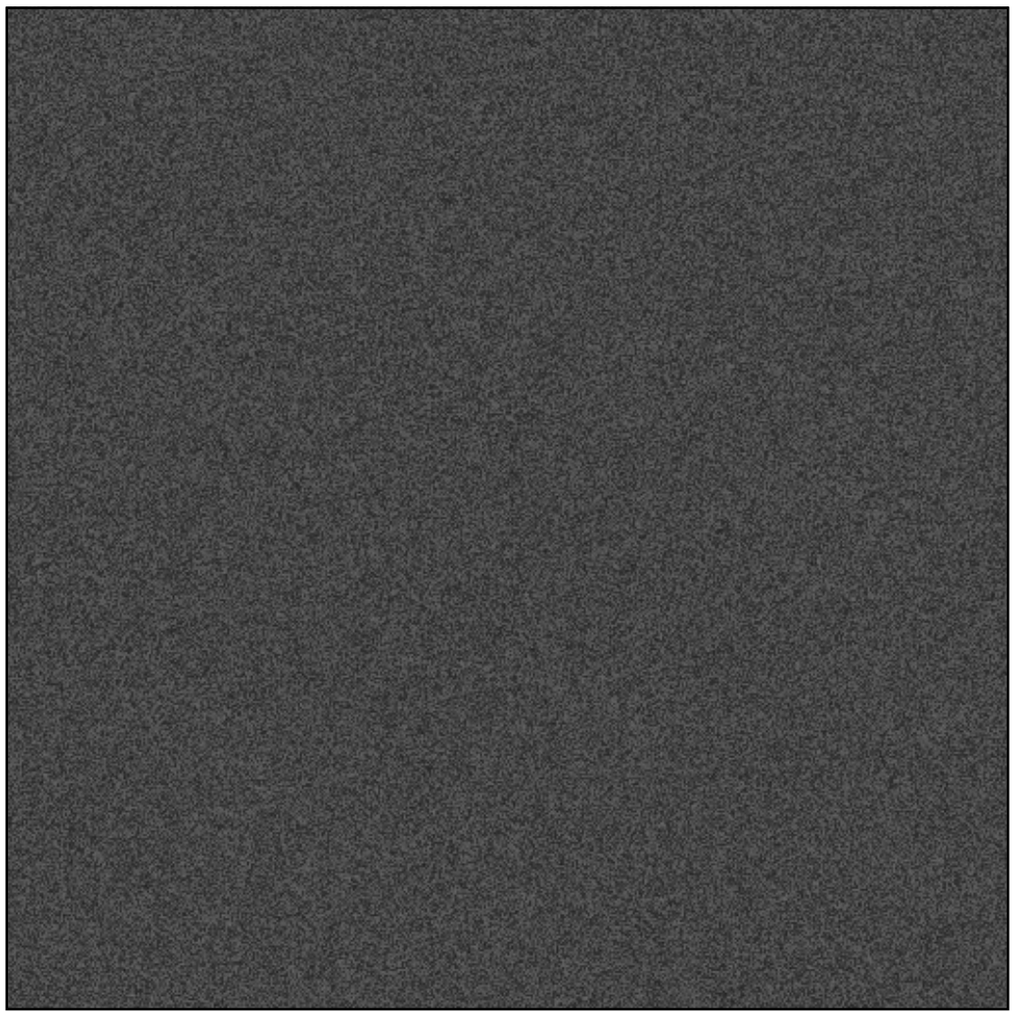
Dynamics of active droplets

Passive droplets



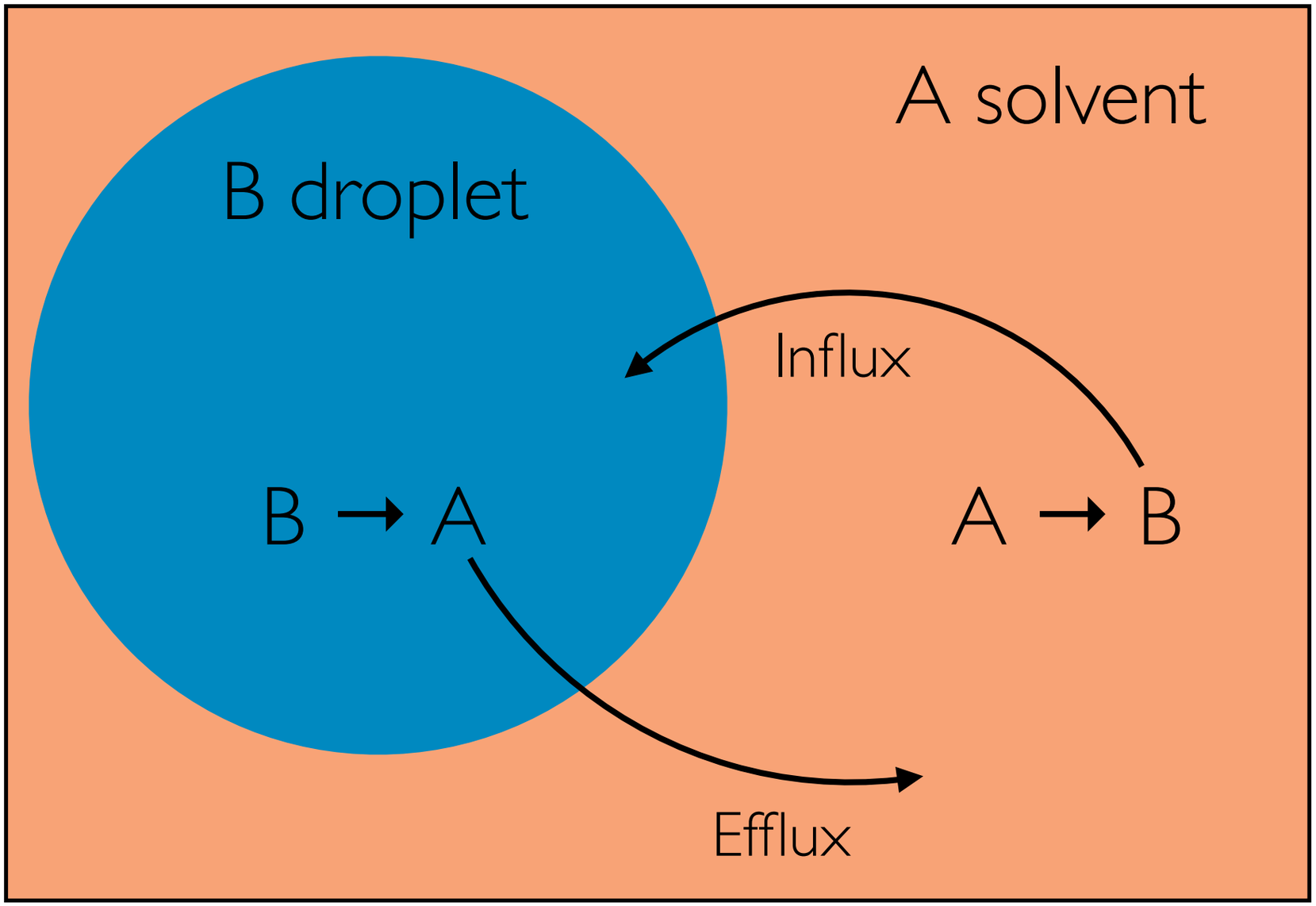
No chemical reaction

Droplets with chemical reactions



$$A \underset{k}{\overset{q}{\rightleftharpoons}} B$$

Chemical reactions drive compositional fluxes



$$A \underset{k}{\overset{q}{\rightleftharpoons}} B$$

Zwicker et al., *PRE* 92 (2015)

Compositional fluxes stabilize droplet size

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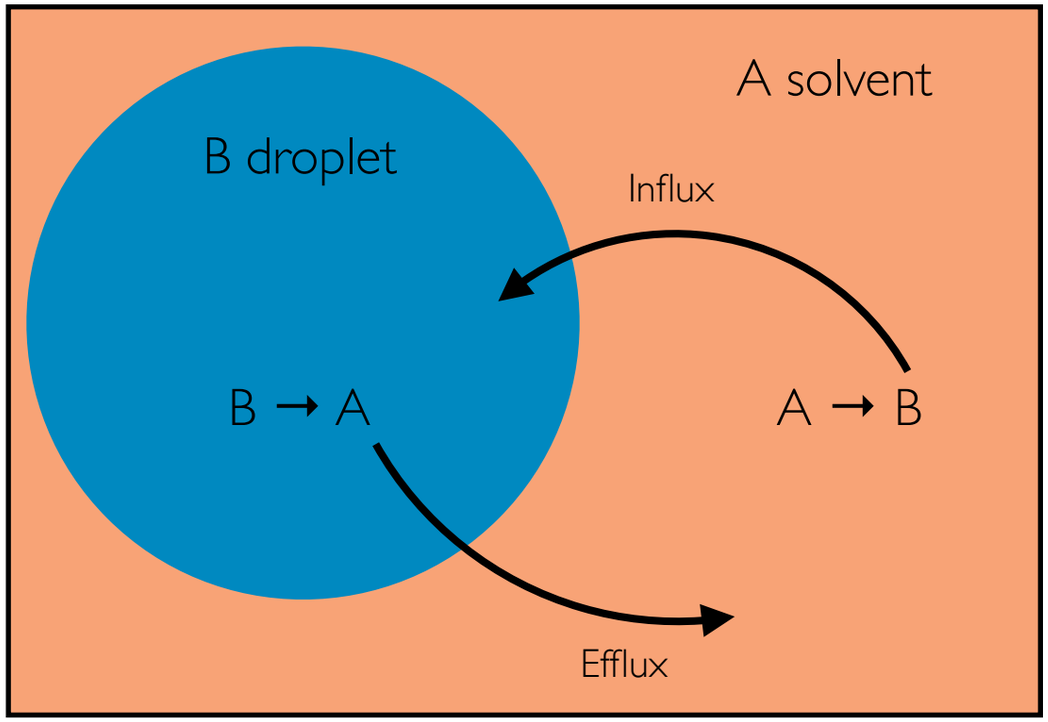

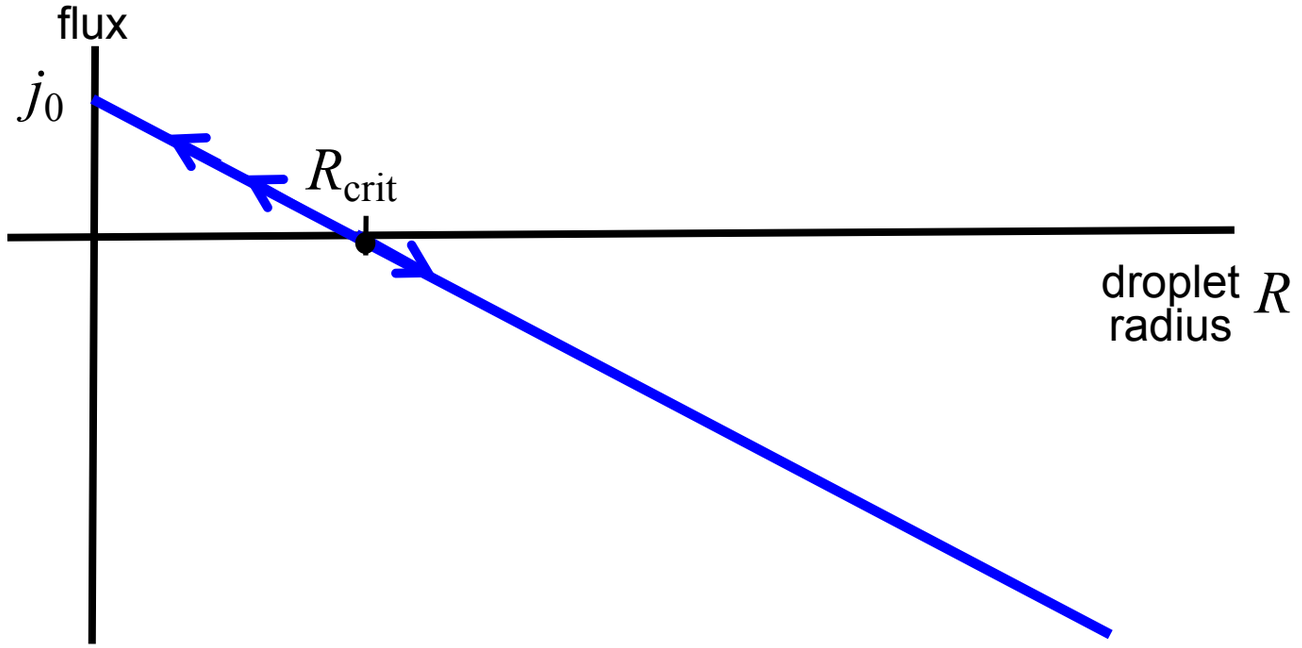

Diffusion-limited influx ~ Radius R

Zwicker et al., *PRE* 92 (2015)

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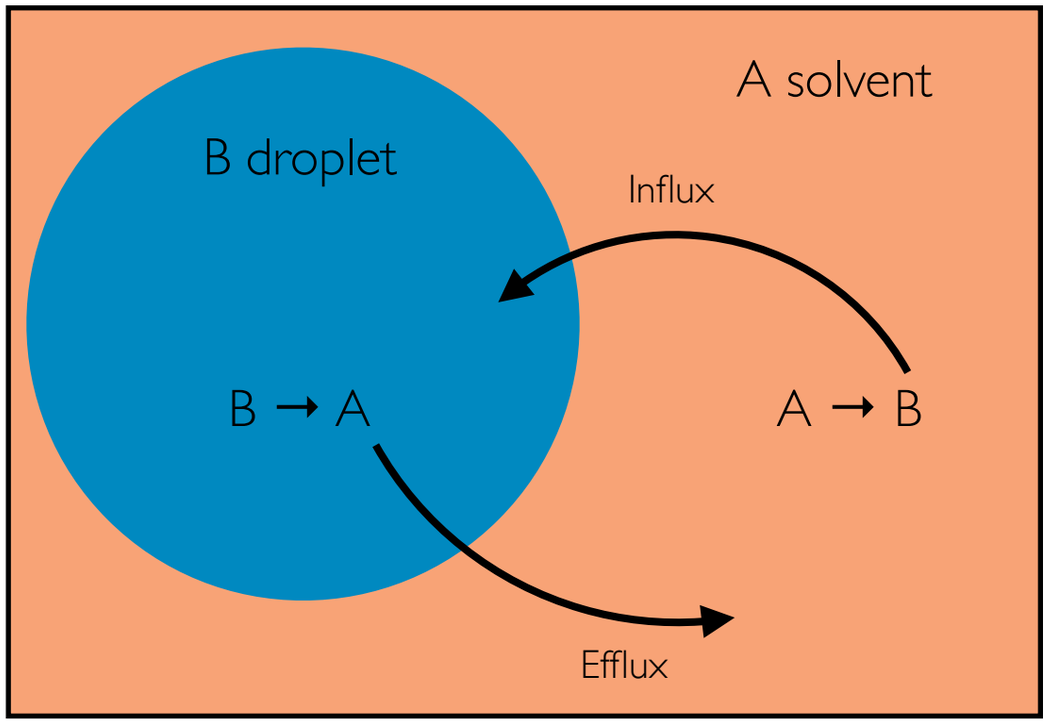

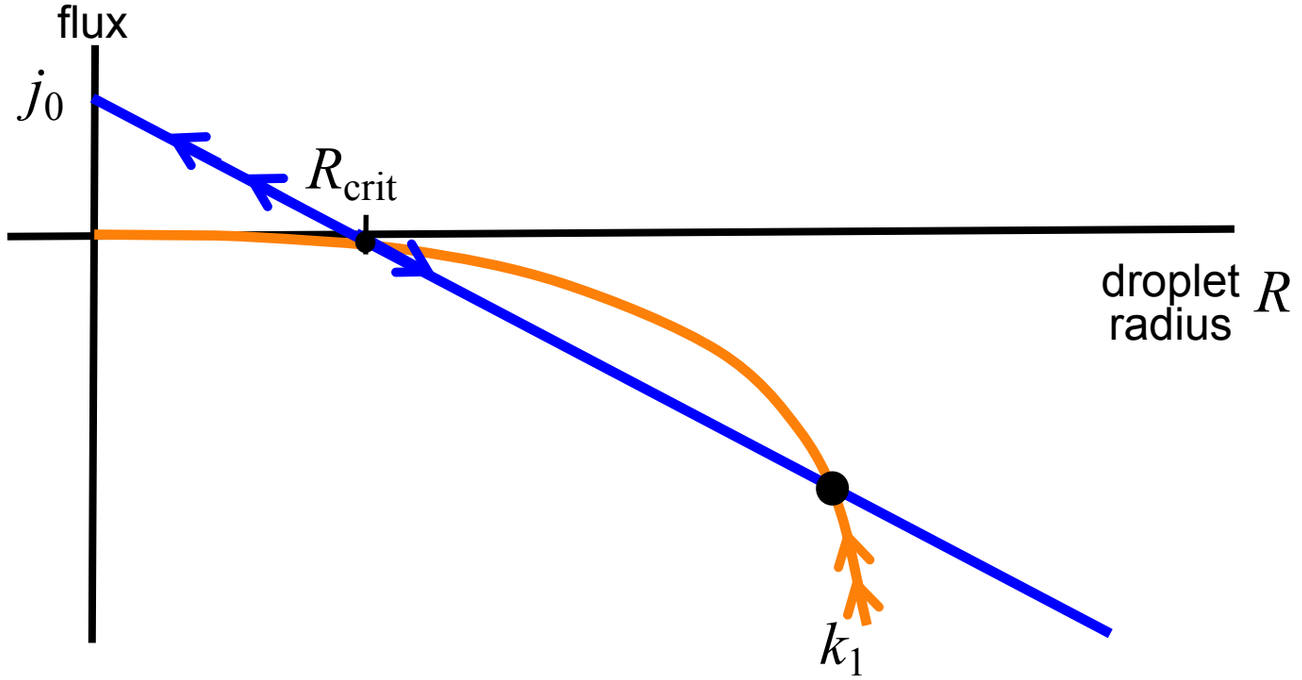

Diffusion-limited influx ~ Radius R

Reaction-limited efflux ~ Volume R^3

$$R_1 \sim \left(\frac{3D\phi_\infty}{k_1}\right)^{\frac{1}{2}}$$

Zwicker et al., *PRE* 92 (2015)

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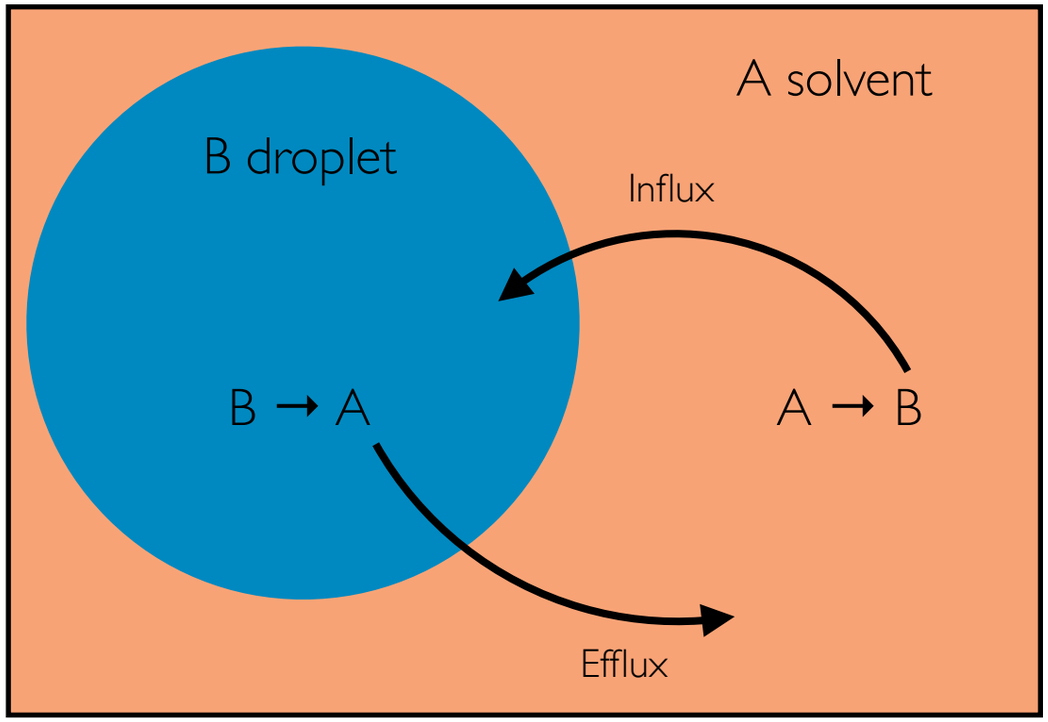

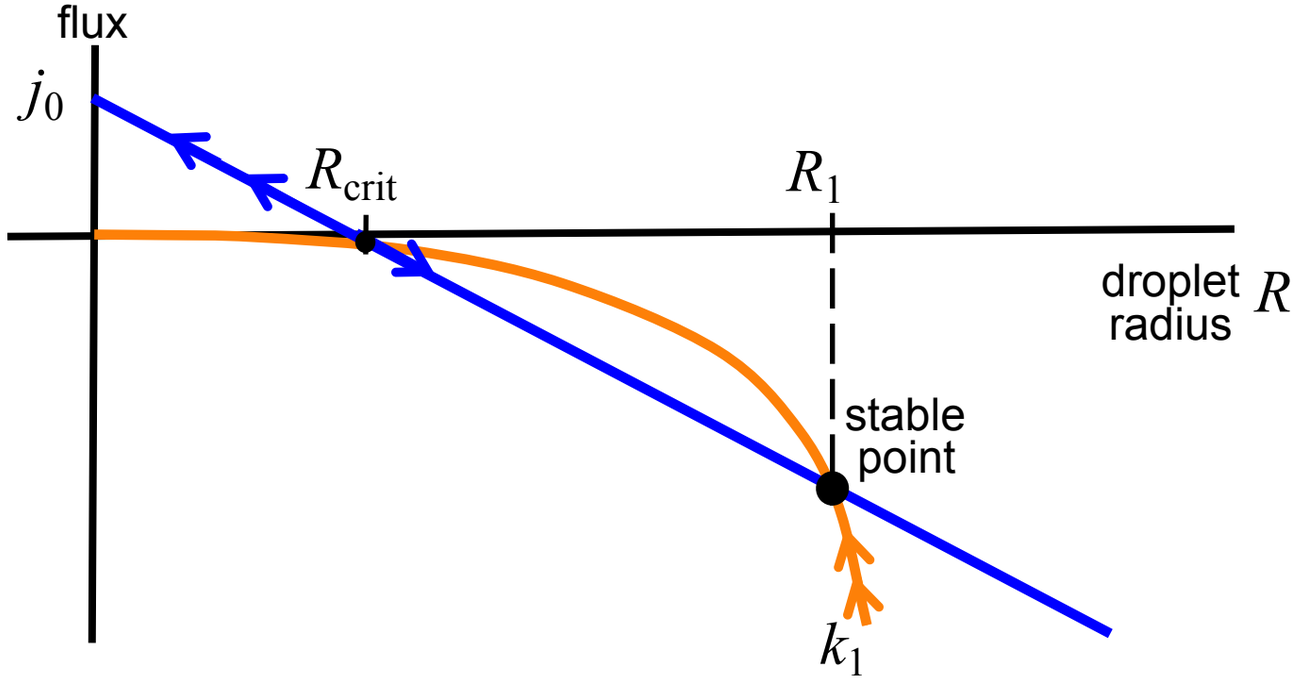

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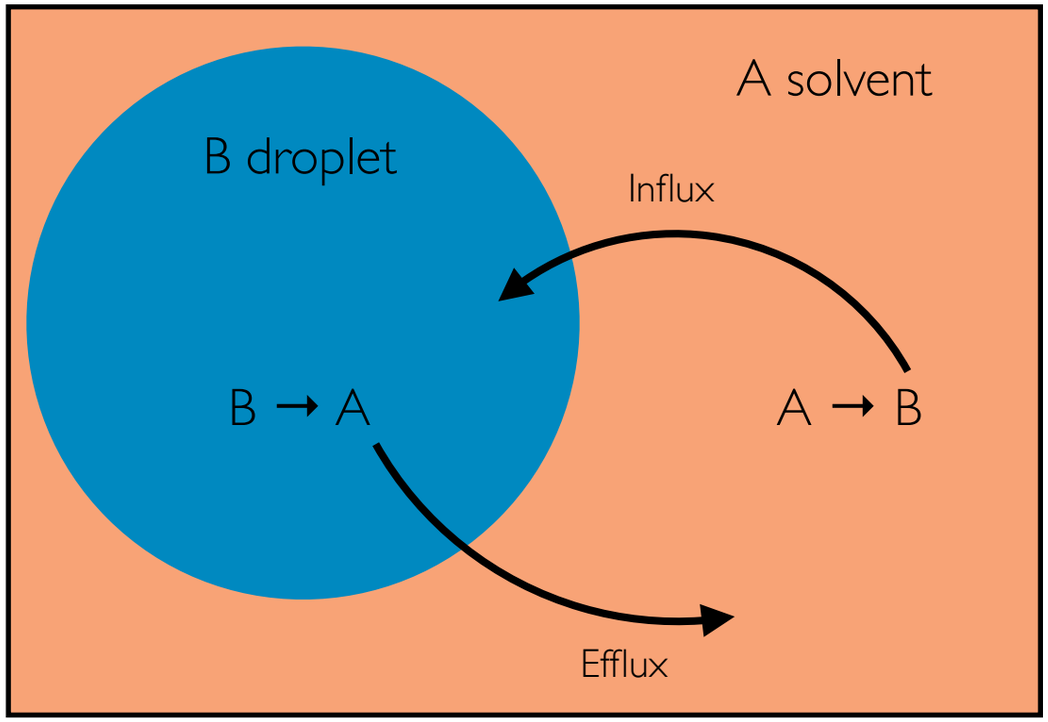

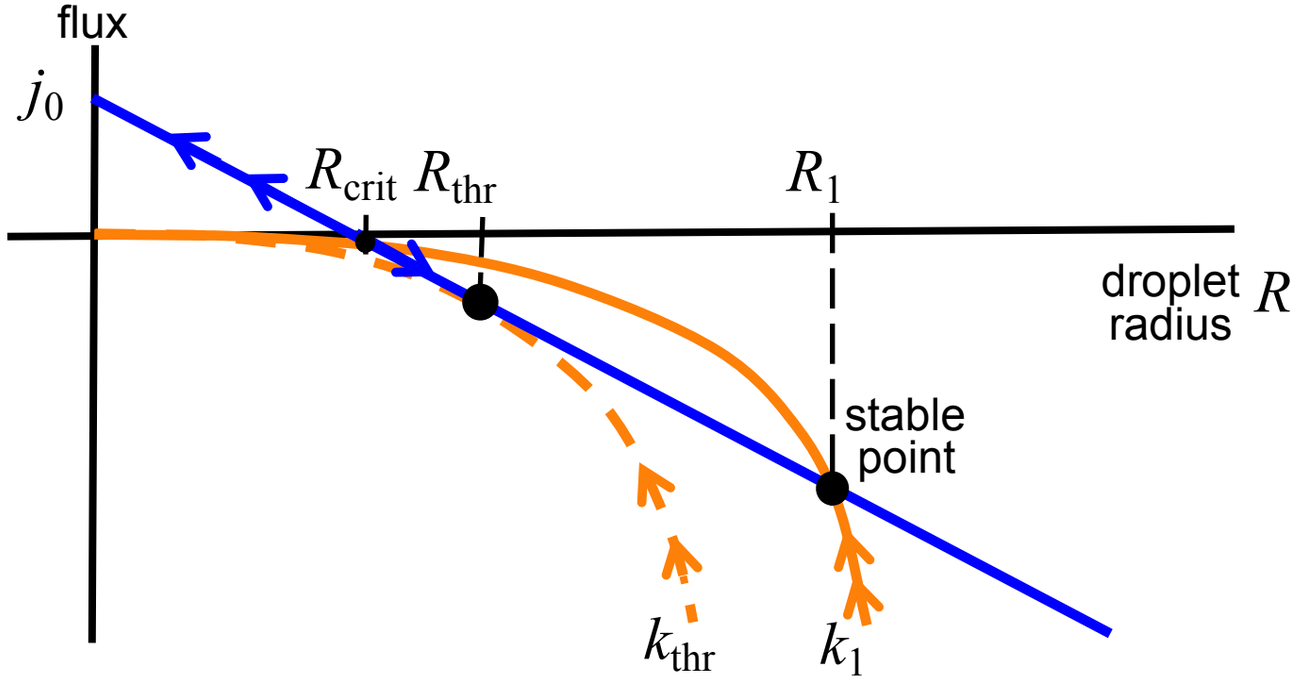

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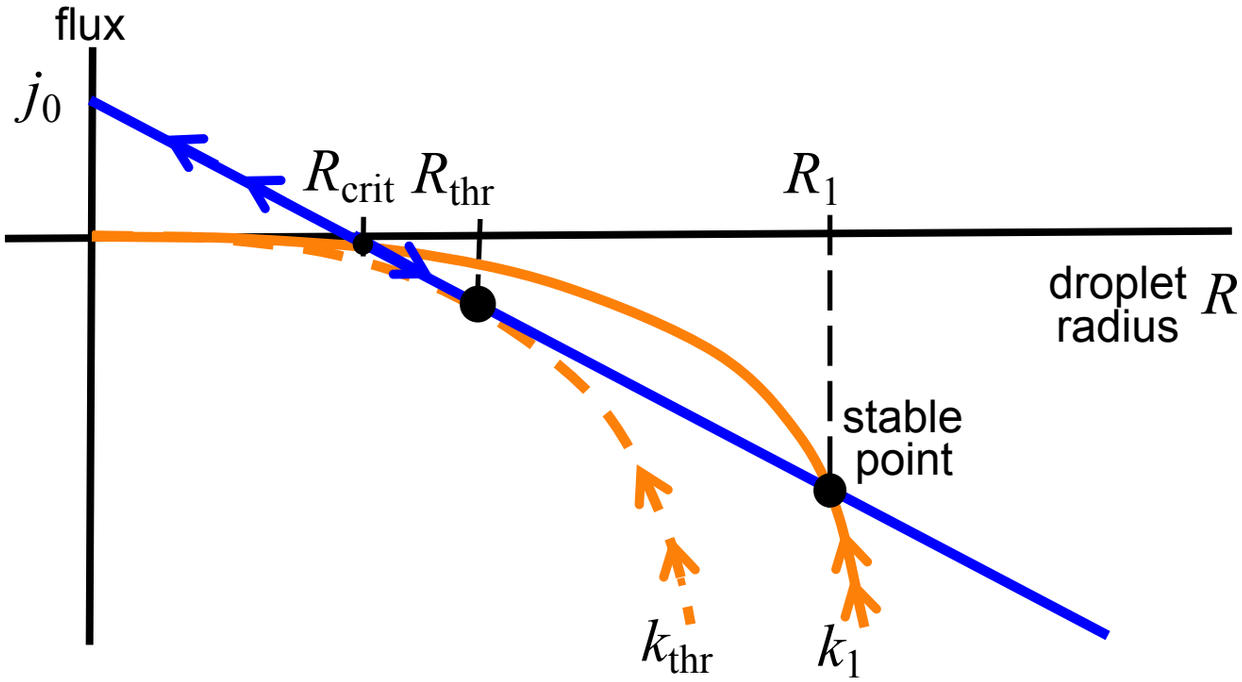

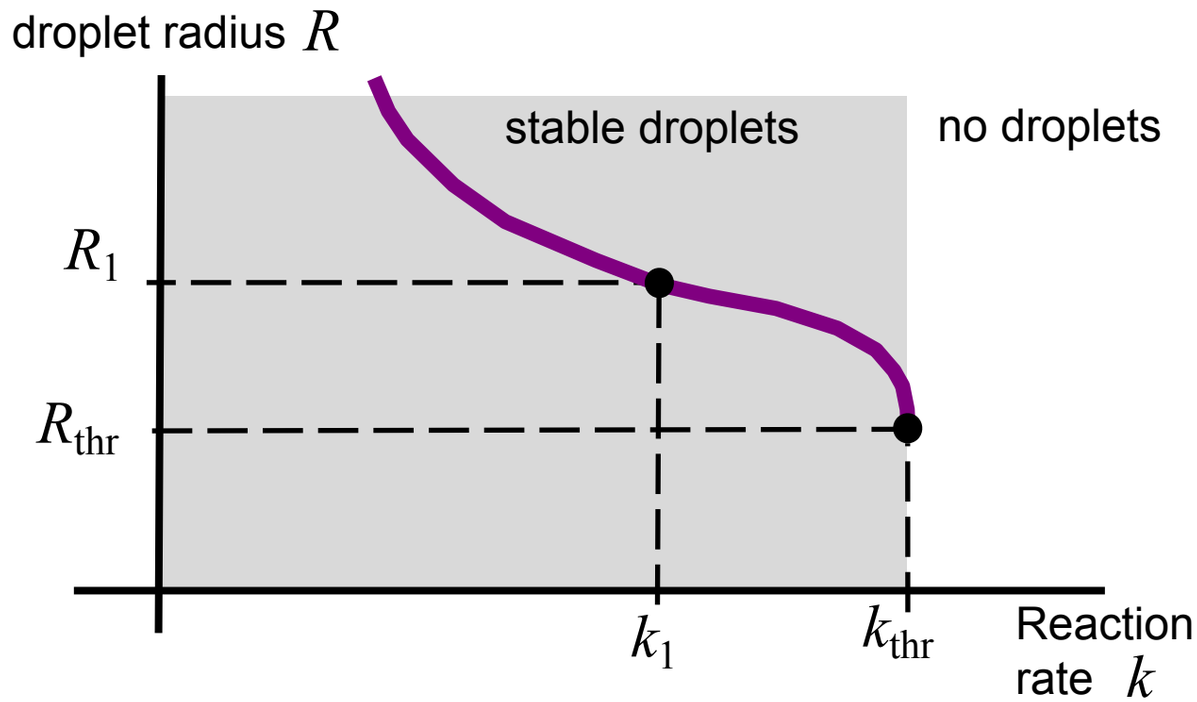

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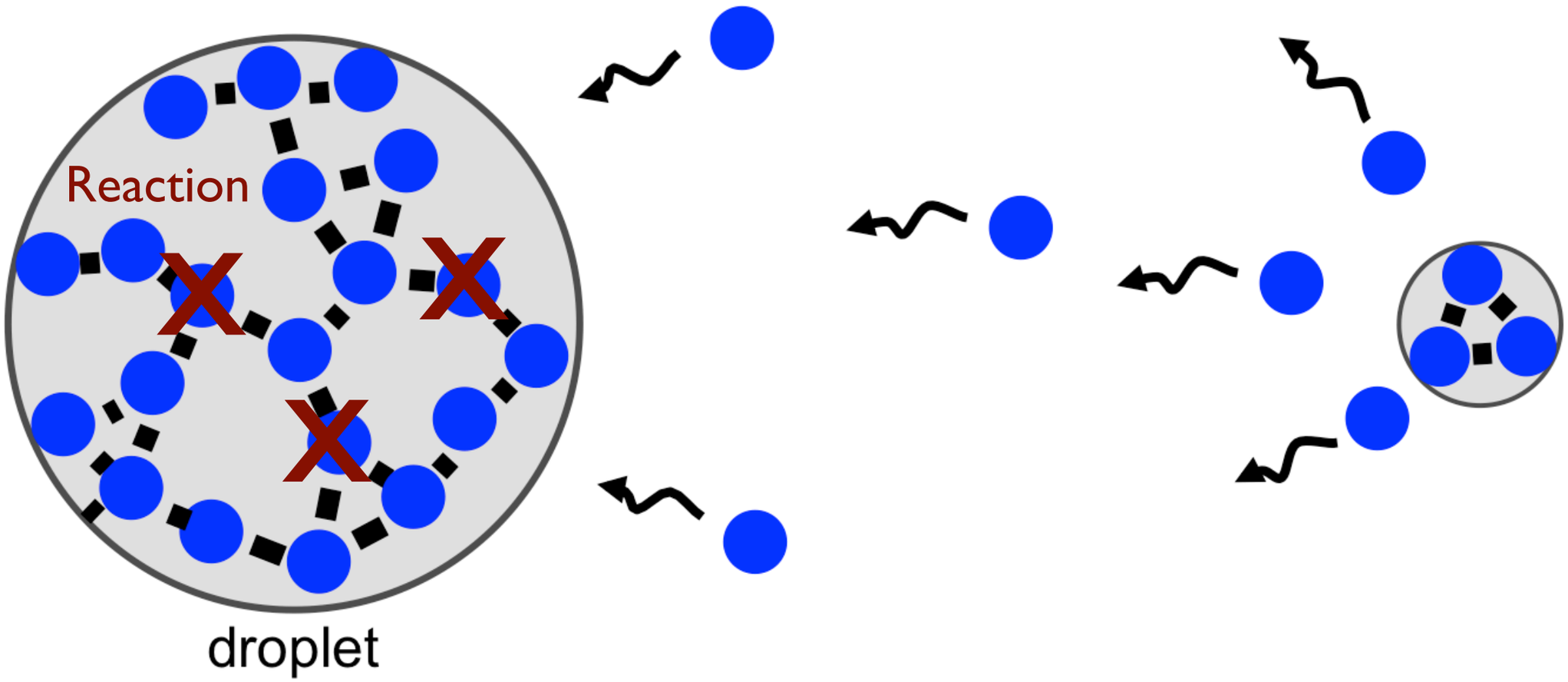
Externally maintained droplets

Alternative 1:
Take material from
large droplets

Alternative 2:
Add material to
small droplets



Weber, Zwicker, Jülicher, Lee, *Rep. Prog. Phys.* 82 (2019)

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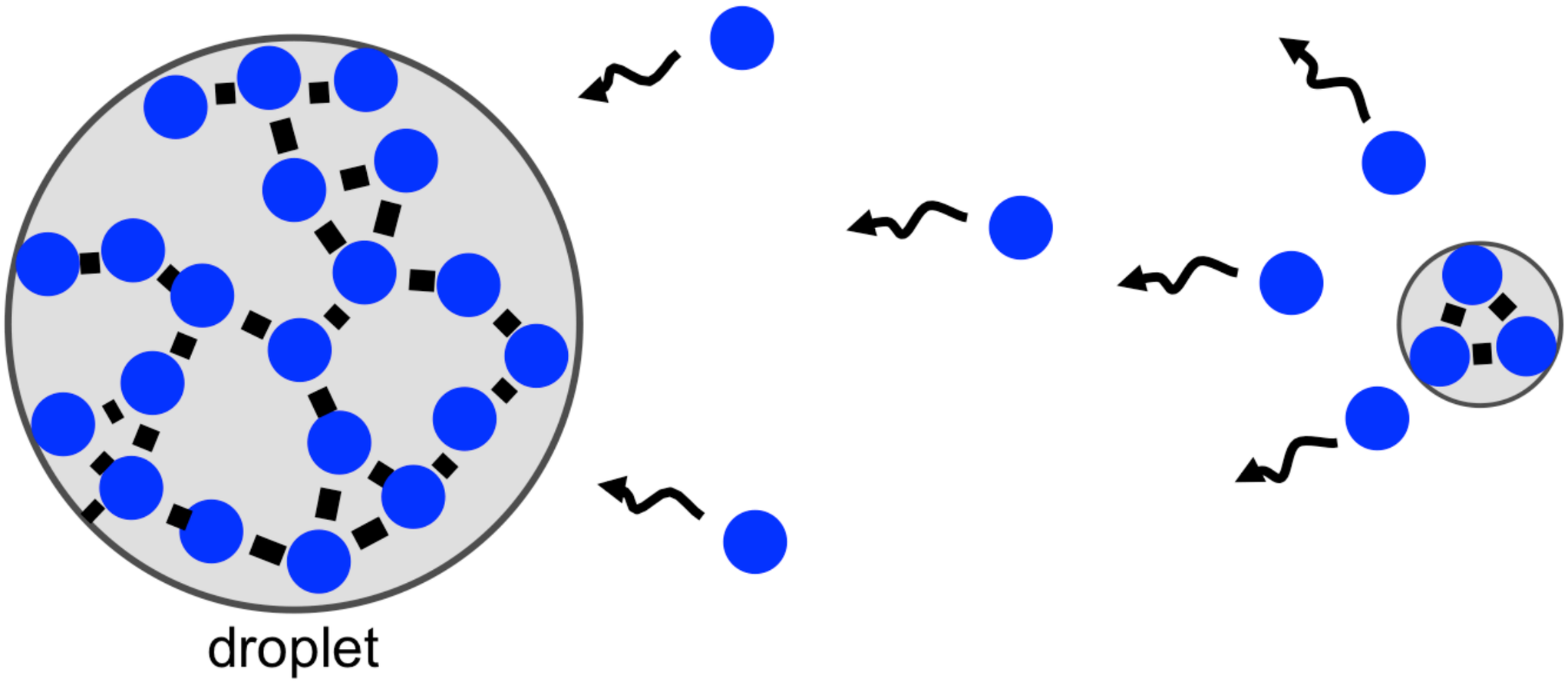

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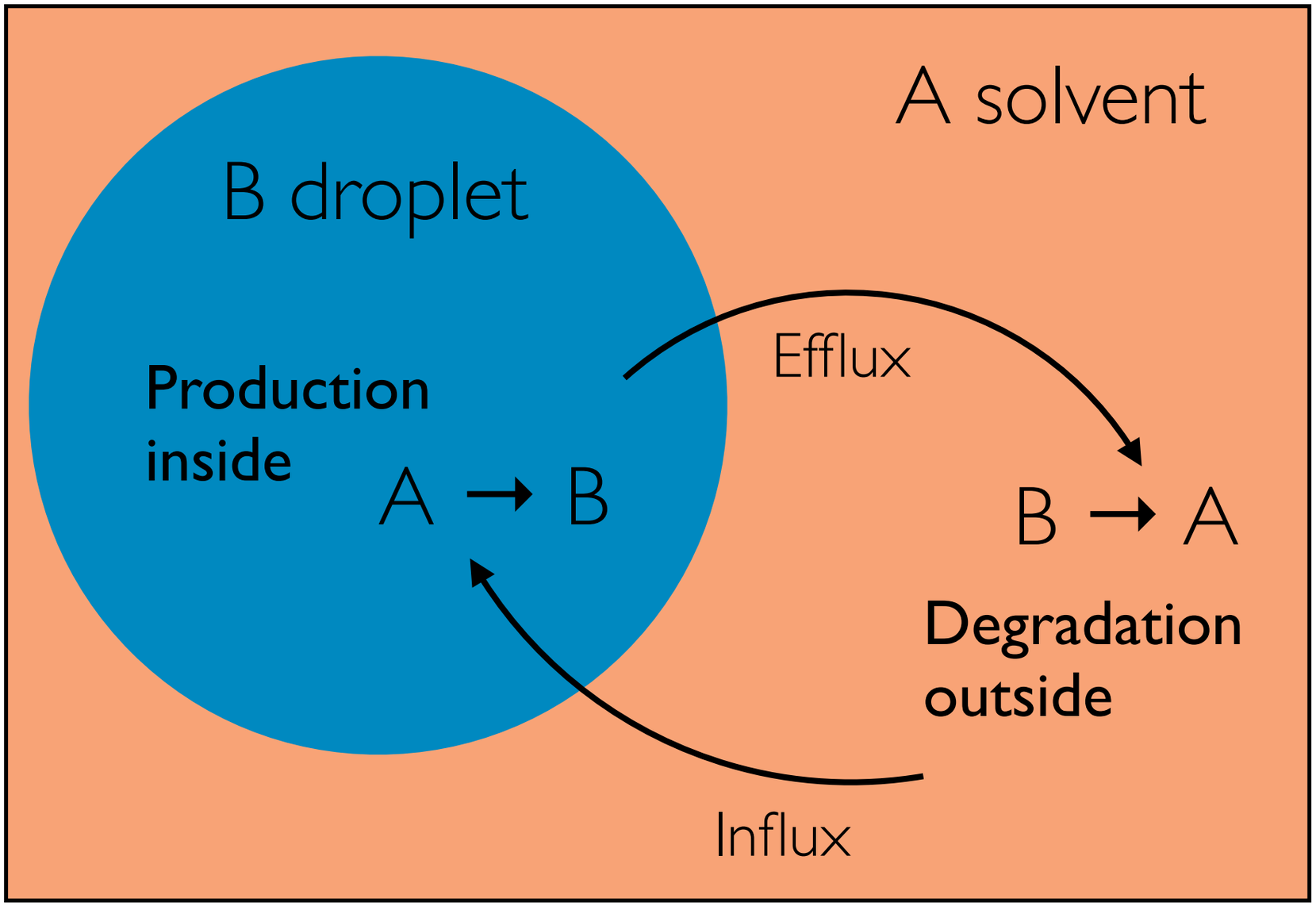
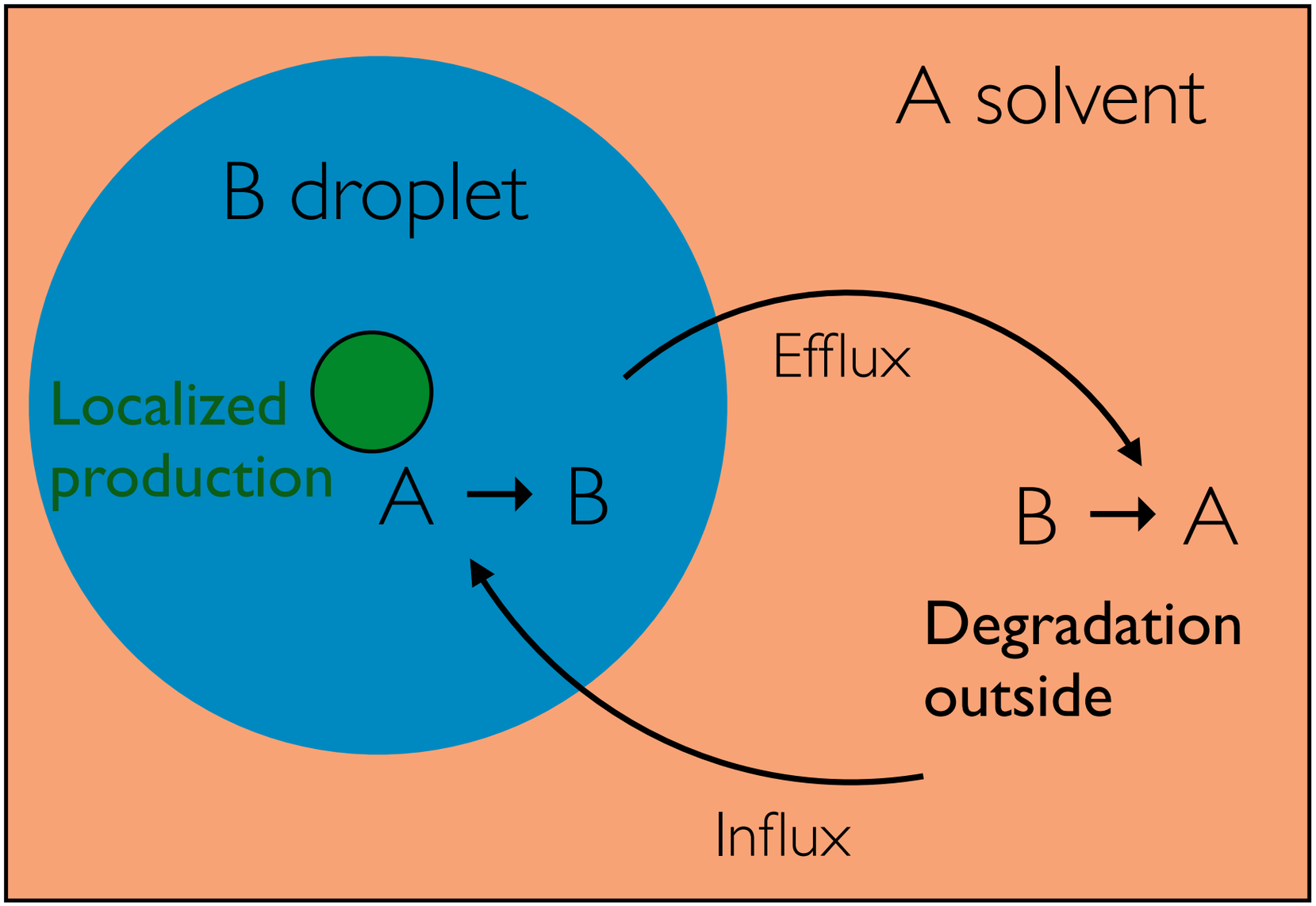


Reaction-limited influx ~ Volume R^3
Diffusion-limited efflux ~ Radius R

⇒ **Unstable!**

Zwicker et al., *PRE* 92 (2015)

Internally maintained droplets

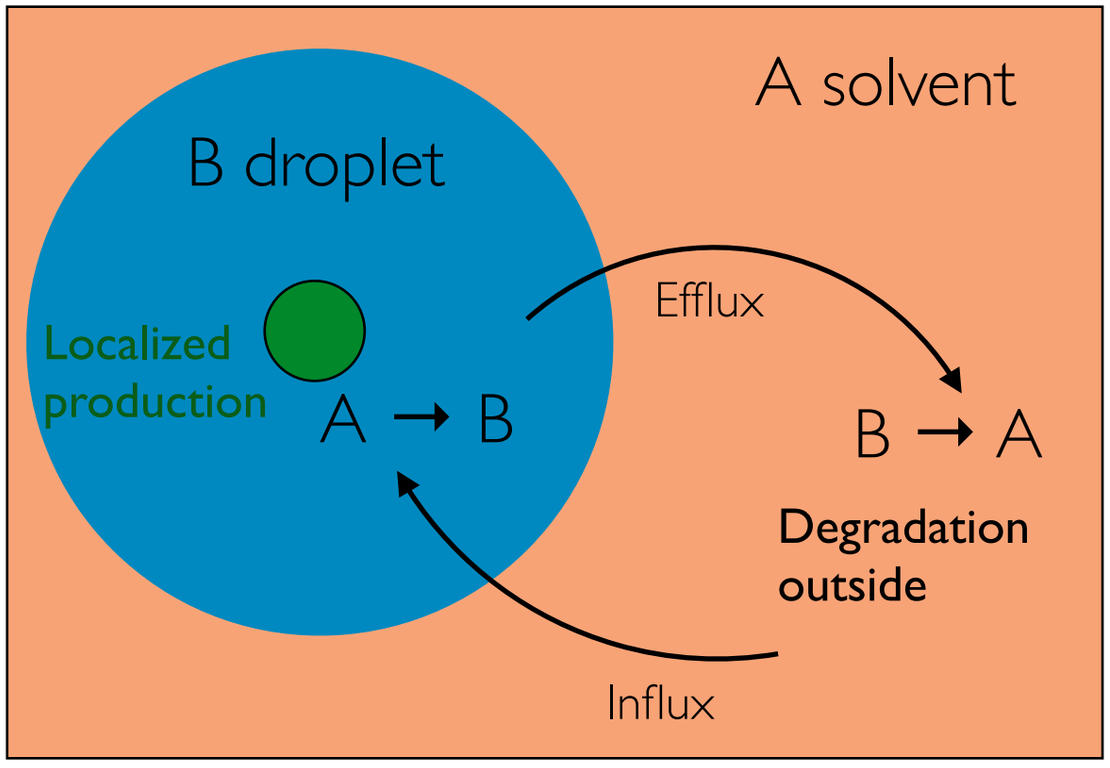


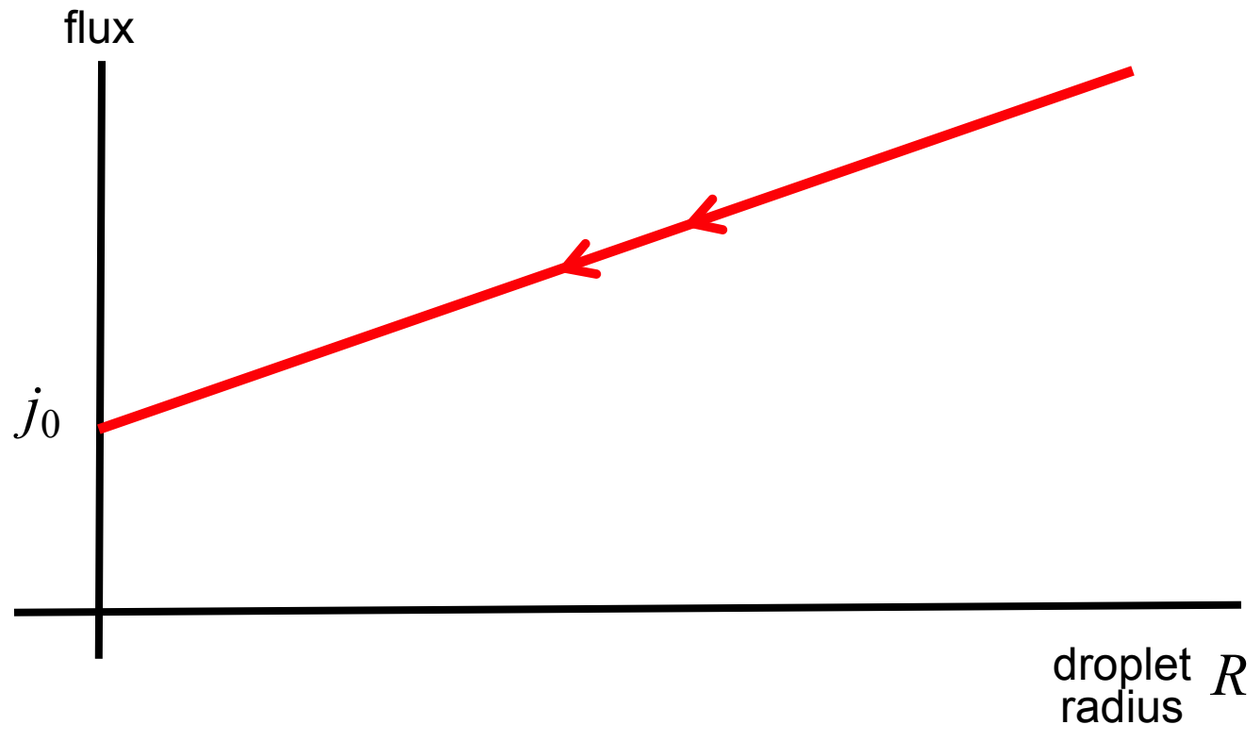
Reaction-limited influx ~ Constant flux Q

Diffusion-limited efflux ~ Radius R

Zwicker et al., *PRE* 92 (2015)

Internally maintained droplets



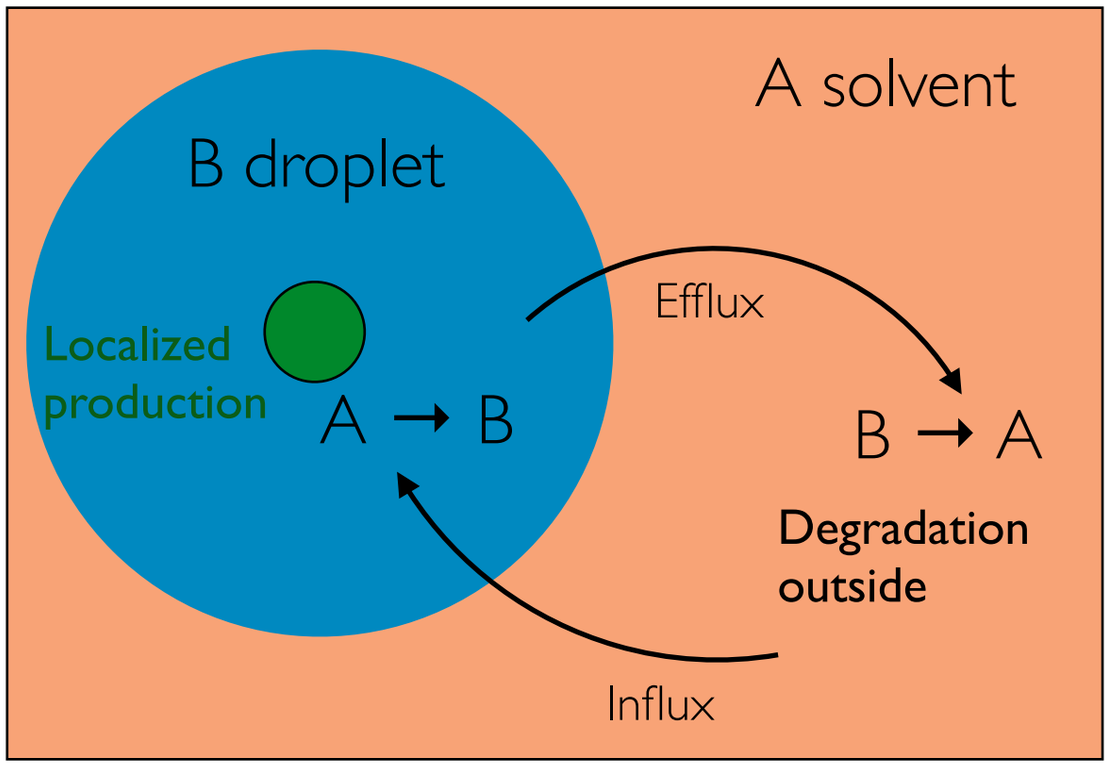


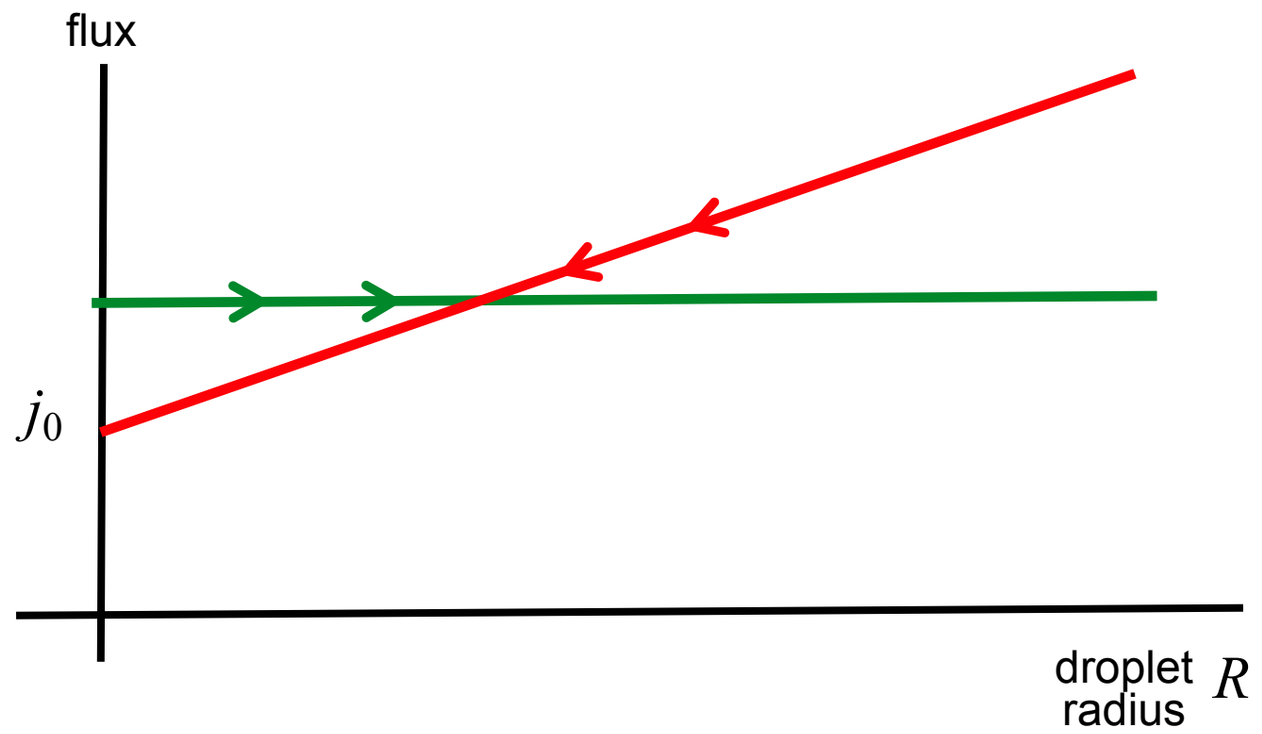
Reaction-limited influx ~ Constant flux Q

Diffusion-limited efflux ~ Radius R

Zwicker et al., *PRE* 92 (2015)

Internally maintained droplets





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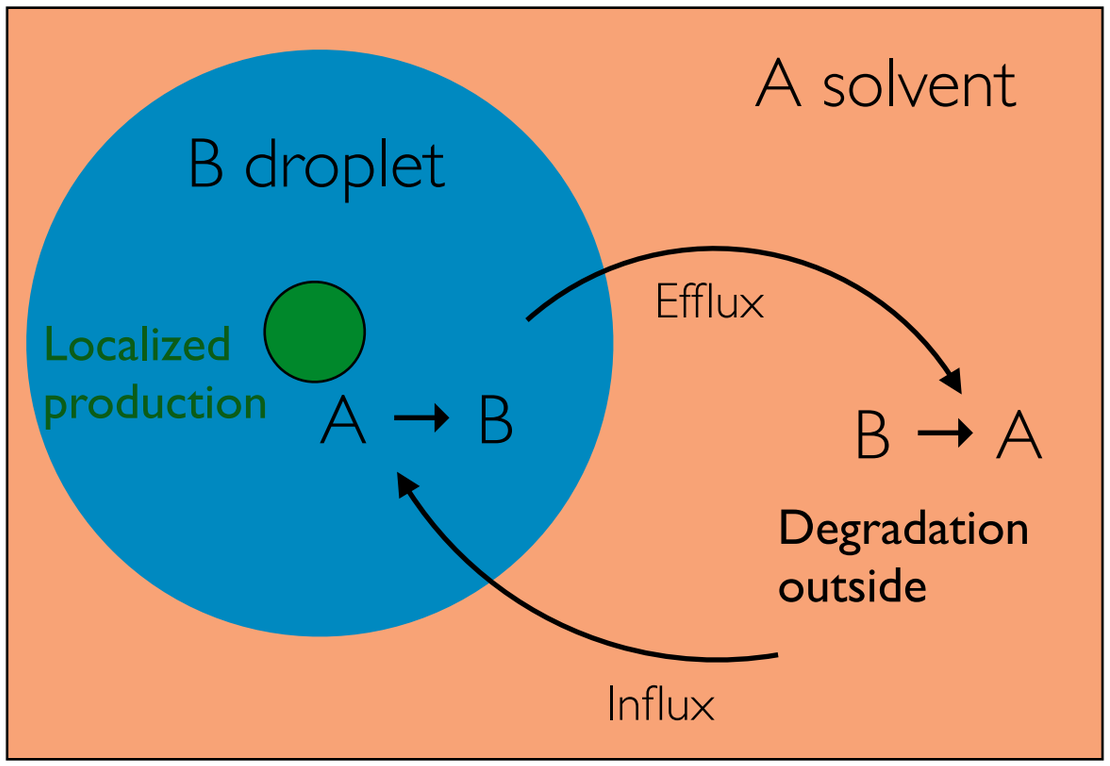
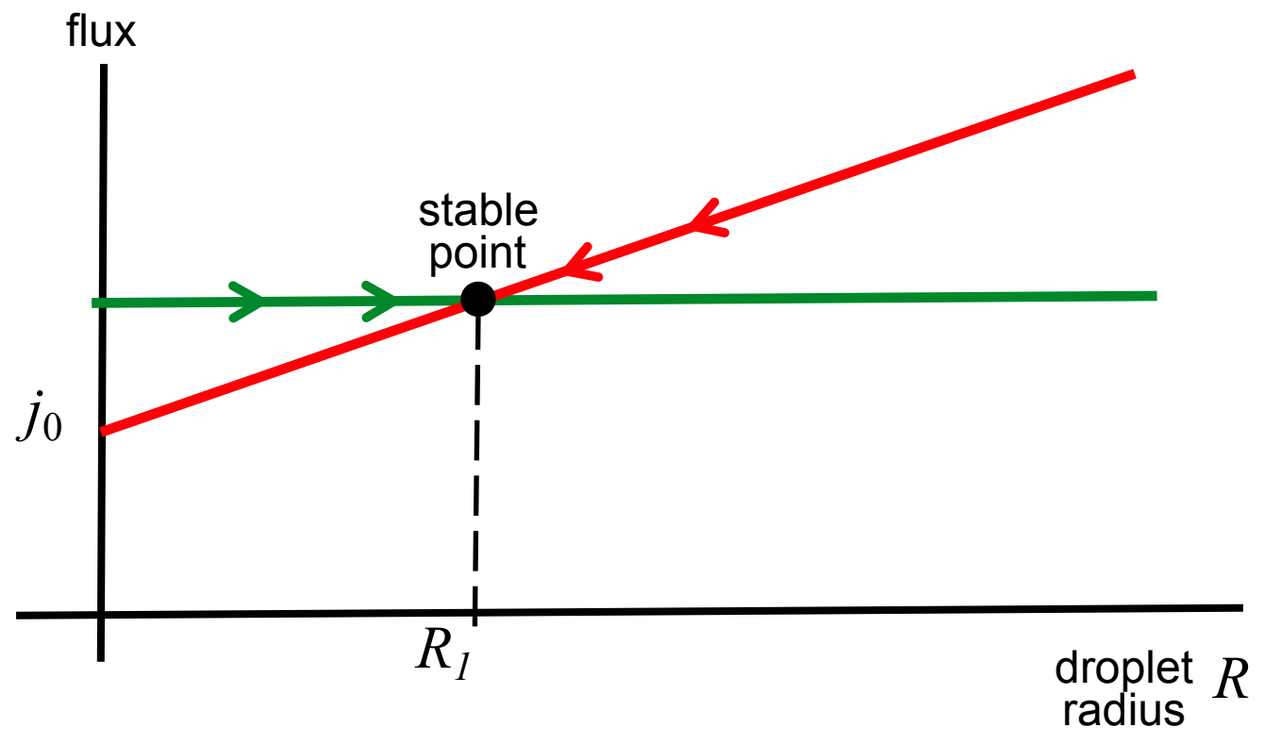
Zwicker et al., *PRE* 92 (2015)

Internally maintained droplets





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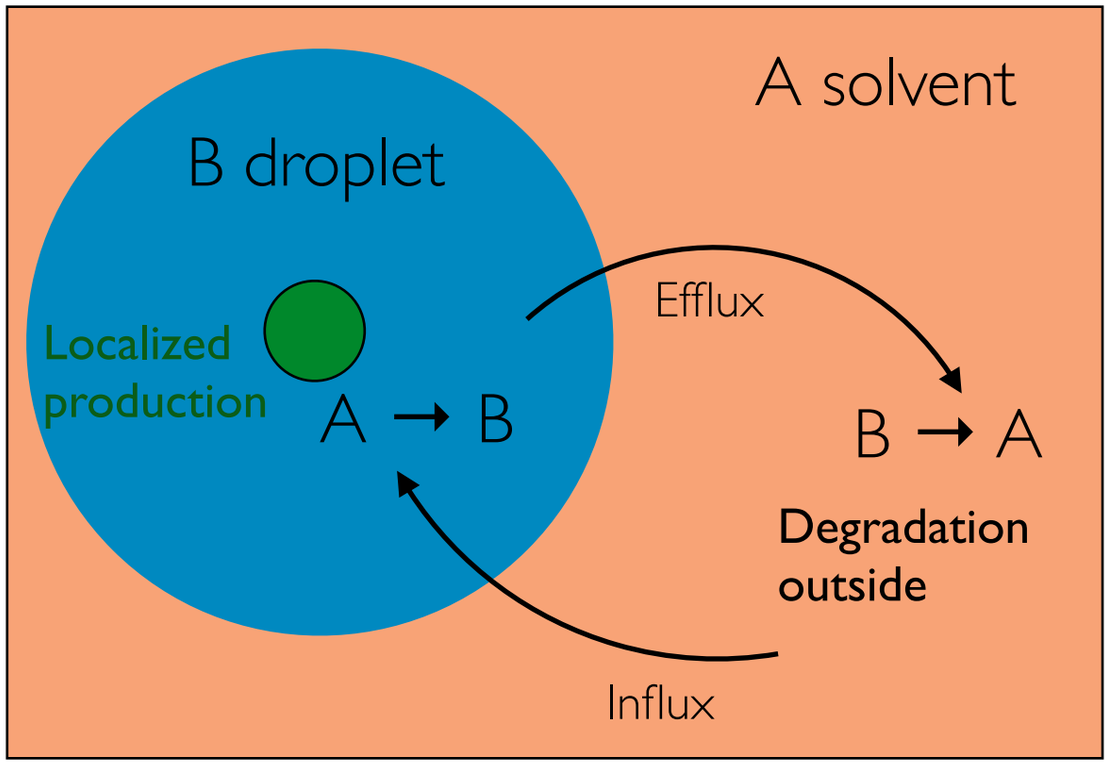
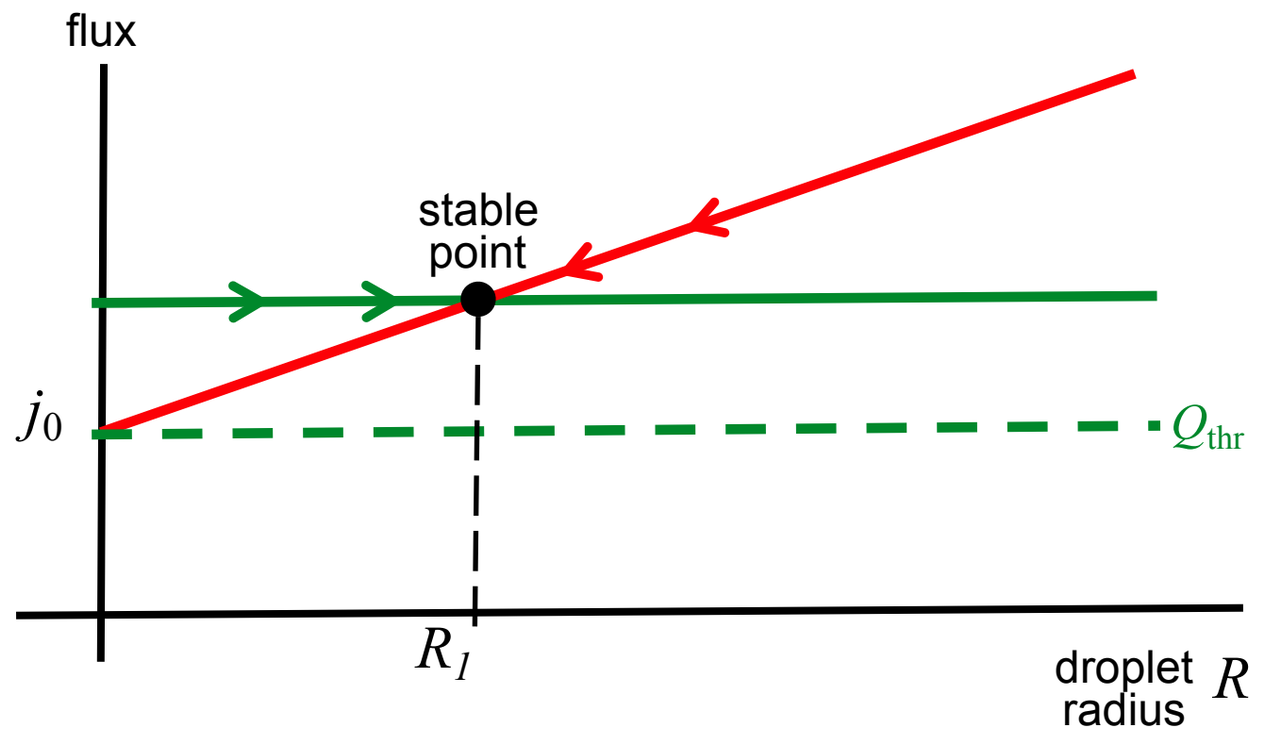
Zwicker et al., *PRE* 92 (2015)

Internally maintained droplets





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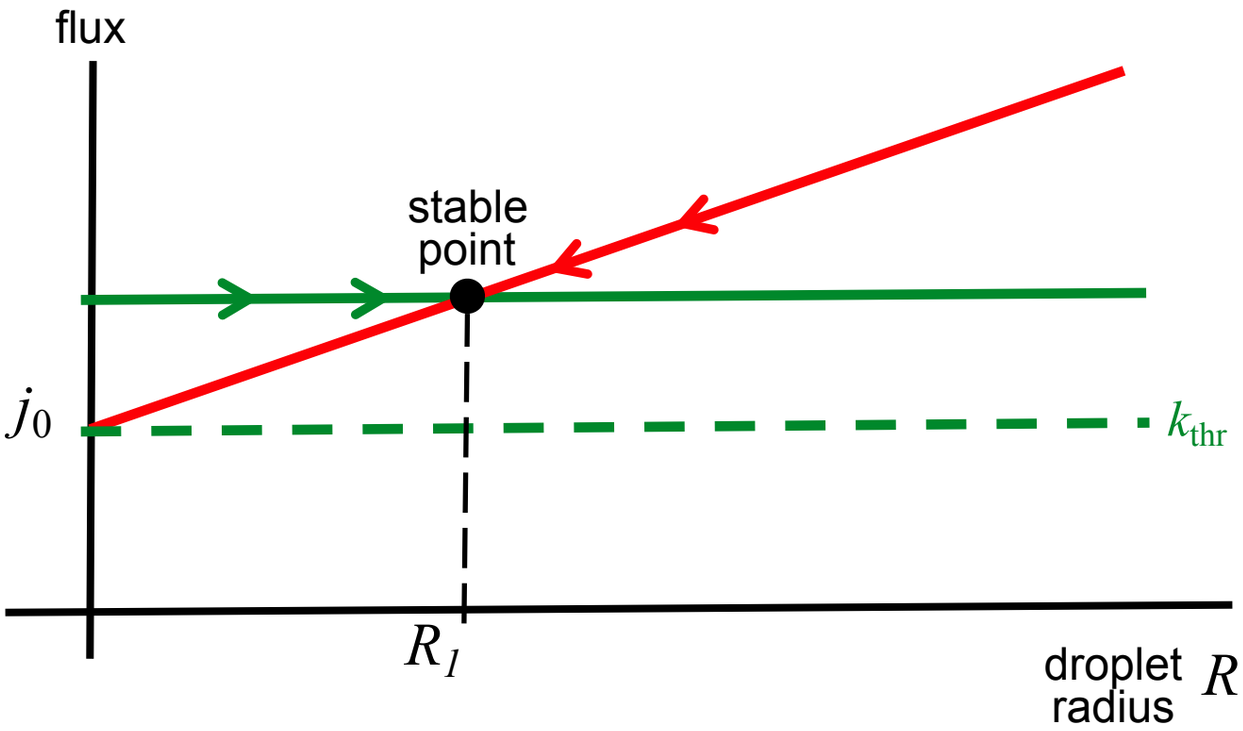
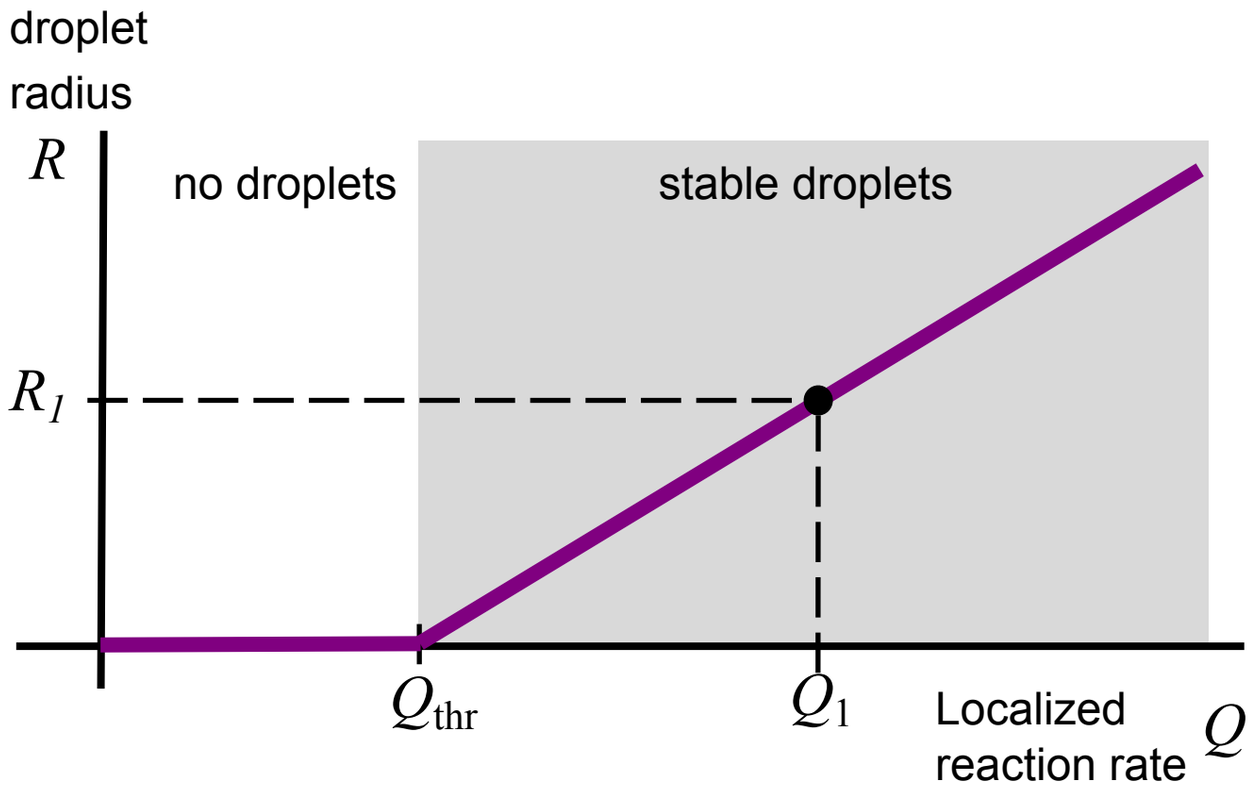
Zwicker et al., *PRE* 92 (2015)

Internally maintained droplets





Reaction-limited influx ~ Constant flux Q

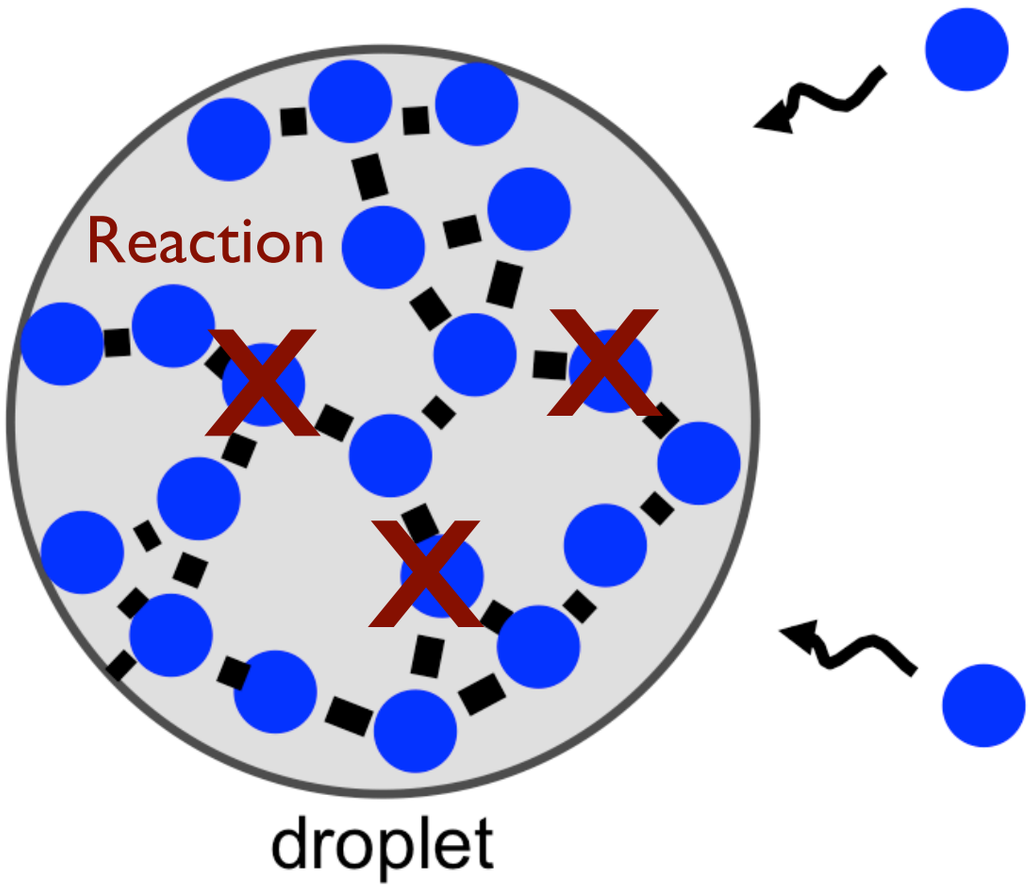
Diffusion-limited efflux ~ Radius R

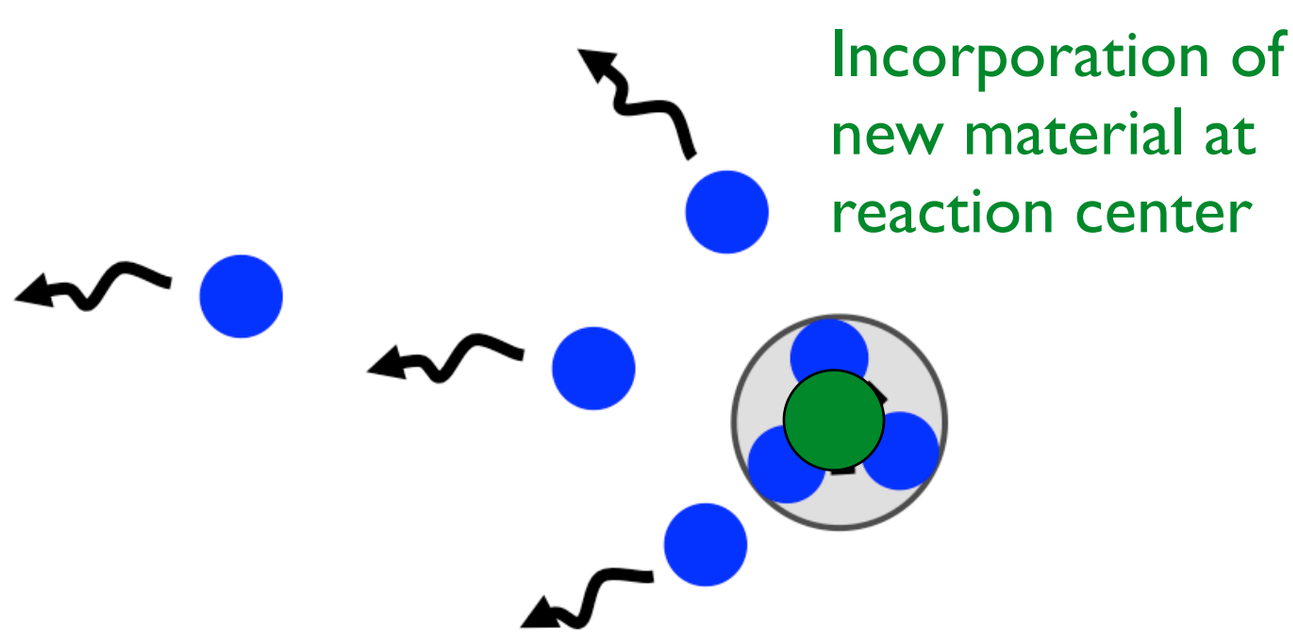
Zwicker et al., *PRE* 92 (2015)

Two scenarios of active droplets

Externally maintained
Take material from
large droplets

Internally maintained
Add material to
small droplets



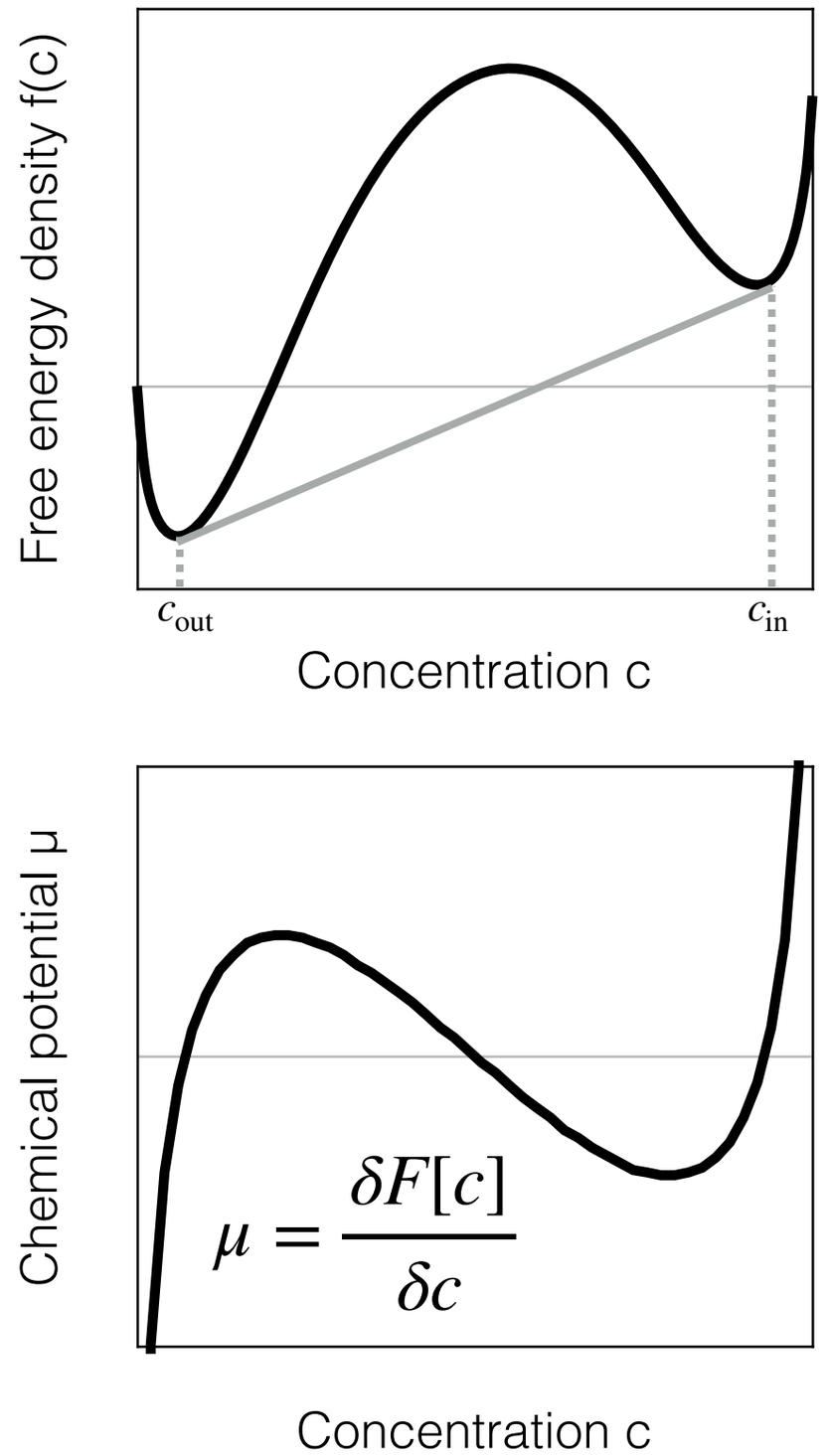


Weber, Zwicker, Jülicher, Lee, *Rep. Prog. Phys.* 82 (2019)

Non-equilibrium thermodynamics of active droplets

Phenomenological:

$$\partial_t c = \underbrace{D\nabla^2 c}_{\text{diffusion}} + \underbrace{s(c)}_{\text{reactions}}$$



Weber, Zwicker, Jülicher, Lee, *Rep. Prog. Phys.* 82 (2019)

Non-equilibrium thermodynamics of active droplets

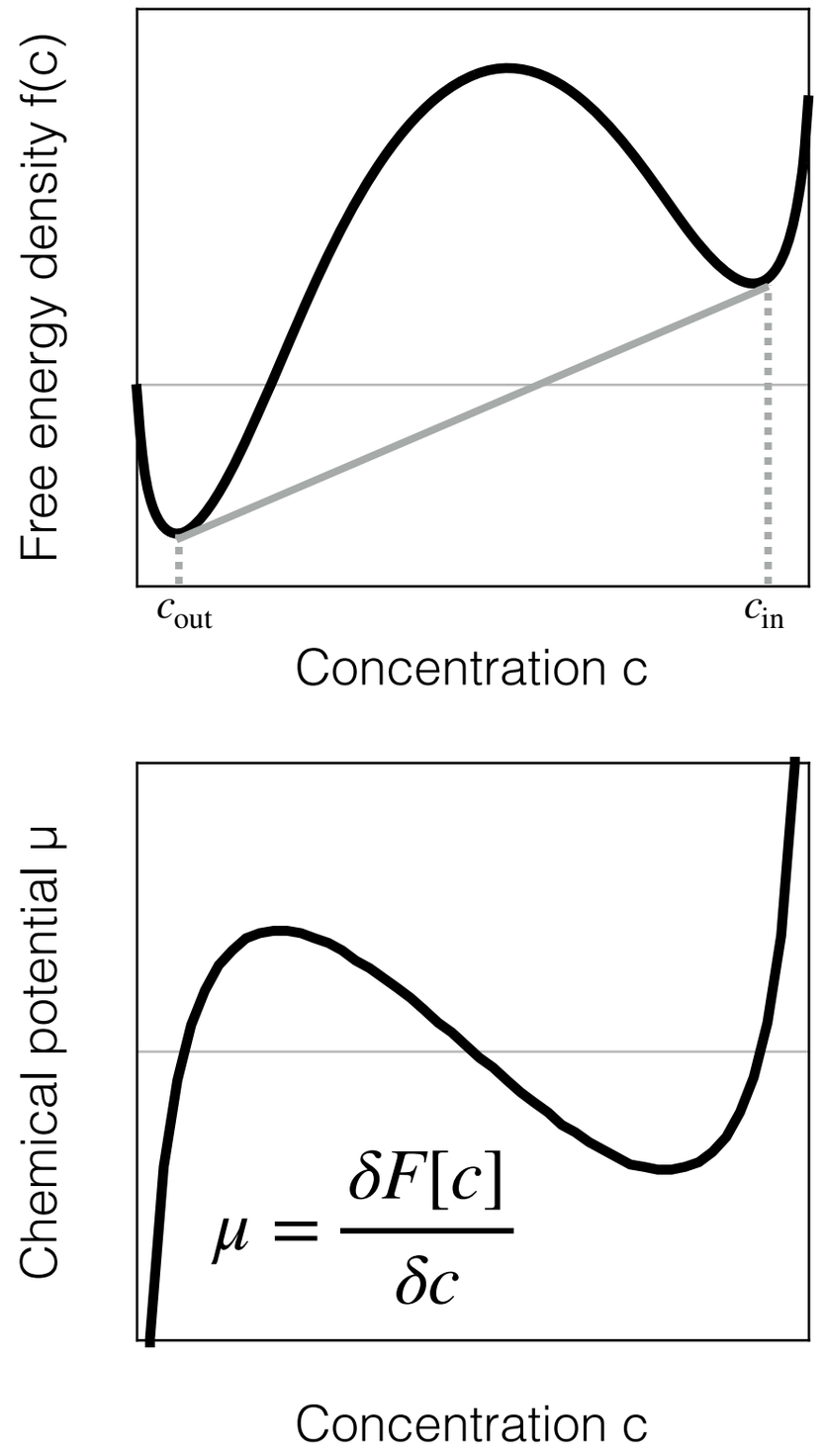
Phenomenological:

$$\partial_t c = \underbrace{D\nabla^2 c}_{\text{diffusion}} + \underbrace{s(c)}_{\text{reactions}}$$

Thermodynamically consistent:

$$\partial_t c = \underbrace{\Lambda\nabla^2\mu}_{\text{diffusive flux}} - \underbrace{\Lambda_1\mu}_{A \rightleftharpoons B}$$

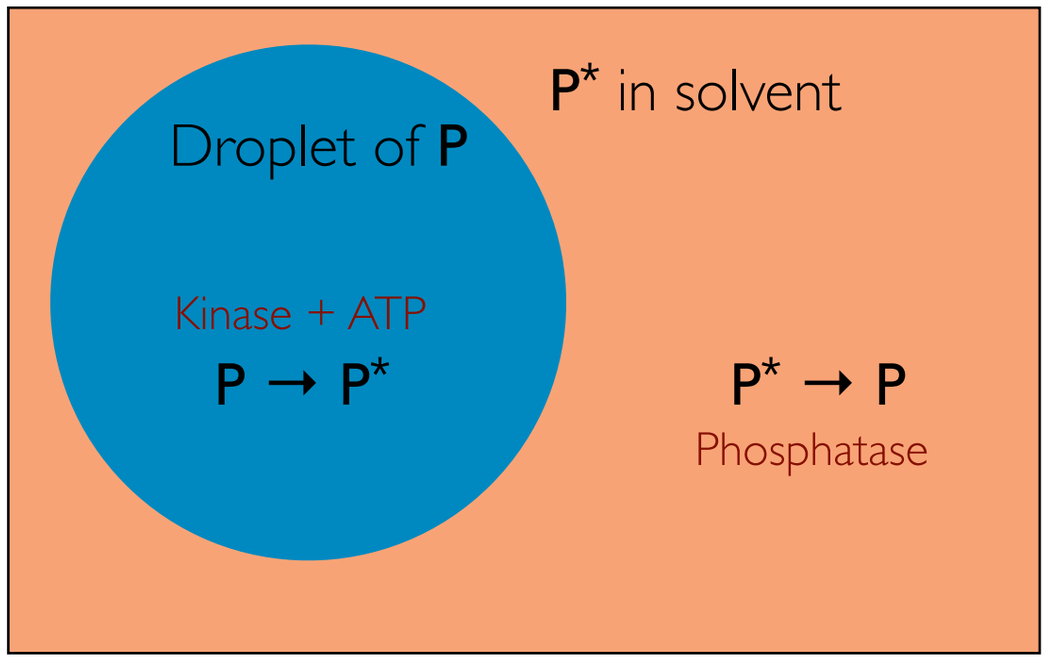
Spontaneous reaction



Weber, Zwicker, Jülicher, Lee, *Rep. Prog. Phys.* 82 (2019)

Two distinct models of active droplets

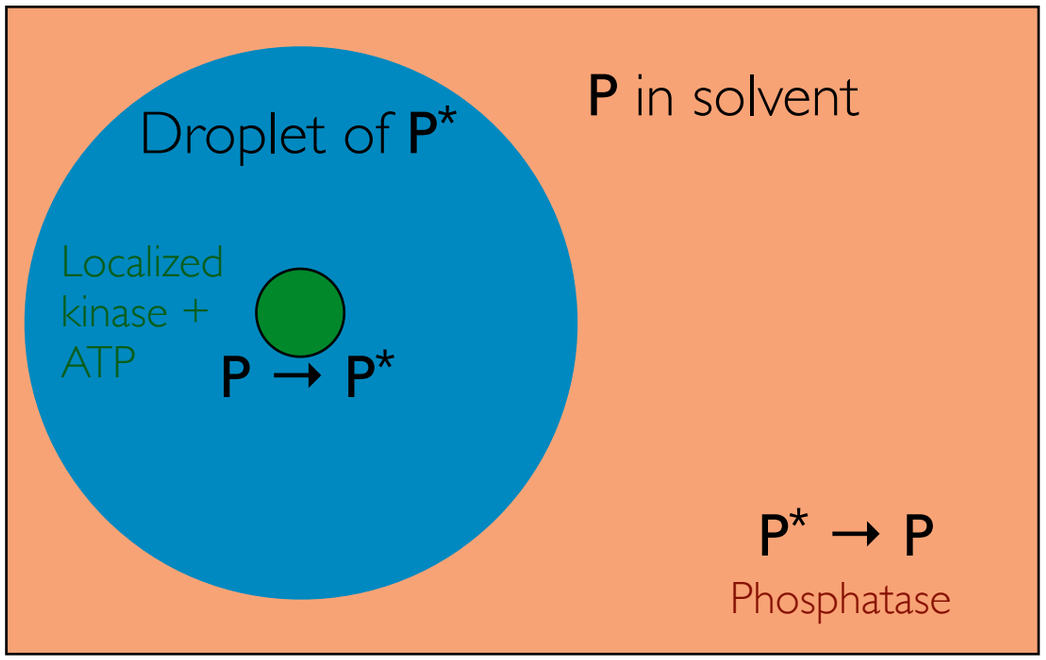
Externally maintained droplets



Enrichment-inhibition model

P granules
Stress granules
Splicing speckles
Cajal bodies
Synaptic vesicles

Internally maintained droplets

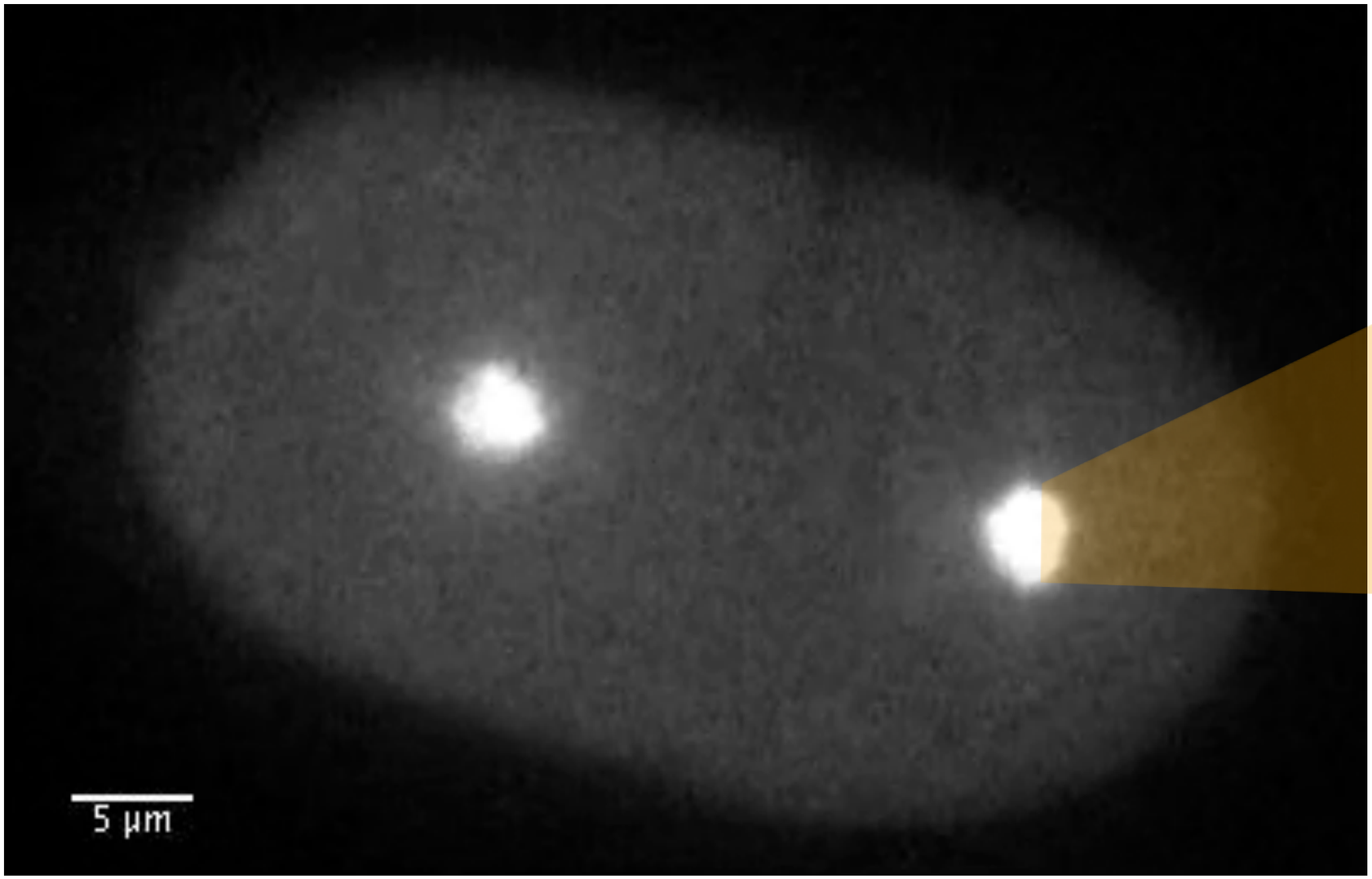


Localization-induction model

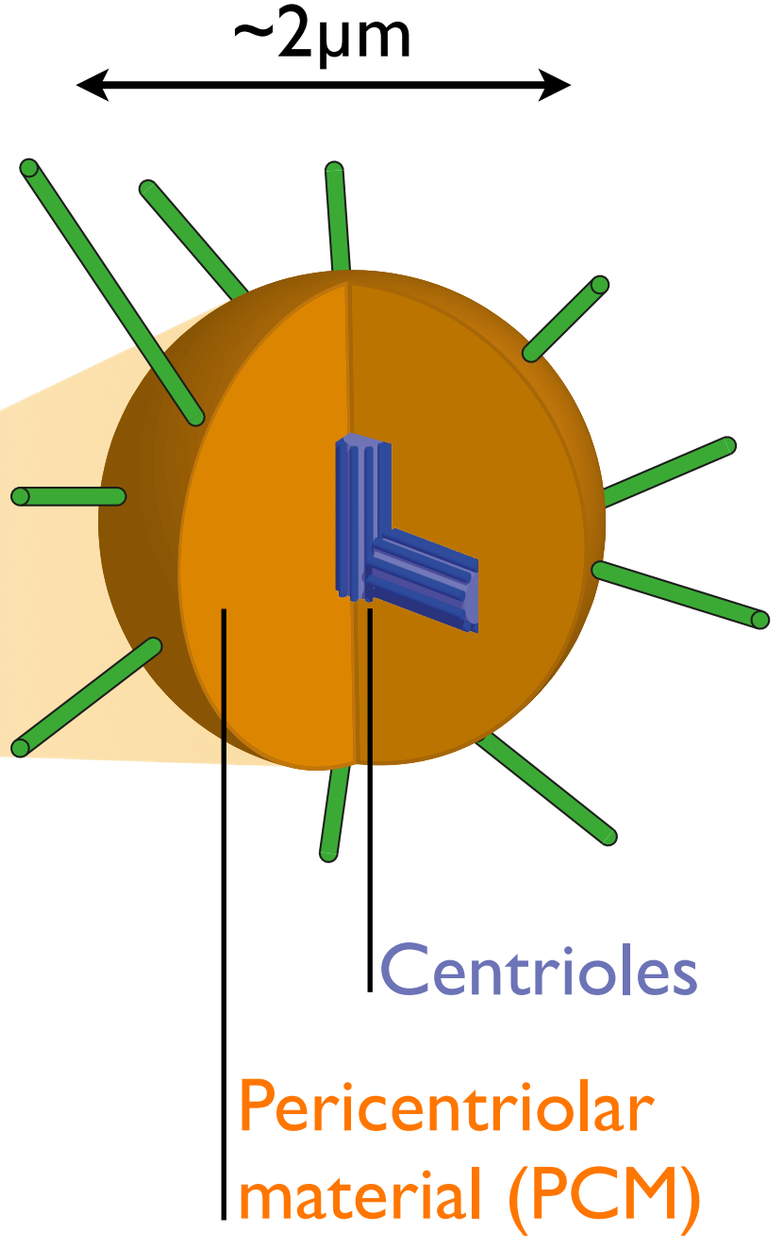
Centrosomes
T-cell signal transduction
Transmembrane receptor clusters
BuGZ condensates
Transcription initiation condensates?

Söding et al, bioRxiv/694406

Internally maintained droplets: Centrosomes



C. elegans embryo, GFP::SPD-5 Maximum projection
recorded by B. Gomes, Hyman lab, MPI-CBG



Zwicker et al., *PNAS* 111 (2014)
Zwicker et al., *PRL* 121 (2018)

Externally maintained droplet: Stress granules

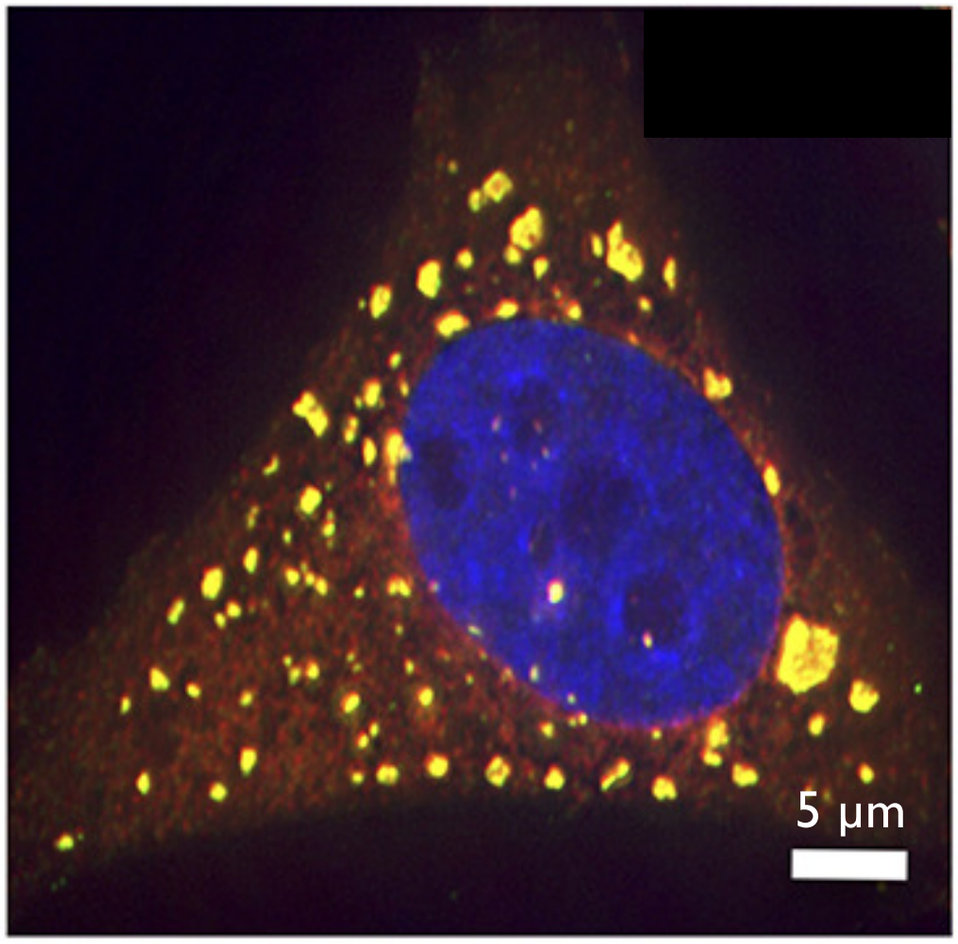
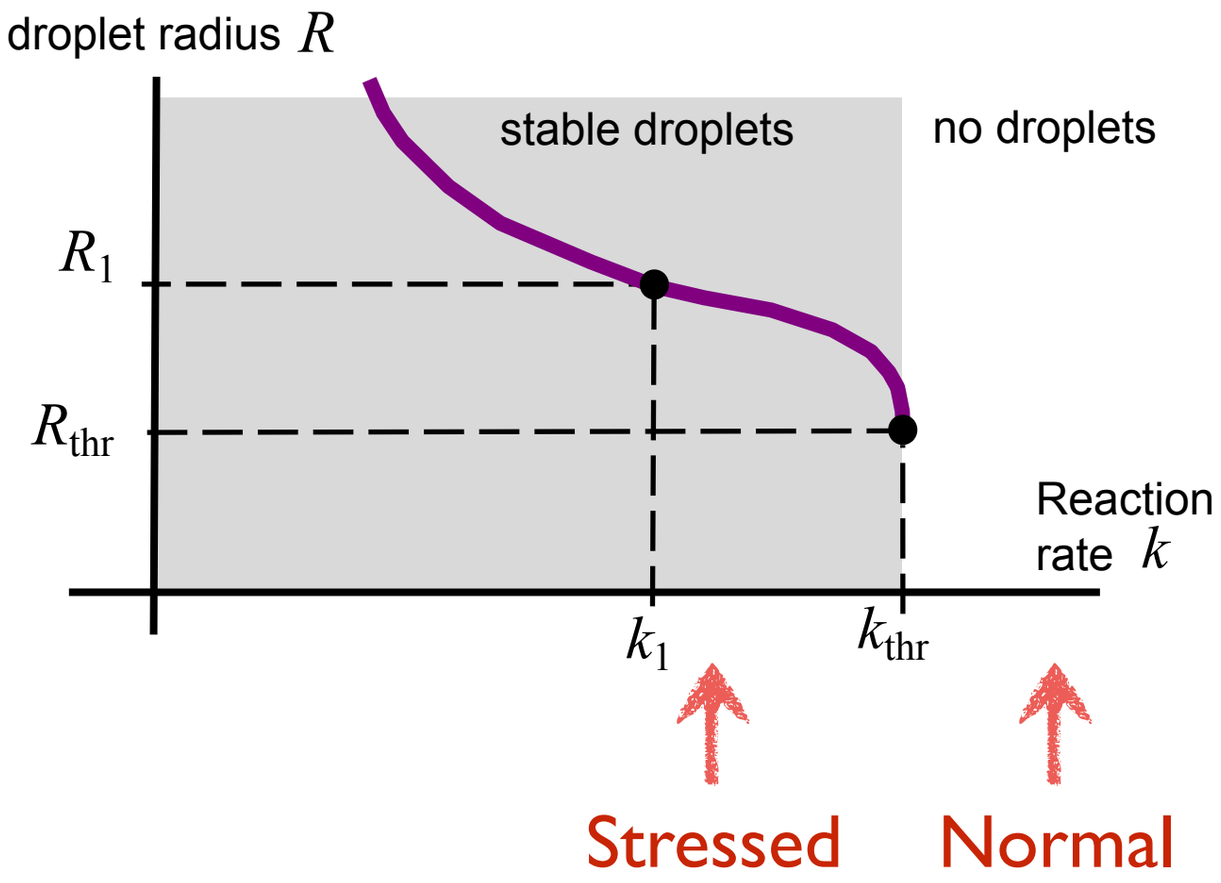


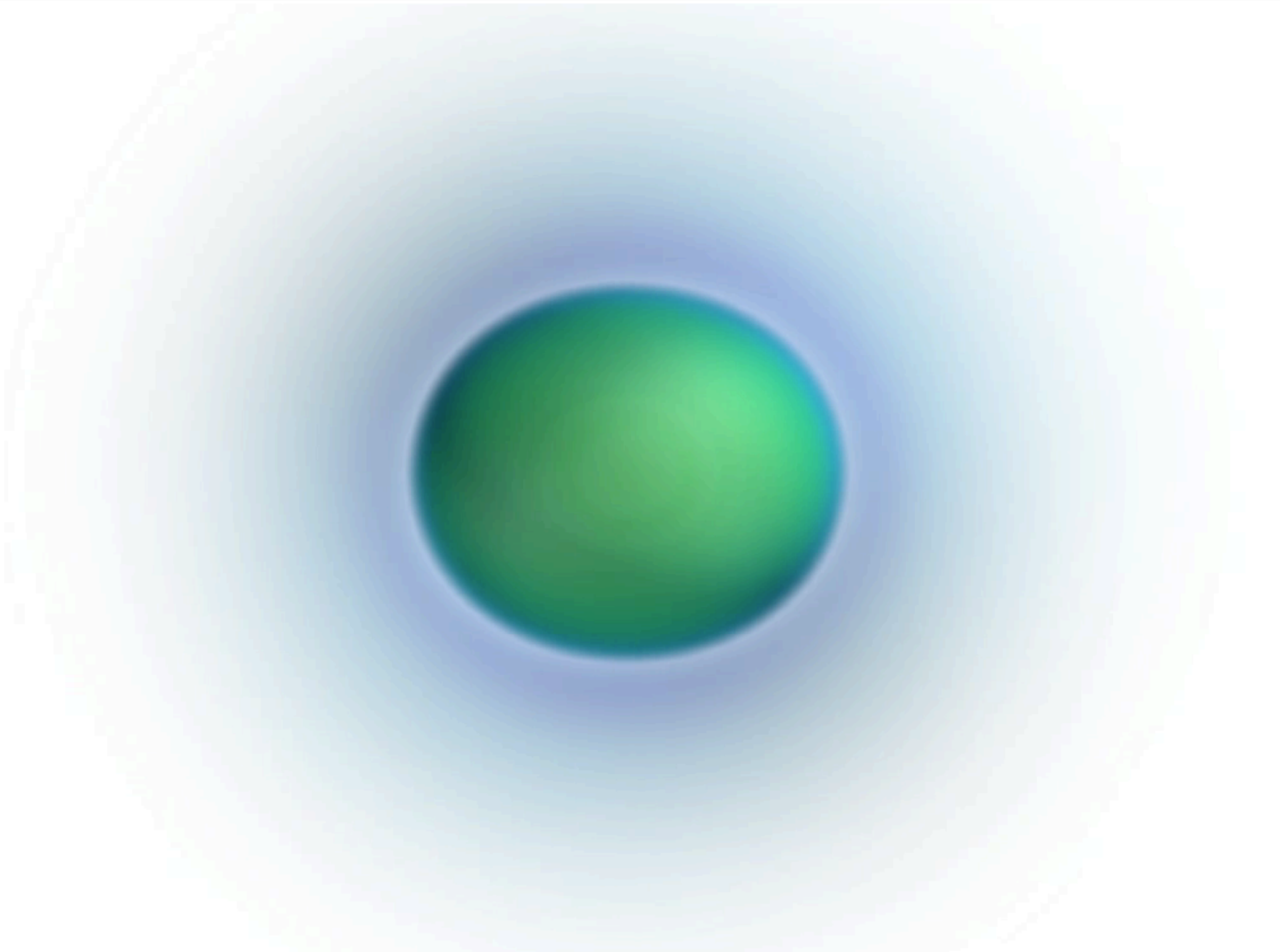
Image from Wheeler et al., Elife 5 (2016)



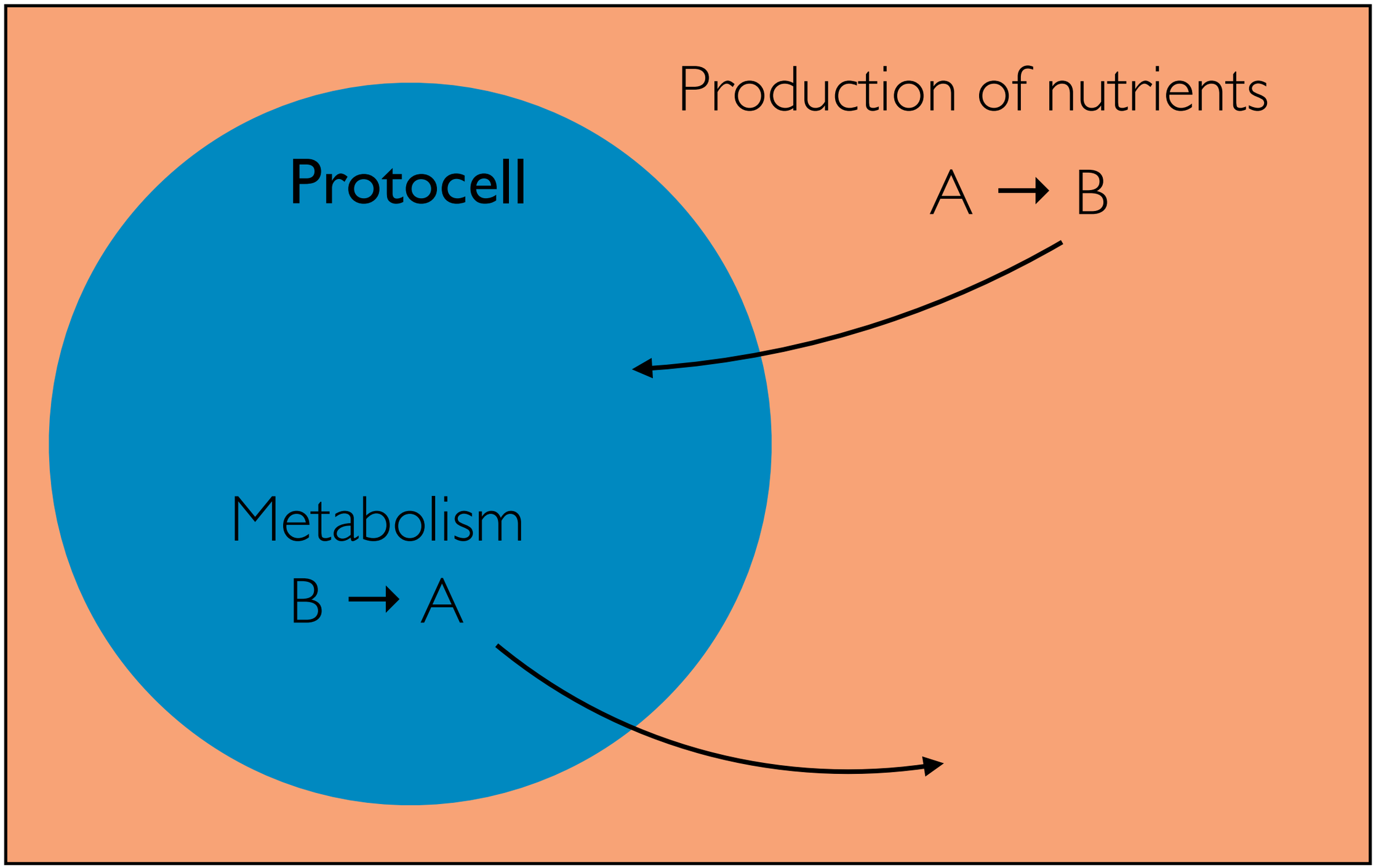
Stress granules form under conditions of reduced ATP

Wurtz, Lee, *New J. Phys.* 20 (2018)

Externally maintained droplets: Spontaneous division

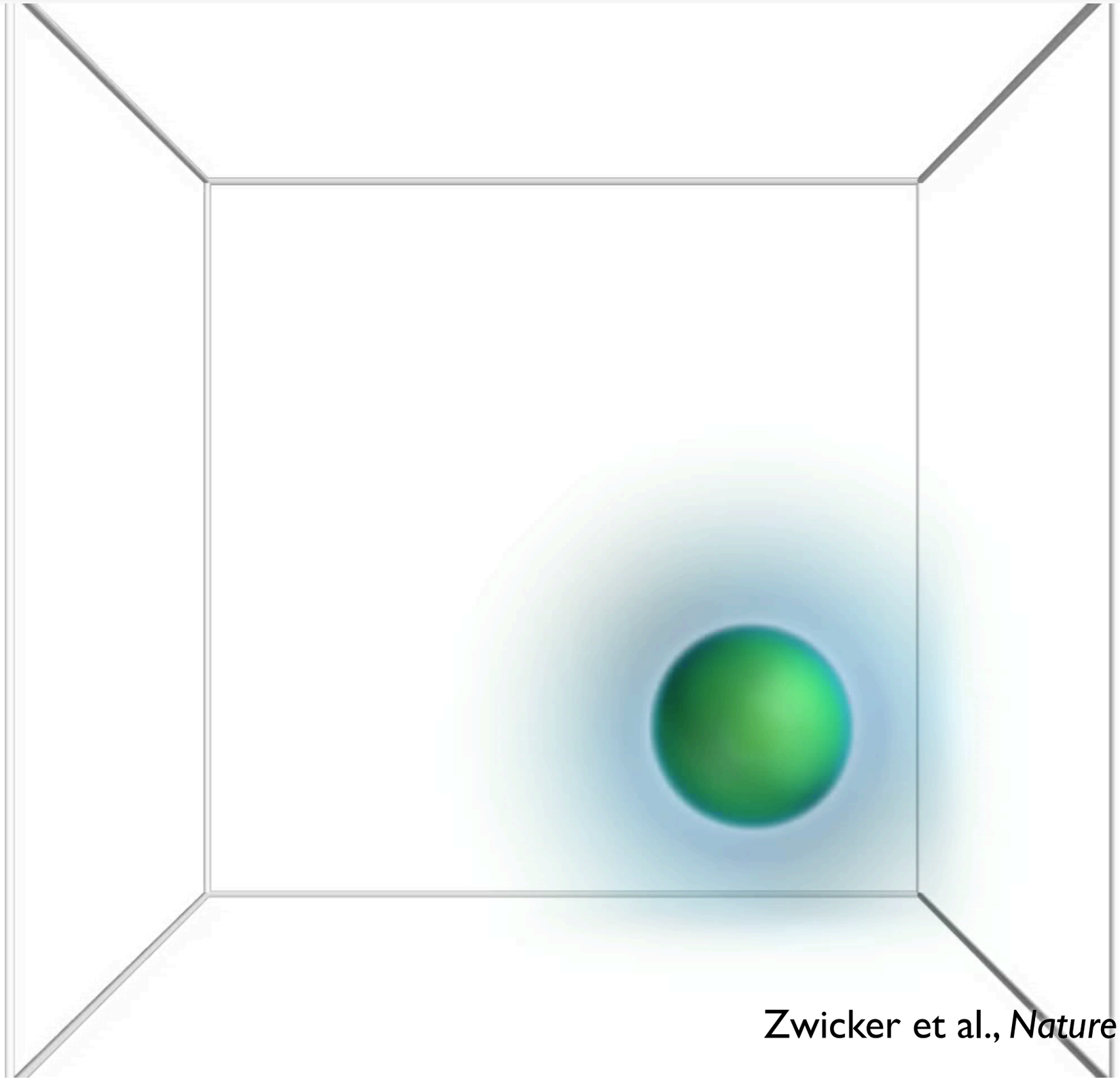


Externally maintained droplets: Protocell model



Zwicker et al., *Nature Physics* 13 (2017)

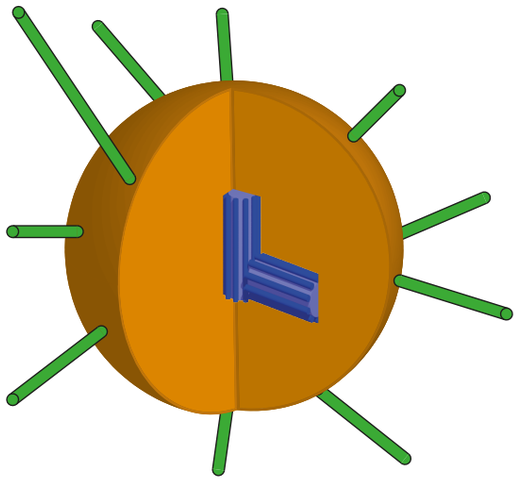
Externally maintained droplets: Protocell model



Zwicker et al., *Nature Physics* 13 (2017)

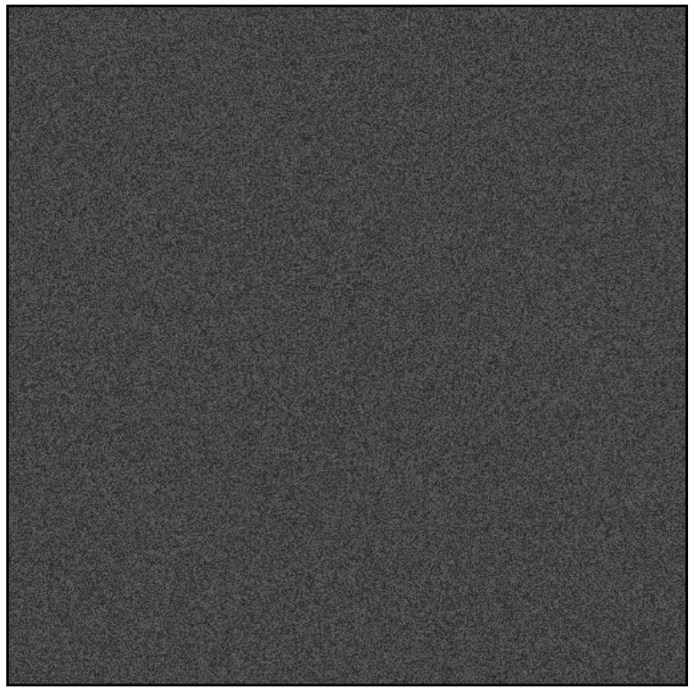
Chemical reactions can control droplets

Controlled nucleation



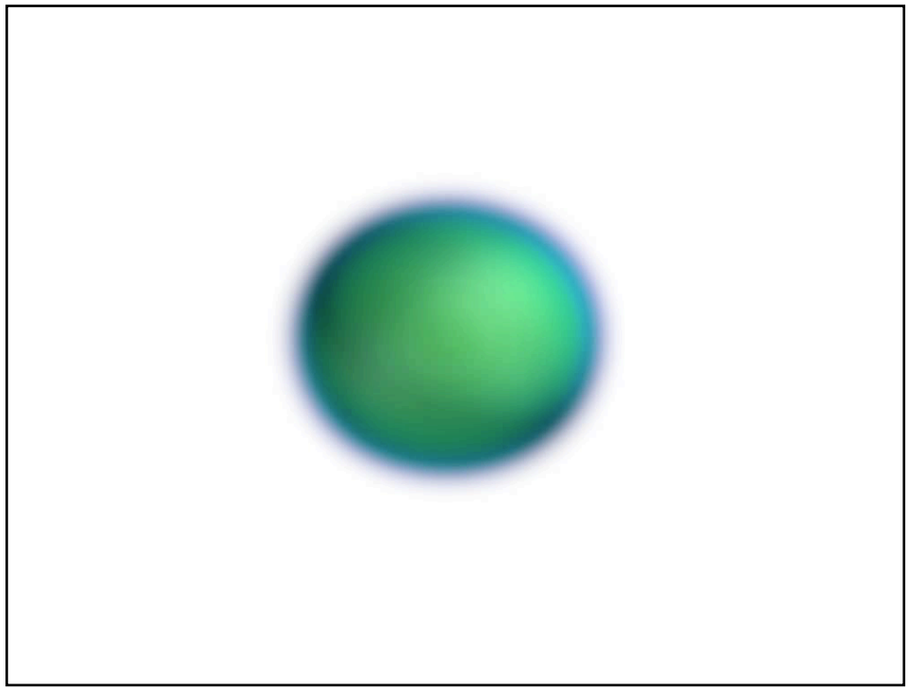
DZ et al., *PNAS* 111 (2014)
DZ et al., *PRL* 121 (2018)

Controlled droplet size



DZ et al., *PRE* 92 (2015)
Söding et al., bioRxiv/694406

Spontaneous drop division



DZ et al., *Nature Physics* 13 (2017)

Review "Physics of Active Emulsions" *Rep. Prog. Phys.* 82 (2019)