Physics of active emulsions: Implications for stress granules

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Phase separation vs. emulsions

Phase separation

A stable emulsion
Why an emulsion can be a good thing?

Carboxysomes in bacteria

Many small drops can be better than one big drop

F Hinzpeter, U Gerland & F Tostevin (2016) Biophys. J.
Plan

1. Instabilities in emulsions
2. Non-equilibrium (active) phase separation
3. Implications for stress granule formation
4. Summary & Outlook
1. Instabilities in emulsions
Emulsions tend to be unstable

Creaming / Sedimentation
- Differential buoyancy

Flocculation
- Coagulation of drops

Coalescence
- Fusion of drops

Ostwald ripening
- Big drops grow by sucking material from small drops at a distance
Sedimentation

Precipitation of nucleoli (Red) and Histone locus bodies (Green) in *Xenopus* germinal vesicles upon actin filament disruption

Flocculation

Processing bodies (Green) & P granules (Red) in *C. elegans* embryos

Coalescence

TAR-DNA binding protein 43 (TDP-43) Ribonucleoprotein granules in neurons

PP Gopal, JJ Nirschl, E Klinman & ELF Holzbaurt (2017) PNAS
Ostwald ripening

Nucleoli in \textit{C. elegans} embryo

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{image}
\caption{Nucleoli in \textit{C. elegans} embryo during Ostwald ripening process. Coalescence and dissolution are indicated at specific time points.}
\end{figure}

\text{J Berry, SC Weber, N Vaidya, M Haataja & CP Brangwynne (2015) PNAS}
Focus on the late-stage / steady-state

- Creaming / sedimentation
- Flocculation
- Coalescence
- Ostwald ripening

Gravity not important

Macromolecular crowding -> drops diffuse less as they grow
Ostwald ripening: big drops grow at the expense of small drops

1. Gibbs-Thomson relation:

\[ \rho(R) = \rho(R = \infty) \left(1 + \frac{l_c}{R}\right) \]

2. Solute diffuses between drops

\[ \langle R(t) \rangle \sim t^{1/3} \]
Second law of thermodynamics

No rotation

Time

Time
Second law of thermodynamics

No rotation

Time

Time

?
2. Non-equilibrium (active) phase separation
Two hallmarks of living matter

• Self-generated mechanical force
  • motility via ATP-driven molecular motors

• Driven chemical reactions
  • metabolism, ATP-driven phosphorylation)
Motility-induced phase separation [MIPS]

• Phase separation without attractive interactions
Ostwald-ripening in MIPS

1. Gibbs-Thomson relation: [Solute] outside a big drop < [Solute] outside a small drop

2. Active particles diffuse between drops

\[ R(t) \sim t^{1/3} \]

Chemical reaction-controlled phase separation

Separating state ($P$) & Soluble state ($S$)

\[
\begin{align*}
\frac{\partial P_{\text{in,out}}}{\partial t} &= D \nabla^2 P_{\text{in,out}} - k P_{\text{in,out}} + h S_{\text{in,out}}, \\
\frac{\partial S_{\text{in,out}}}{\partial t} &= D \nabla^2 S_{\text{in,out}} + k P_{\text{in,out}} - h S_{\text{in,out}}.
\end{align*}
\]

Phase separation with chemical reactions

\[ P(x) \]

\[ x \]
Phase separation with chemical reactions
Phase separation with chemical reactions

\[ P(x) \]

\[ k \]

\[ h \]
Chemical reaction can stop coarsening

Novel phase diagram

Stable, multi-drop system

3. Implications for stress granule formation
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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2. No SG at normal [ATP], but SG form at 50% [ATP]

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

Model A

\[ \text{ATP}_P \xrightarrow{k} \text{ATP}_S \]

[ATP]

\[ \text{[ATP]} \xrightarrow{\text{Time}} \]

\[ R \xrightarrow{\text{Time}} \]

SG maximal radius

Stable, monodisperse SG

Unstable SG (coarsening)

No SG

\( \alpha_c \) (Normal)

ATP concentration \( \alpha (K^{-1}_A s^{-1}) \)

JD Wurtz & CFL (2018)
# Insurance mechanism

<table>
<thead>
<tr>
<th></th>
<th>Cell</th>
<th>Car</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Normal conditions</strong></td>
<td>ATP consumption</td>
<td>Monthly payment</td>
</tr>
<tr>
<td><strong>Stress conditions / Accident</strong></td>
<td>SG formation for free</td>
<td>Insurance coverage</td>
</tr>
</tbody>
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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

Biology inspires new physics

Physics allows us to do quantitative biology

Thank you for your attention!

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