Active phase separation in mixtures of chemically interacting particles

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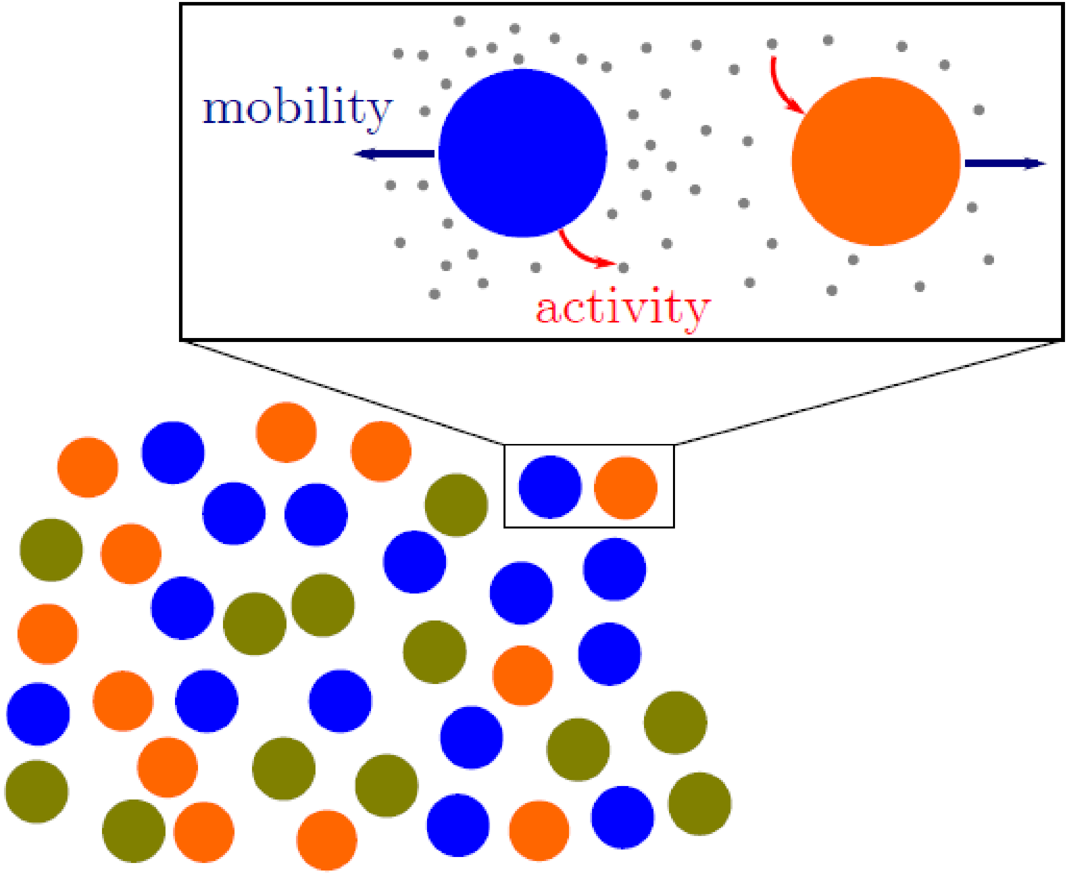
Chemically interacting particles: ???

microorganisms, catalytic colloids, enzymes…

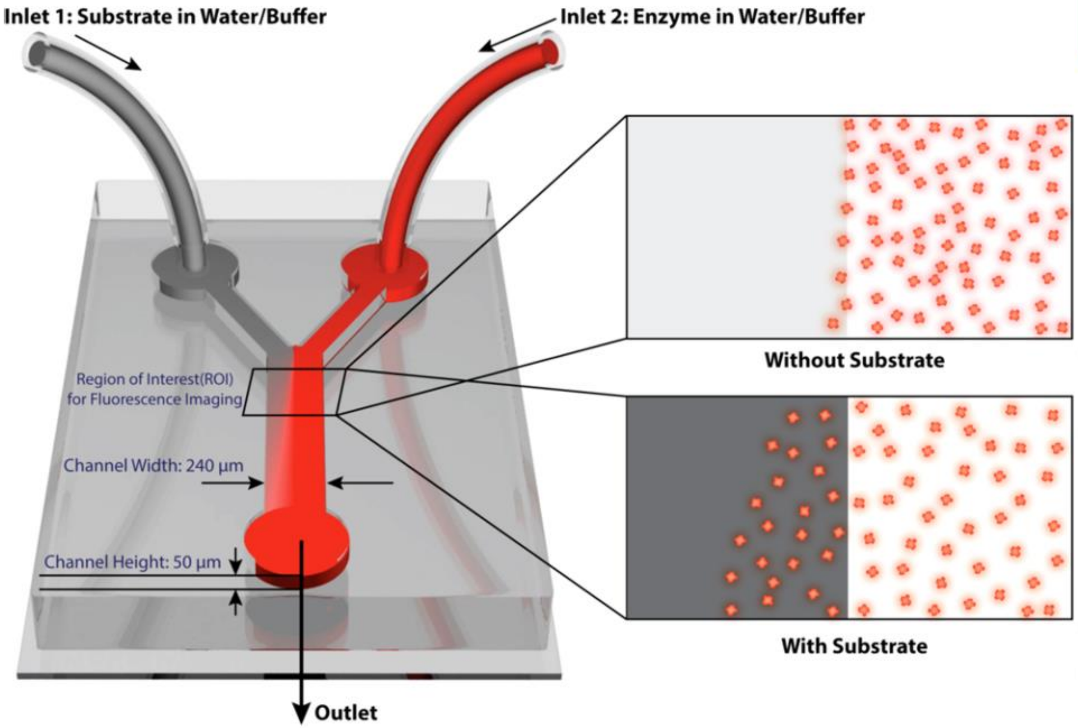


▶ **will such a mixture remain homogeneous?**

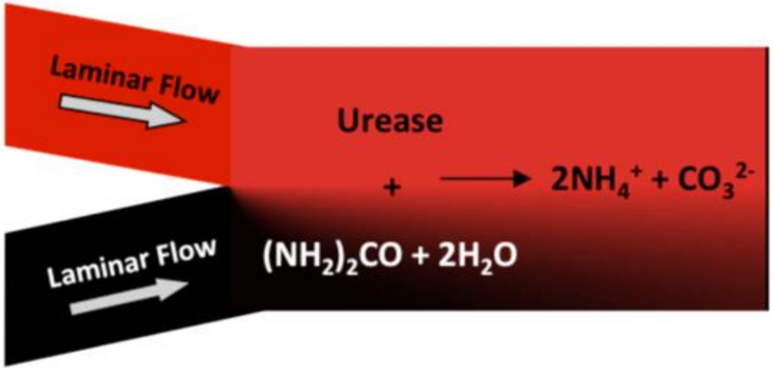
Detour:

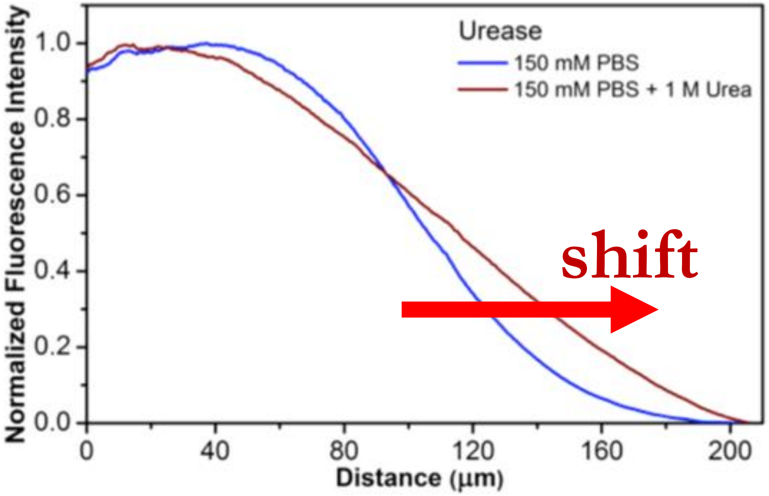
Chemotaxis of catalytic enzymes in the presence of their substrate

Experimental Observations of Enzyme Chemotaxis



S. Sengupta,…, A. Sen, JACS, 135(4), 1406–1414 (2013).





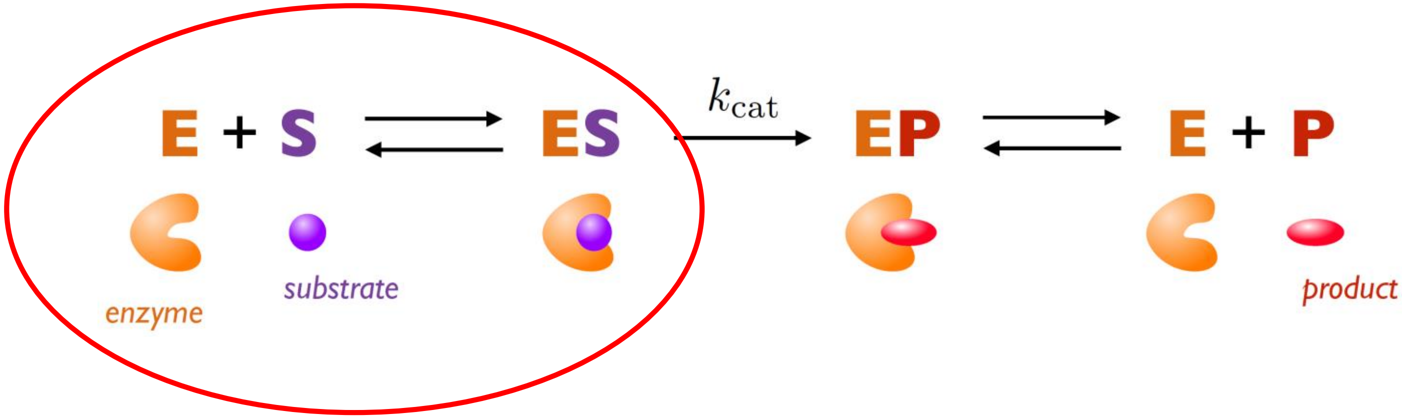
Typically towards the substrate, occasionally away from it

Experimental Observations of Enzyme Chemotaxis

- Yu et al. JACS, 131(16), 5722–5723 (2009)
  RNA polymerase: Chemotaxis
- Sengupta et al. JACS 135(4), 1406–1414 (2013)
  Catalase, urease: Chemotaxis
- Sengupta et al. ACS Nano, 8(3), 2410–2418 (2014)
  DNA polymerase: Chemotaxis
- Zhao et al. Nat. Chem, 10, 311–317 (2018)
  Hexokinase, aldolase: Chemotaxis
- Jee et al. PNAS, 139(44), 15588–15591 (2018)
  Urease, acetylcholinesterase: Antichemotaxis (!)

Conflicting observations for urease!

What is the mechanism of enzyme chemotaxis?

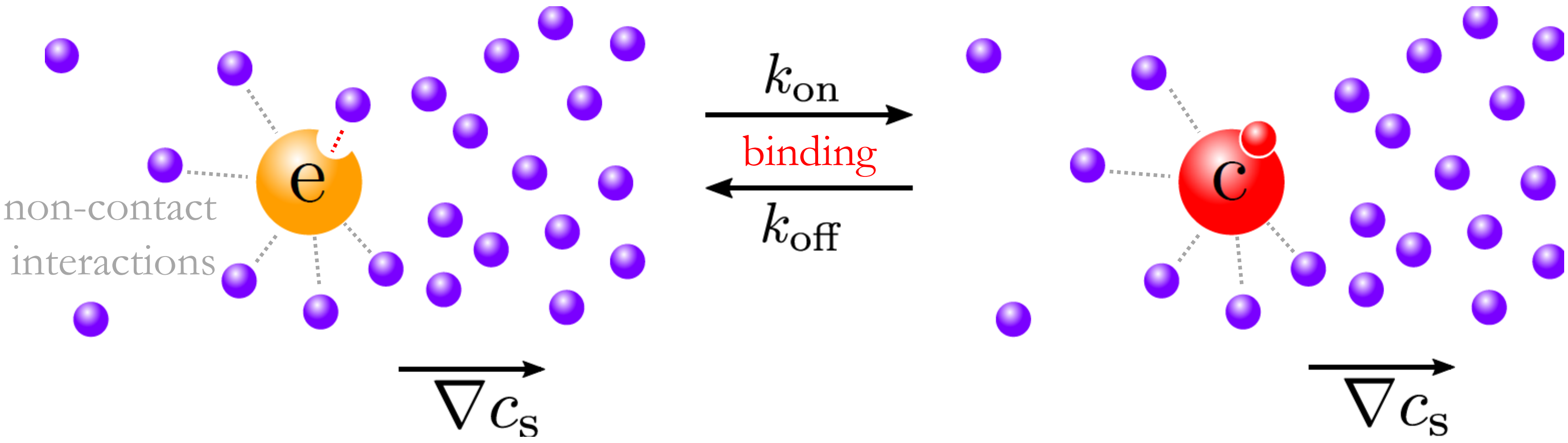


- **Active** mechanisms (self-phoresis, stochastic swimming…) depending on the catalytic step seem to be **too weak to explain observations**

  [Golestanian, R. (2015). *Phys. Rev. Lett.*, *115*(10), 108102.]

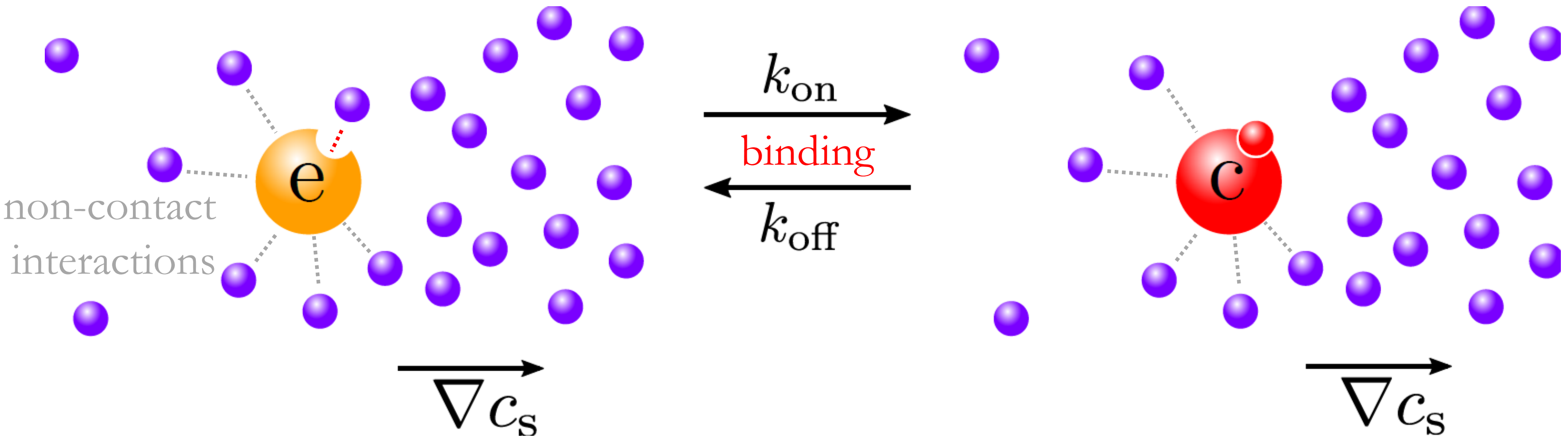
- Could **passive** mechanisms (just binding-unbinding) explain the observations?

A Microscopic Model of Enzyme Chemotaxis



- **Interactions between enzyme and substrate:**
    - **Binding to form a complex**
    - **Non-contact (electrostatic, van der Waals, etc.)**
    - **Hydrodynamic**

A Microscopic Model of Enzyme Chemotaxis



- **Starting from the full Fokker-Planck equation for the (N+1)-particle probability distribution, integrating out the substrate we obtain:**

$$\begin{aligned}
\partial_t c_{\mathrm{e}}(\boldsymbol{R};t) &= \nabla_{\boldsymbol{R}} \cdot \left[D_{\mathrm{e}} \nabla_{\boldsymbol{R}} c_{\mathrm{e}} - \boldsymbol{v}_{\mathbf{e}}(\boldsymbol{R}) c_{\mathrm{e}} \right] - k_{\mathrm{on}} c_{\mathrm{e}} c_{\mathrm{s}} + k_{\mathrm{off}} c_{\mathrm{c}} \\
\partial_t c_{\mathrm{c}}(\boldsymbol{R};t) &= \nabla_{\boldsymbol{R}} \cdot \left[D_{\mathrm{c}} \nabla_{\boldsymbol{R}} c_{\mathrm{c}} - \boldsymbol{v}_{\mathbf{c}}(\boldsymbol{R}) c_{\mathrm{c}} \right] + k_{\mathrm{on}} c_{\mathrm{e}} c_{\mathrm{s}} - k_{\mathrm{off}} c_{\mathrm{c}}
\end{aligned}$$

↑ diffusion ↑ phoresis ↑ binding ↑ unbinding

A Microscopic Model of Enzyme Chemotaxis

$$\begin{aligned}\partial_t c_{\mathrm{e}}(\boldsymbol{R};t) &= \nabla_{\boldsymbol{R}}\cdot\left[D_{\mathrm{e}}\nabla_{\boldsymbol{R}}c_{\mathrm{e}} - \boldsymbol{v}_{\mathbf{e}}(\boldsymbol{R})c_{\mathrm{e}}\right] - k_{\mathrm{on}}c_{\mathrm{e}}c_{\mathrm{s}} + k_{\mathrm{off}}c_{\mathrm{c}}\\ \partial_t c_{\mathrm{c}}(\boldsymbol{R};t) &= \nabla_{\boldsymbol{R}}\cdot\left[D_{\mathrm{c}}\nabla_{\boldsymbol{R}}c_{\mathrm{c}} - \boldsymbol{v}_{\mathbf{c}}(\boldsymbol{R})c_{\mathrm{c}}\right] + k_{\mathrm{on}}c_{\mathrm{e}}c_{\mathrm{s}} - k_{\mathrm{off}}c_{\mathrm{c}}\end{aligned}$$

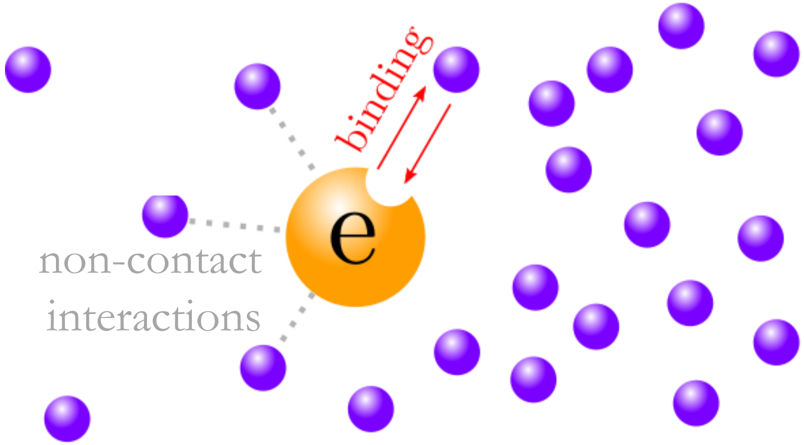
Diffusion coefficients of free enzyme and complex different in general $D_{\mathrm{e}} \neq D_{\mathrm{c}}$ **(conformational changes!)**

Phoresis due to non-contact interactions with substrate:

$$\begin{aligned}\boldsymbol{v}_{\mathbf{e}}(\boldsymbol{R}) &\approx \frac{k_{\mathrm{B}}T}{\eta}\left[\int_0^\infty \mathrm{d}h\,h\left(\mathrm{e}^{-\phi^{\mathrm{es}}(h)/k_{\mathrm{B}}T}-1\right)\right]\nabla_{\boldsymbol{R}}c_{\mathrm{s}} \equiv \frac{k_{\mathrm{B}}T}{\eta}\lambda_{\mathrm{e}}^2\nabla_{\boldsymbol{R}}c_{\mathrm{s}}\\ \boldsymbol{v}_{\mathbf{c}}(\boldsymbol{R}) &\approx \frac{k_{\mathrm{B}}T}{\eta}\left[\int_0^\infty \mathrm{d}h\,h\left(\mathrm{e}^{-\phi^{\mathrm{cs}}(h)/k_{\mathrm{B}}T}-1\right)\right]\nabla_{\boldsymbol{R}}c_{\mathrm{s}} \equiv \frac{k_{\mathrm{B}}T}{\eta}\lambda_{\mathrm{c}}^2\nabla_{\boldsymbol{R}}c_{\mathrm{s}}\end{aligned}$$

Derjaguin lengths of free enzyme and complex different in general $\lambda_{\mathrm{e}} \neq \lambda_{\mathrm{c}}$

A Microscopic Model of Enzyme Chemotaxis



Experiments with fluorescently-labelled enzymes measure the total enzyme concentration

$$c_{\mathrm{e}}^{\mathrm{tot}}(\boldsymbol{R};t) = c_{\mathrm{e}}(\boldsymbol{R};t) + c_{\mathrm{c}}(\boldsymbol{R};t)$$

Binding-unbinding much faster than diffusion; we have instantaneous local binding equilibrium

$$k_{\mathrm{on}} c_{\mathrm{e}}(\boldsymbol{R};t) c_{\mathrm{s}}(\boldsymbol{R};t) \approx k_{\mathrm{off}} c_{\mathrm{c}}(\boldsymbol{R};t)$$

Diffusion and Chemotaxis of an Enzyme

We finally obtain:

$$\boxed{\partial_t c_{\mathrm{e}}^{\mathrm{tot}}(\boldsymbol{R};t) = \nabla_{\boldsymbol{R}} \cdot \left\{ D(\boldsymbol{R}) \cdot \nabla_{\boldsymbol{R}} c_{\mathrm{e}}^{\mathrm{tot}} - [\boldsymbol{V}_{\mathrm{ph}}(\boldsymbol{R}) + \boldsymbol{V}_{\mathrm{bi}}(\boldsymbol{R})] c_{\mathrm{e}}^{\mathrm{tot}} \right\}}$$

Substrate-dependent diffusion coefficient

$$D(\boldsymbol{R}) = D_{\mathrm{e}} + (D_{\mathrm{c}} - D_{\mathrm{e}}) \frac{c_{\mathrm{s}}(\boldsymbol{R})}{K + c_{\mathrm{s}}(\boldsymbol{R})}$$

With Michaelis-Menten style dependence…

Substrate-dependent phoretic velocity

$$\boldsymbol{V}_{\mathrm{ph}}(\boldsymbol{R}) = \boldsymbol{v}_{\mathbf{e}}(\boldsymbol{R}) + [\boldsymbol{v}_{\mathbf{c}}(\boldsymbol{R}) - \boldsymbol{v}_{\mathbf{e}}(\boldsymbol{R})] \frac{c_{\mathrm{s}}(\boldsymbol{R})}{K + c_{\mathrm{s}}(\boldsymbol{R})}$$

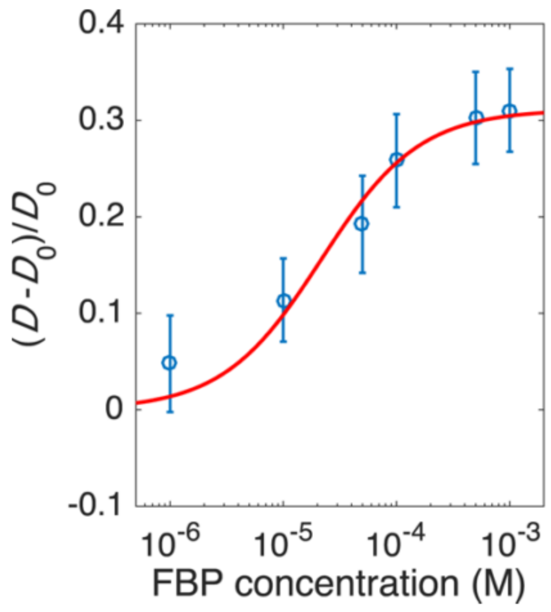
New binding-induced contribution to chemotaxis

$$\boldsymbol{V}_{\mathrm{bi}}(\boldsymbol{R}) = -(D_{\mathrm{c}} - D_{\mathrm{e}}) \nabla_{\boldsymbol{R}} \left(\frac{c_{\mathrm{s}}(\boldsymbol{R})}{K + c_{\mathrm{s}}(\boldsymbol{R})} \right)$$

Aside: Enhanced Diffusion

It has been observed experimentally that most enzymes exhibit enhanced diffusion in the presence of their substrate

Example: Aldolase



$$D(\boldsymbol{R}) = D_\mathrm{e} + (D_\mathrm{c} - D_\mathrm{e})\frac{c_\mathrm{s}(\boldsymbol{R})}{K + c_\mathrm{s}(\boldsymbol{R})}$$

with $D_\mathrm{c} > D_\mathrm{e}$

associated to binding-induced changes in the average shape and shape fluctuation spectrum of enzymes

P. Illien et al., Nano Lett. 17(7), 4415–4420. (2017)

P. Illien, T. Adeleke-Larodo, and R. Golestanian, EPL 119, 40002. (2017)

J.A-C., T. Adeleke-Larodo, P. Illien, & R. Golestanian, Acc. Chem. Res. 51, 2365. (2018)

Relating Enhanced Diffusion and Chemotaxis

Binding-induced contribution to chemotaxis can be rewritten as

$$\boldsymbol{V}_{\mathrm{bi}}(\boldsymbol{R}) = -(D_{\mathrm{c}} - D_{\mathrm{e}})\nabla_{\boldsymbol{R}}\left(\frac{c_{\mathrm{s}}(\boldsymbol{R})}{K + c_{\mathrm{s}}(\boldsymbol{R})}\right) = -\nabla_{\boldsymbol{R}} D(\boldsymbol{R})$$

If enhanced diffusion $D_{\mathrm{c}} > D_{\mathrm{e}} \Rightarrow \boldsymbol{V}_{\mathrm{bi}}$ **points away from substrate**

If hindered diffusion $D_{\mathrm{c}} < D_{\mathrm{e}} \Rightarrow \boldsymbol{V}_{\mathrm{bi}}$ **points towards substrate**

However, there is also the phoretic contribution…

Competition between Enhanced Diffusion and Phoresis

Two distinct chemotactic mechanisms:

1. Phoresis due to non-contact interactions

$$\boldsymbol{V}_{\mathrm{ph}} \approx \frac{k_{\mathrm{B}}T}{\eta}\lambda_{\mathrm{e}}^{2}\nabla_{\boldsymbol{R}}c_{\mathrm{s}} \quad (\lambda_{\mathrm{c}} \approx \lambda_{\mathrm{e}})$$

Typically towards substrate because interactions are predominantly attractive

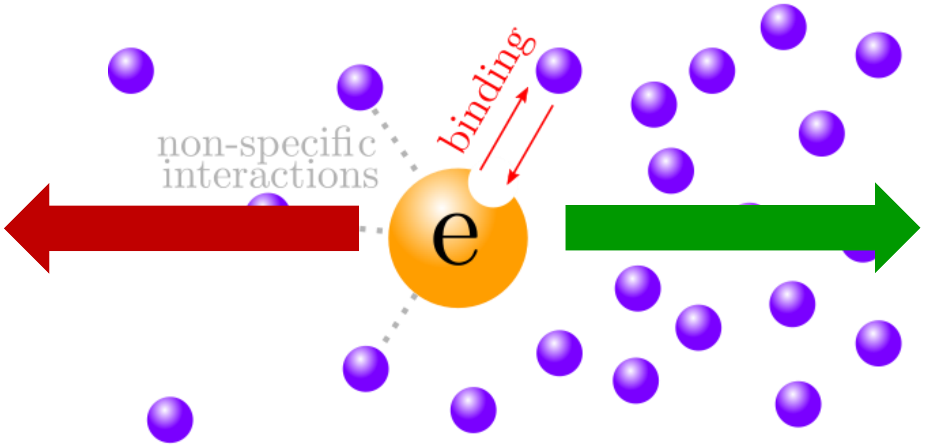
2. Binding-induced changes in diffusion

$$\boldsymbol{V}_{\mathrm{bi}} = -(D_{\mathrm{c}} - D_{\mathrm{e}})\nabla_{\boldsymbol{R}}\left(\frac{c_{\mathrm{s}}(\boldsymbol{R})}{K + c_{\mathrm{s}}(\boldsymbol{R})}\right)$$

Typically away from substrate because enzymes display enhanced diffusion

Competition between Enhanced Diffusion and Phoresis

Enhanced Diffusion



Phoresis

$$\boxed{\boldsymbol{V}_{\mathrm{bi}} = -(D_{\mathrm{c}} - D_{\mathrm{e}})\frac{K}{(K+c_{\mathrm{s}})^2}\nabla_{\boldsymbol{R}} c_{\mathrm{s}}}$$

$$\boxed{\boldsymbol{V}_{\mathrm{ph}} \approx \frac{k_{\mathrm{B}}T}{\eta}\lambda_{\mathrm{e}}^2 \nabla_{\boldsymbol{R}} c_{\mathrm{s}}}$$

Magnitude decreases with c_s

~Independent of c_s

Therefore there is a critical substrate concentration c_s^*

$c_s < c_s^* \Longrightarrow$ Enhanced diffusion dominates

$c_s > c_s^* \Longrightarrow$ Phoresis dominates

Making Sense of **Urease** Chemotaxis

Sengupta at al., JACS (2013):

Chemotaxis

$\boldsymbol{c_s = 1\ \mathrm{M}}$

Dominated by phoresis?

Jee et al., PNAS (2018):

Antichemotaxis

$\boldsymbol{c_s = 1\ \mathrm{mM}}$

Dominated by enhanced diff.?

Critical concentration:

$$\boxed{c_\mathrm{s}^* = \sqrt{\frac{K|\alpha|}{6\pi R_\mathrm{e}|\lambda_\mathrm{e}^2|}} - K}$$

$[\alpha \equiv (D_\mathrm{c} - D_\mathrm{e})/D_\mathrm{e}]$

All parameters are known from experiment except for the Derjaguin length $\boldsymbol{\lambda_e}$

$(K = 3\ \mathrm{mM}, \alpha = 0.3, R_\mathrm{e} = 7\ \mathrm{nm})$

The two experiments will be dominated by the two different mechanisms if:

$$\boldsymbol{1\ \mathrm{M} > c_s^* > 1\ \mathrm{mM} \Leftrightarrow \boxed{0.04\ \text{Å} < \lambda_e < 8\ \text{Å}}}$$

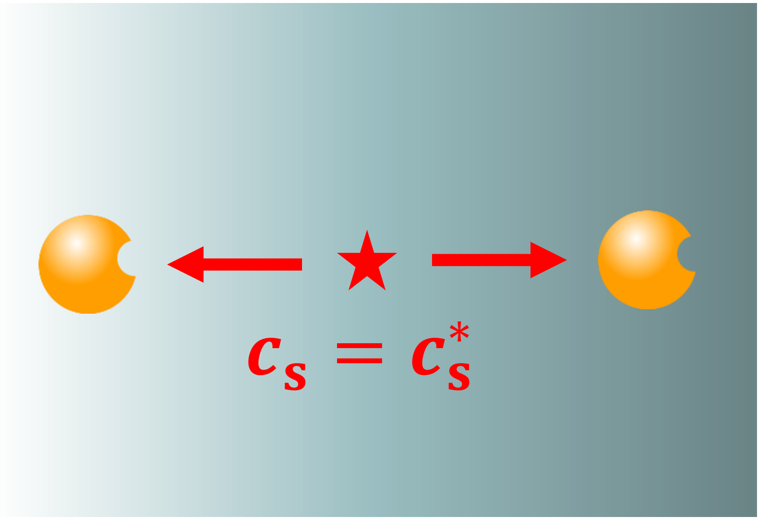
…which is within the expected range of values

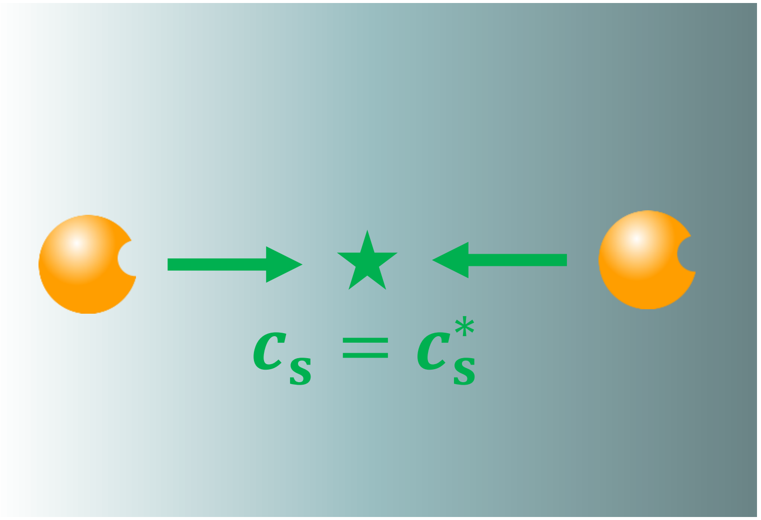
Beyond Enzymes: Designing Directed Nanovehicles

- **Exploiting the competition between mechanisms:**

Enhanced Diffusion
+
Attractive Phoresis:
'repelled' from regions with $c_s = c_s^*$

Inhibited Diffusion
+
Repulsive Phoresis:
'attracted' to regions with $c_s = c_s^*$





Summary I:

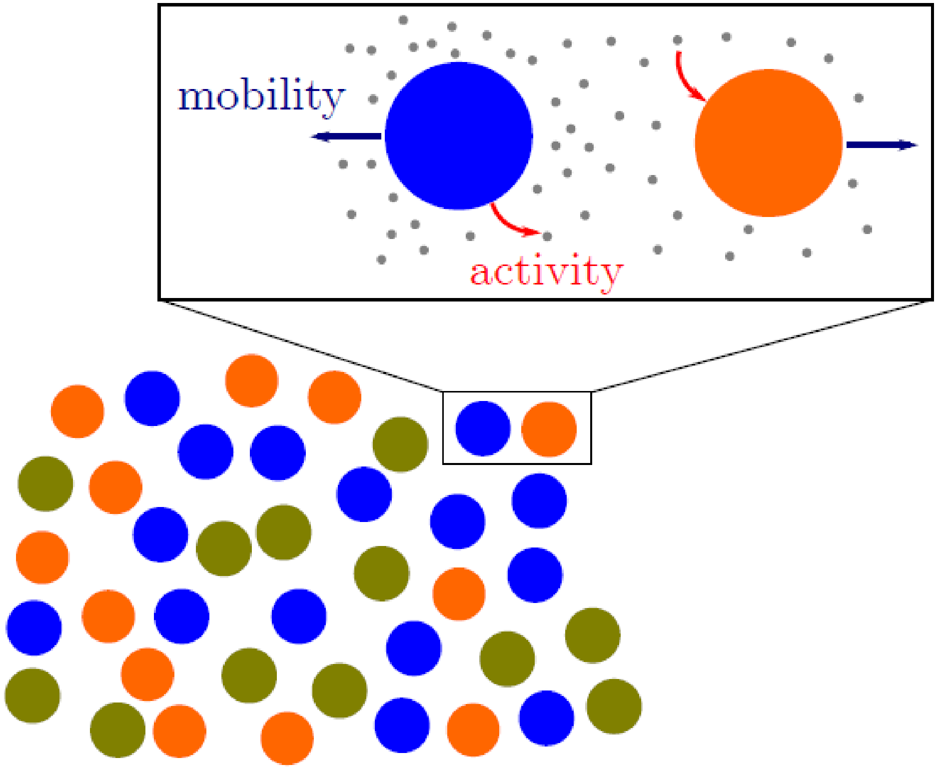
- **Enzymes undergo chemotaxis** in the presence of gradients of their substrate
- **At least two different mechanisms** contribute to chemotaxis
- Competition between phoresis and binding-induced changes in diffusion can **explain conflicting observations** for urease
- Competition between mechanisms can be exploited to engineer nanovehicles with **finely-tuned directed motion**

[Agudo-Canalejo, J., Illien, P., & Golestanian, R. (2018). Phoresis and Enhanced Diffusion Compete in Enzyme Chemotaxis. *Nano Letters*, *18*(4), 2711–2717.]

Back on track:

Active phase separation in mixtures of chemically interacting particles

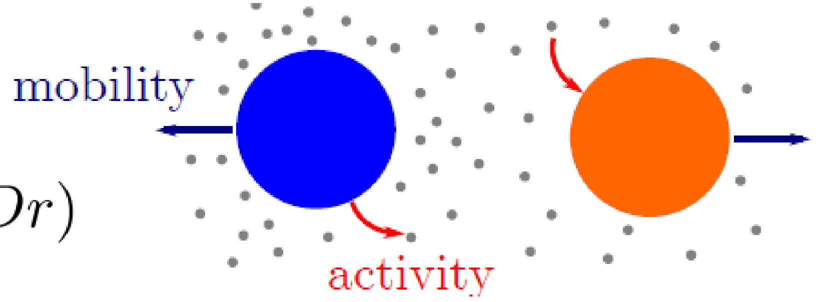
Chemically-interacting particles:
microorganisms, catalytic colloids, enzymes…



- $i = 1, \ldots, M$
  different particle species
- α_i chemical activity
  - positive if emits solute
  - negative if consumes solute
- μ_i chemotactic mobility
  - positive if repelled from solute
  - negative if attracted to solute

► will such a mixture remain homogeneous?

Chemical interactions are generally non-reciprocal



- Concentration of chemical around a single particle: $c(r) = c_0 + \alpha/(4\pi D r)$

- Velocity response to gradient: $\mathbf{V} = -\mu\, \nabla c$

- Velocity of particle ***j*** in the presence of particle ***i***: $V_{ij} \propto \alpha_i \mu_j \boldsymbol{r}_{ij}/|\boldsymbol{r}_{ij}|^3$
  Velocity of ***i*** in the presence of ***j***: $V_{ji} \propto -\alpha_j \mu_i \boldsymbol{r}_{ij}/|\boldsymbol{r}_{ij}|^3$

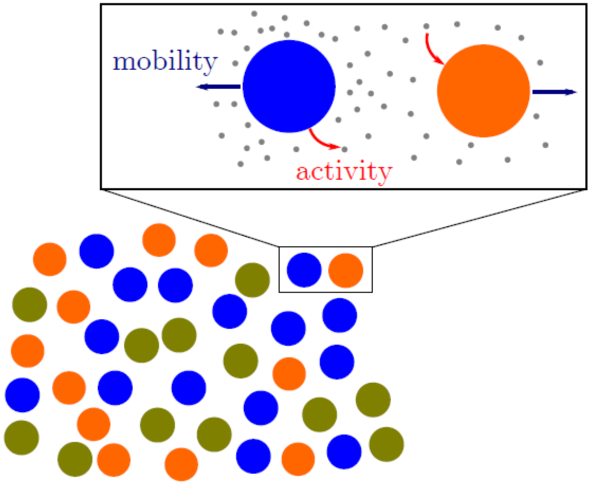
- Generally $V_{ij} \neq -V_{ji}$ because $\boxed{\alpha_i \mu_j \neq \alpha_j \mu_i}$
  $\Rightarrow$ **non-reciprocal interactions!**

- **Action≠reaction, signature of non-equilibrium activity**

Continuum theory for chemically-interacting mixtures

- Concentration field of particles of species $i = 1, \ldots, M$:

$$\partial_t \rho_i(\boldsymbol{r}, t) - \nabla \cdot [D_\mathrm{p} \nabla \rho_i + (\mu_i \nabla c) \rho_i] = 0$$



- Concentration field of chemical:

$$\partial_t c(\boldsymbol{r}, t) - D \nabla^2 c = \sum_i \alpha_i \rho_i$$

- Deviation from homogeneous solution:

$$\rho_i(\boldsymbol{r}, t) = \rho_{0i} + \delta\rho_i(\boldsymbol{r}, t)$$

$$c(\boldsymbol{r}, t) = c_0 + At + \delta c(\boldsymbol{r}, t) \quad \text{with} \quad A \equiv \sum_i \alpha_i \rho_{0i}$$

- Equation for chemical can be rewritten as:

$$\partial_t \delta c(\boldsymbol{r}, t) - D \nabla^2 \delta c = \sum_i \alpha_i \delta\rho_i$$

- Fast-diffusing chemical → instantaneous steady state

$$D \nabla^2 \delta c = - \sum_i \alpha_i \delta\rho_i$$

Continuum theory for chemically-interacting mixtures

- Concentration field of particles of species i to **linear order**:

$$\boxed{\partial_t \delta\rho_i(\boldsymbol{r},t) = D_{\mathrm{p}} \nabla^2 \delta\rho_i - \frac{\mu_i \rho_{0i}}{D} \sum_j \alpha_j \delta\rho_j}$$

- M coupled equations → $M \times M$ eigenvalue problem in Fourier space

- We find $M-1$ identical eigenvalues which are always negative
$\lambda_- = -D_{\mathrm{p}} \boldsymbol{q}^2$ → corresponding modes are always stable

- **… and one eigenvalue which can become positive**

$\boxed{\lambda_+ = -D_{\mathrm{p}} \boldsymbol{q}^2 - \sum_i \mu_i \alpha_i \rho_{0i}/D}$ **→ corresponding mode**
can become unstable!

Continuum theory: macroscopic instability

$$\boxed{\lambda_+ = -D_\mathrm{p}\boldsymbol{q}^2 - \textstyle\sum_i \mu_i \alpha_i \rho_{0i}/D}$$

- **Instability** occurs whenever $$\boxed{\sum_i \mu_i \alpha_i \rho_{0i} < 0}$$
- The modes with $q^2 < -\frac{\sum_i \mu_i \alpha_i \rho_{0i}}{D D_\mathrm{p}}$ are unstable
- **Macroscopic phase separation** with $q = 0$ as the first and most unstable mode
- The corresponding eigenvectors can be calculated as

$$\boxed{(\delta\rho_1, \delta\rho_2, \ldots, \delta\rho_M) = \left(1, \frac{\mu_2 \rho_{02}}{\mu_1 \rho_{01}}, \ldots, \frac{\mu_M \rho_{0M}}{\mu_1 \rho_{01}}\right) \delta\rho_1}$$

and tell us about the **stoichiometry** at the onset of the instability

Continuum theory: single species

- Instability occurs whenever $\boxed{\mu\alpha < 0}$
- Stoichiometry is trivial
- This is the **Keller-Segel instability (1970):**
  - If effective interactions are attractive, aggregation instability
  - If effective interactions are repulsive, no instability
- Boring…
- **However, phenomenology explodes when we add a second species!**

Continuum theory: binary mixtures

- For mixtures of only two species we have

$$\boxed{\mu_1\alpha_1\rho_{01} + \mu_2\alpha_2\rho_{02} < 0 \qquad \text{and} \qquad \delta\rho_2 = \frac{\mu_2\rho_{02}}{\mu_1\rho_{01}}\delta\rho_1}$$

→ **aggregation if the two mobilities have same sign**

→ **separation if the two mobilities have opposite sign**

- Two qualitatively different cases depending on the sign of the activities:

  1. If $(\alpha_1, \alpha_2) = (+, -)$, i.e. **producer + consumer**
     then instability when $\mu_2|\alpha_2|\rho_{02} > \mu_1|\alpha_1|\rho_{01}$

  2. If $(\alpha_1, \alpha_2) = (+, +)$, i.e. **two producers**
     then instability when $\mu_2|\alpha_2|\rho_{02} > -\mu_1|\alpha_1|\rho_{01}$
     [the case of two consumers $(\alpha_1, \alpha_2) = (-, -)$ is equivalent under the transformation $\mu_i \to -\mu_i$]

Simulations of chemically-interacting mixtures

- Far-field approximation → superimpose the solute concentration fields generated by each colloid → pair-wise additive velocities
- Overdamped limit → **Brownian dynamics simulation**

$$\boxed{\frac{d\mathbf{r}_i}{dt} = V_0 \sum_{k\neq i} \widetilde{\alpha}_k \widetilde{\mu}_i \frac{\sigma^2 \mathbf{r}_{ki}}{|\mathbf{r}_{ki}|^3} + \sum_{k\neq i} \mathbf{U}_{ik} + \boldsymbol{\xi}_i(t)}$$

white noise of intensity $2D_c$

hard-sphere repulsion

Velocity scale $V_0 = \frac{\alpha_0 \mu_0}{24\pi D}$

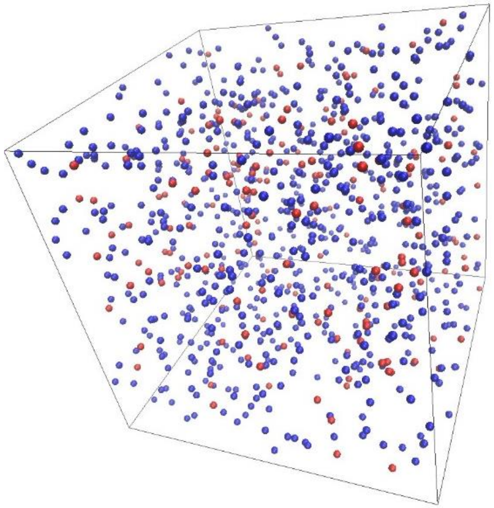
Noise $\widetilde{D}_c = D_c / V_0 \sigma$

Activity $\widetilde{\alpha} = \alpha / \alpha_0$

Mobility $\widetilde{\mu} = \mu / \mu_0$

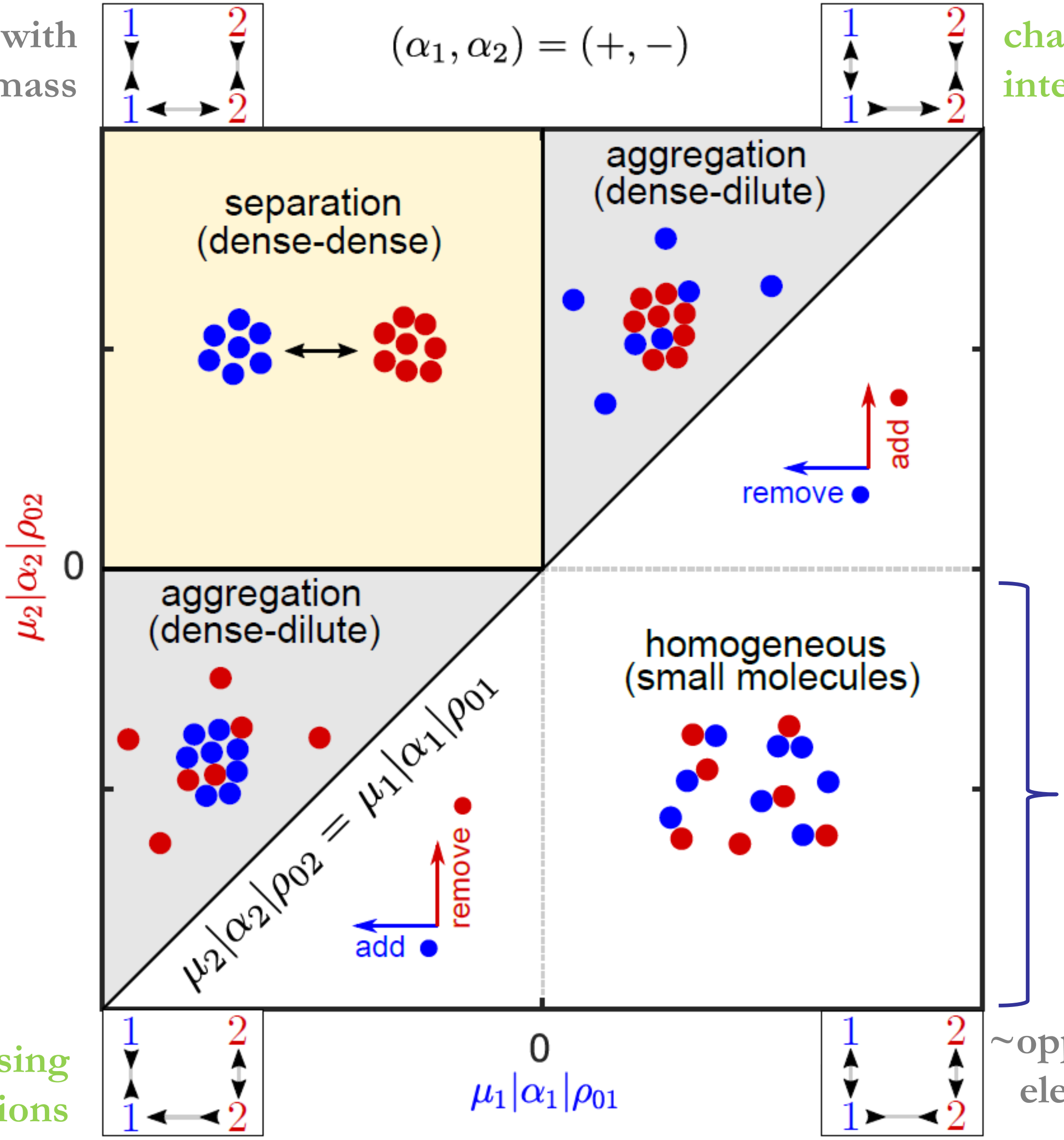
[Soto, R., & Golestanian, R. Phys. Rev. Lett 112, 068301 (2014), Phys. Rev. E 91, 052304 (2015)]

Simulations of chemically-interacting mixtures



- Cubic 3D box with periodic boundary conditions:
  - Either $N_{\text{tot}} = 1000$ and $L/\sigma = 48$ → Volume fraction 0.0047
  - Or $N_{\text{tot}} = 4000$ and $L/\sigma = 76$ → Volume fraction 0.0048
- Noise $\widetilde{D}_c = 0.01$
- Time step $\delta t = 0.001\sigma/V_0$
- Run time between $5 \cdot 10^4$ and $8 \cdot 10^5$ steps

Phase diagram for mixtures of producer + consumer



~ gravity with
negative mass

chasing
interactions

chasing
interactions

~opposite-charge
electrostatics

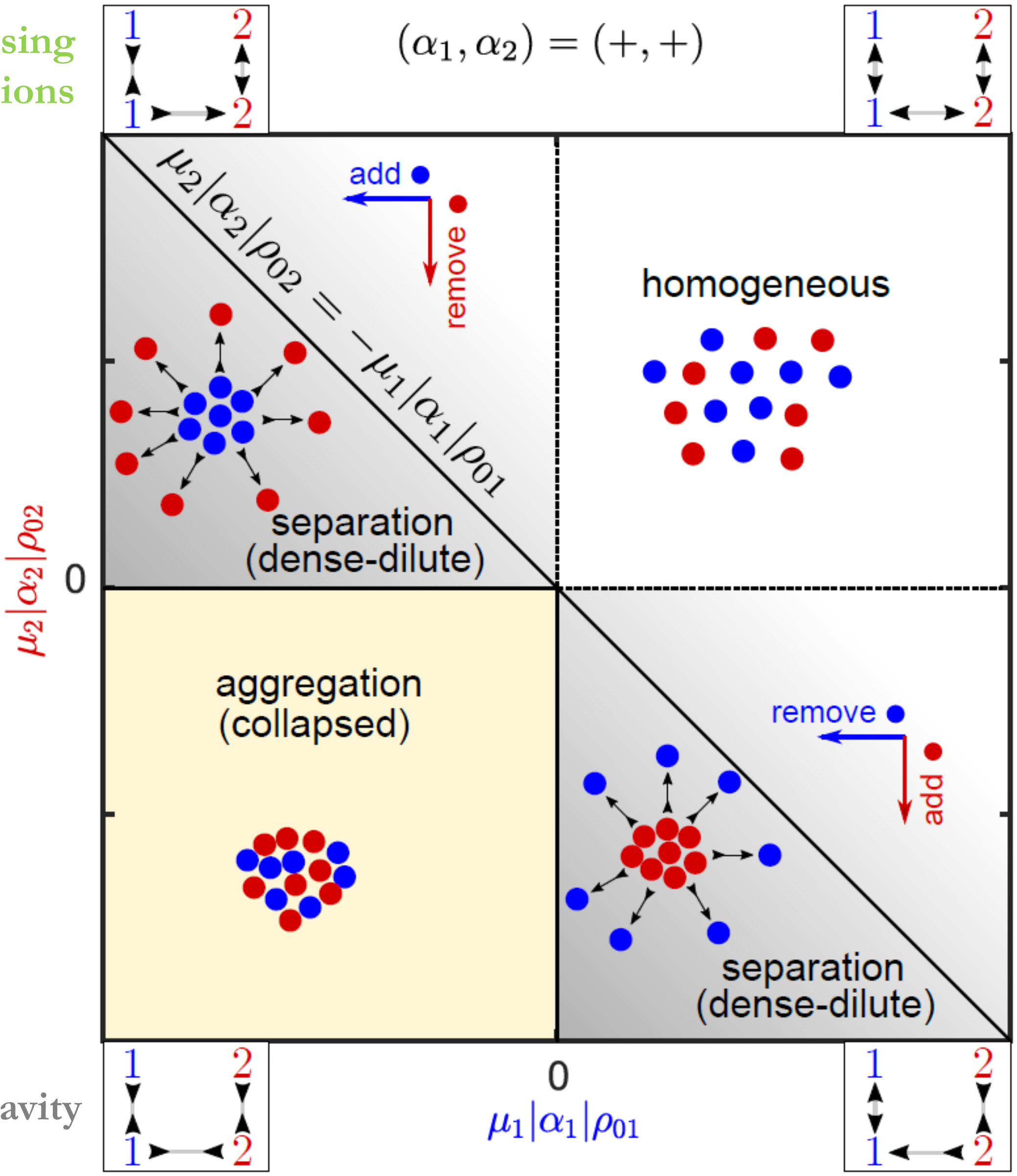
[Soto & Golestanian
PRL 112, 068301 (2014),
PRE 91, 052304 (2015)]

Phase diagram for mixtures of **two producers**

$(\alpha_1, \alpha_2) = (+,+)$

chasing interactions

~like-charge electrostatics

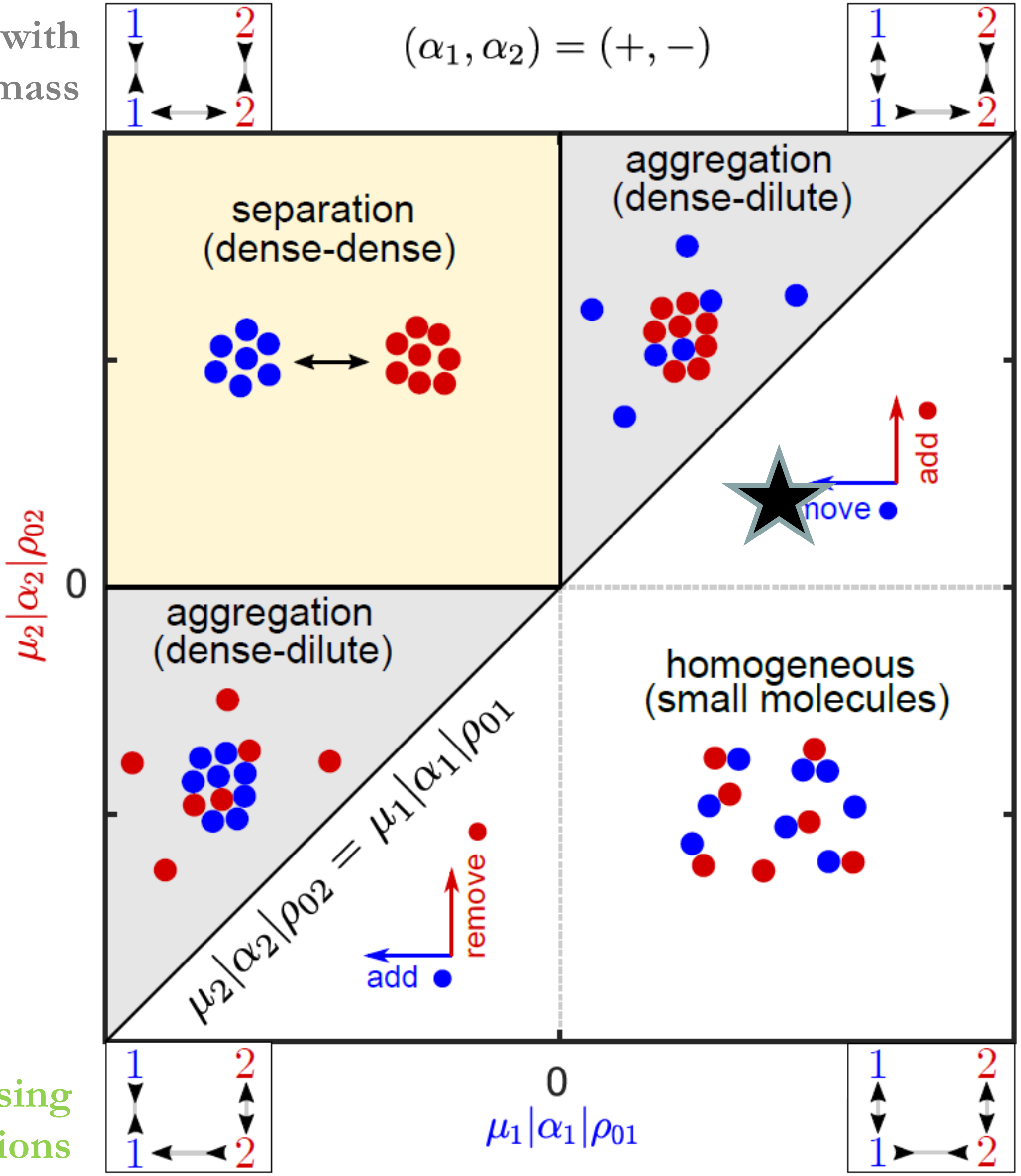


~ gravity

chasing interactions

Producer+consumer:

homogeneous state with active molecule formation



~ gravity with negative mass

chasing interactions

chasing interactions

~opposite-charge electrostatics

[Soto & Golestanian PRL 112, 068301 (2014), PRE 91, 052304 (2015)]

Producer+consumer:

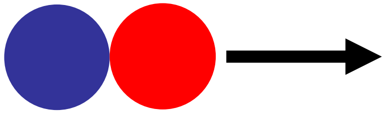
homogeneous state with active molecule formation

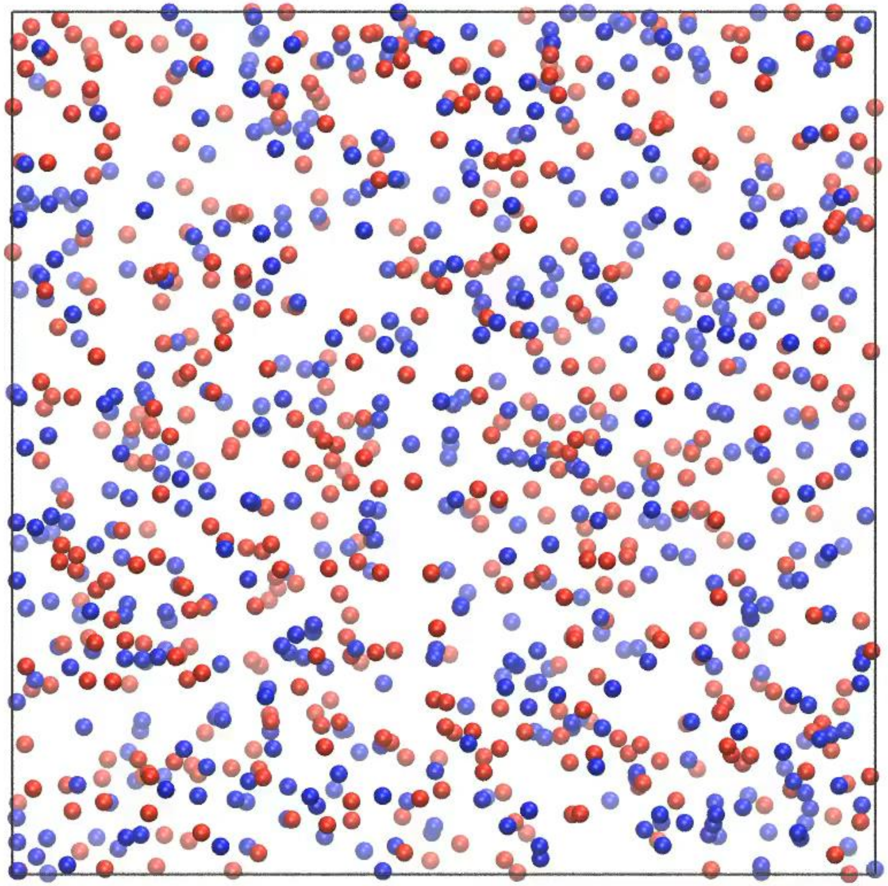
$$\tilde{\alpha} = (1, -1)$$

$$\tilde{\mu} = (1, 1/2)$$

$$N = (500, 500)$$

In this case, formation of self-propelled dimers





3D realisation of the 2D active molecules explored in

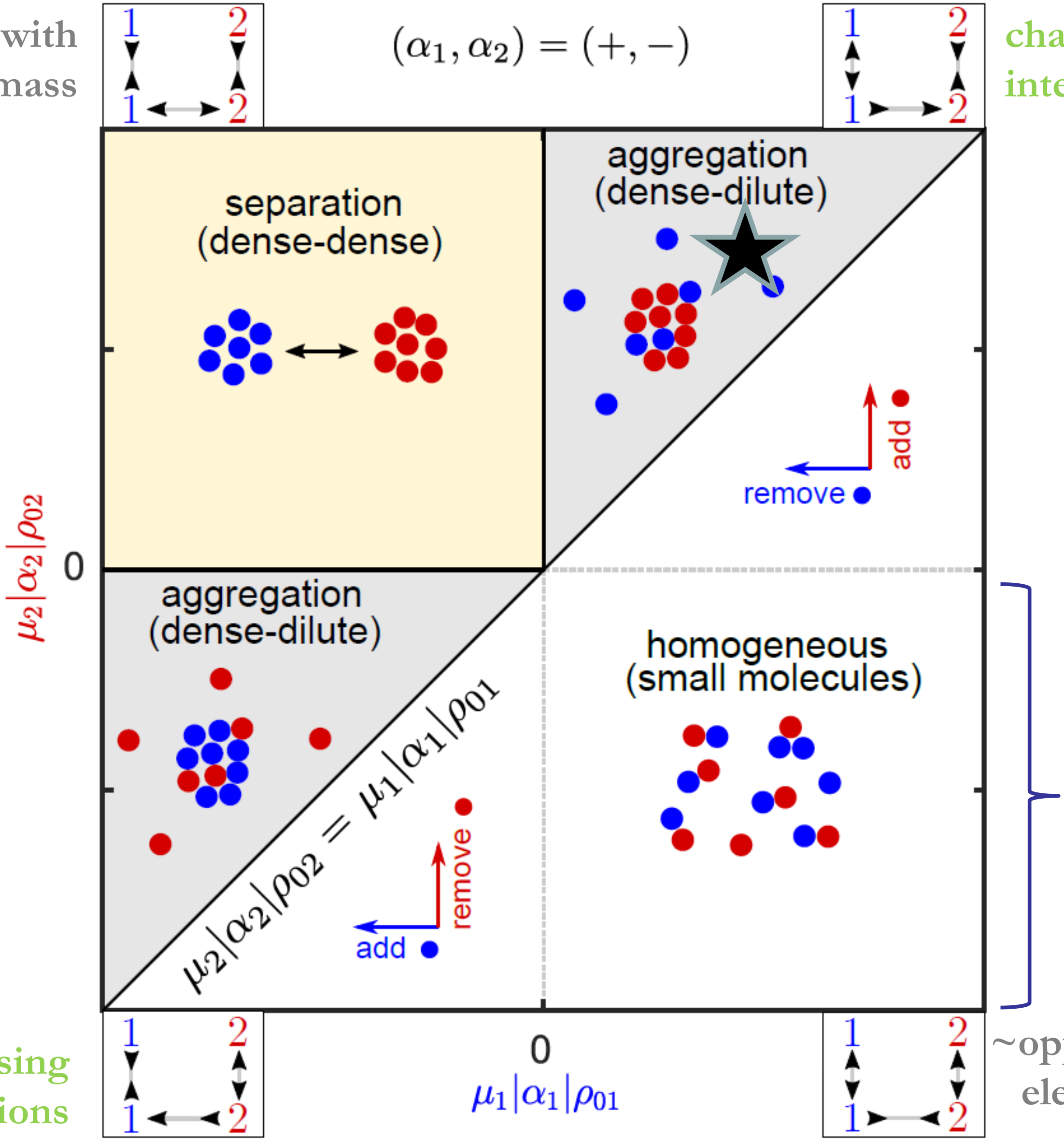
[Soto, R., & Golestanian, R. Phys. Rev. Lett 112, 068301 (2014), Phys. Rev. E 91, 052304 (2015)]

Producer+consumer:

aggregation into cluster with defined stoichiometry

~ gravity with negative mass

chasing interactions



chasing interactions

~opposite-charge electrostatics

[Soto & Golestanian PRL 112, 068301 (2014), PRE 91, 052304 (2015)]

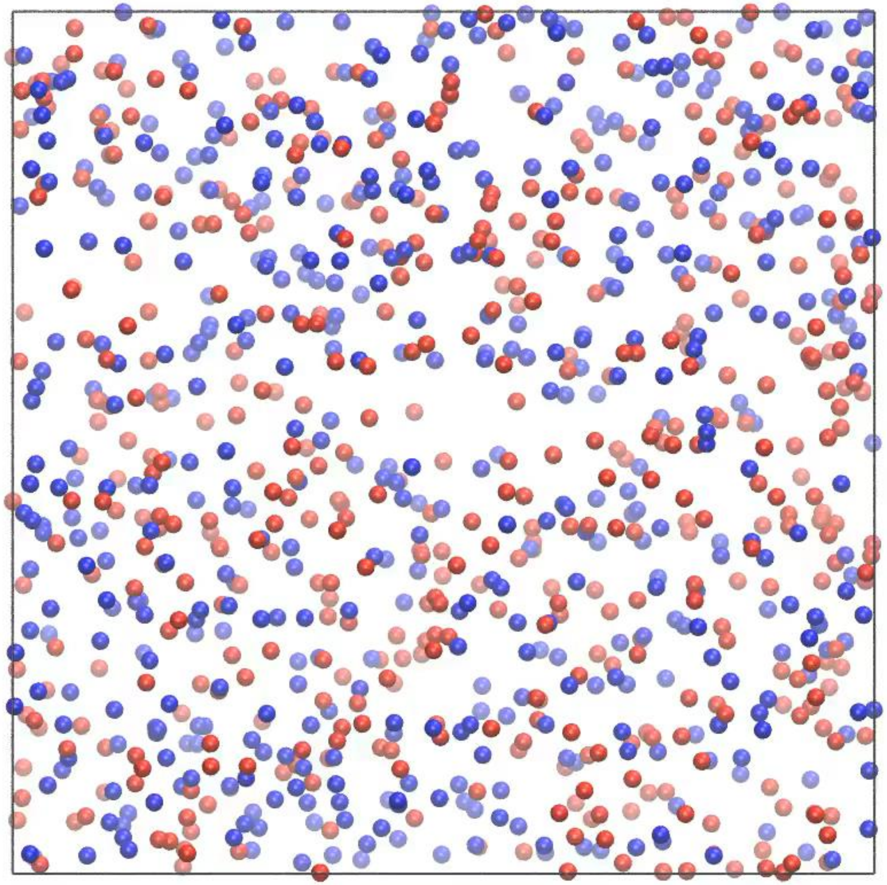
Producer+consumer:

aggregation into cluster with defined stoichiometry

$$\tilde{\alpha} = (1, -1/2)$$

$$\tilde{\mu} = (1,6)$$

$$N = (500,500)$$

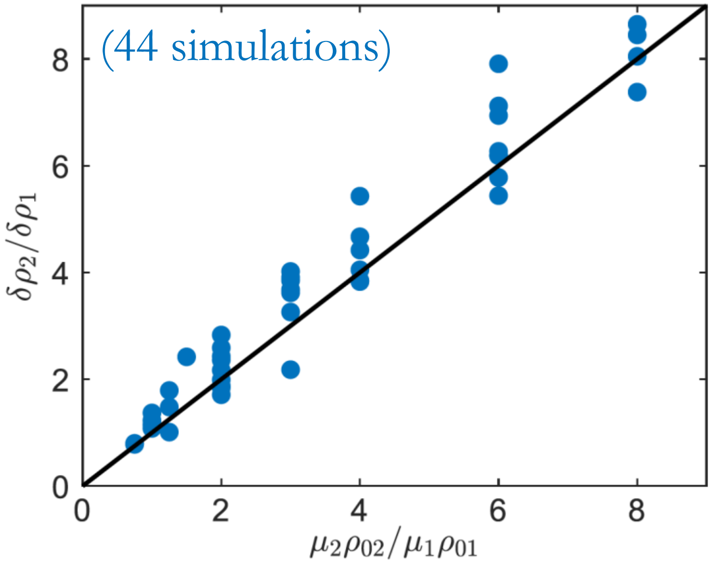


Producer+consumer:
aggregation into cluster with defined stoichiometry

- The initial stoichiometry of the simulations is well captured by the continuum theory prediction

$$\boxed{\delta\rho_2 = \frac{\mu_2\rho_{02}}{\mu_1\rho_{01}}\delta\rho_1}$$

(for a binary mixture)



Initial stoichiometry depends only on mobility, independent of activity

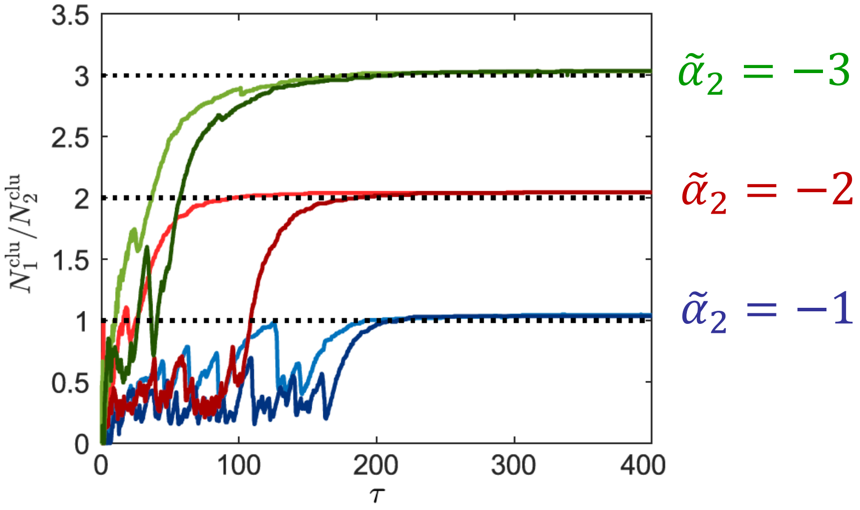
Producer+consumer:
aggregation into cluster with defined stoichiometry

- The final stoichiometry of the cluster is determined by:

1. All particles of the self-attractive type are in the cluster

$$N_2^{\mathrm{clu}} = \mathrm{N}_2$$

2. Particles of the self-repelling type are added until neutrality is reached $$\alpha_1 N_1^{\mathrm{clu}} + \alpha_2 N_2^{\mathrm{clu}} = 0$$



Final stoichiometry depends only on activity, independent of mobility

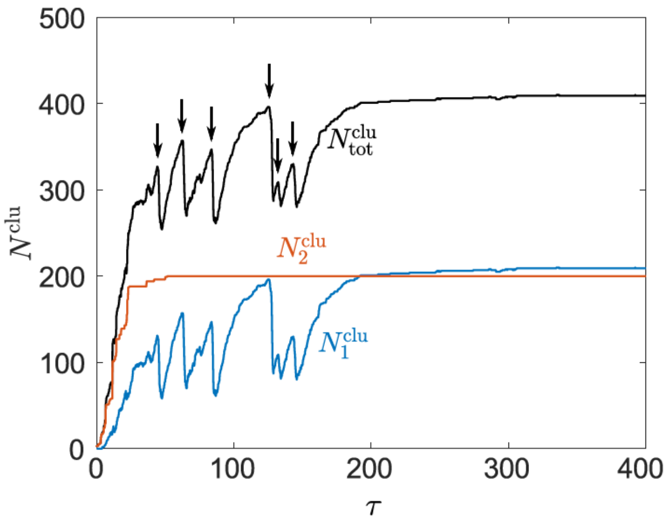
► **Metabolon formation: all product of one enzyme is channeled in the exact amount as substrate to the next enzyme**

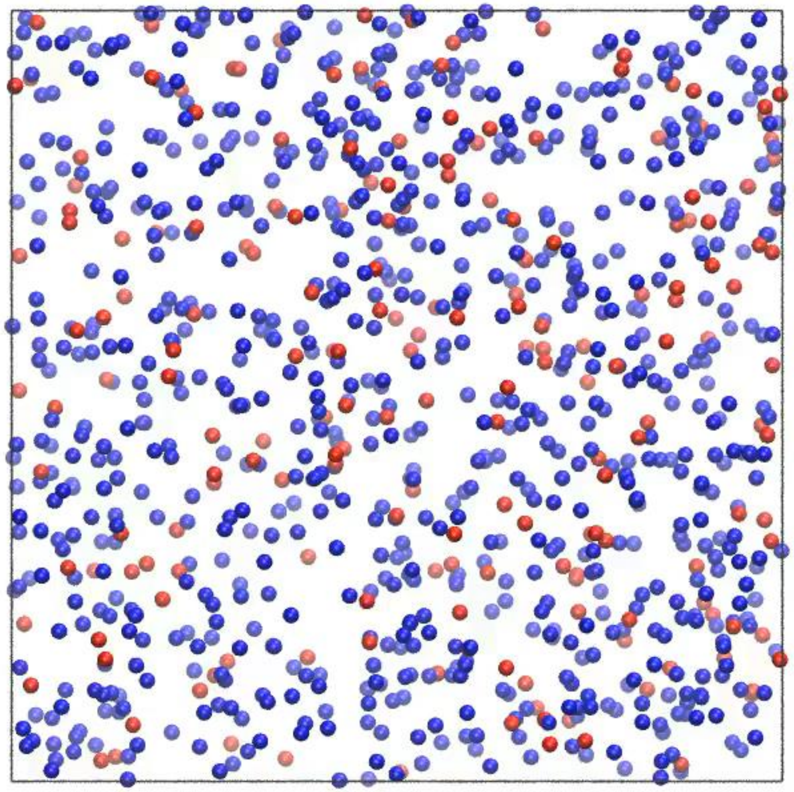
Producer+consumer:

aggregation into cluster with defined stoichiometry
→ shape-instability towards self-propelled state

$$\tilde{\alpha} = (1,-1)$$
$$\tilde{\mu} = (1,8)$$
$$N = (800,200)$$

Bistability between static and self-propelled





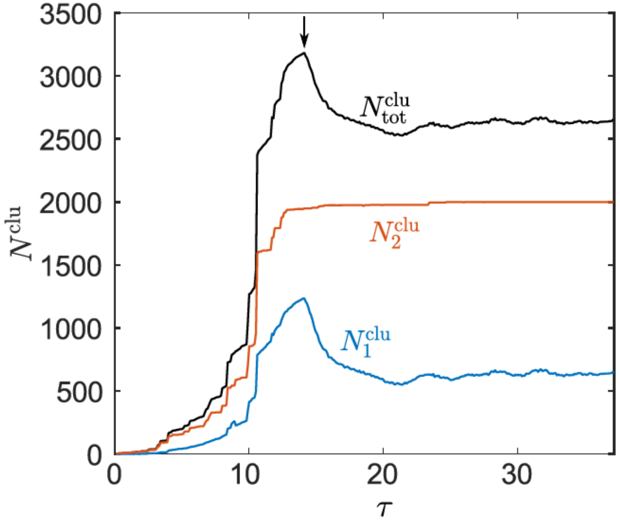
Self-propelled states typically observed when $|\alpha_2|\mu_2 \gg |\alpha_1|\mu_1$

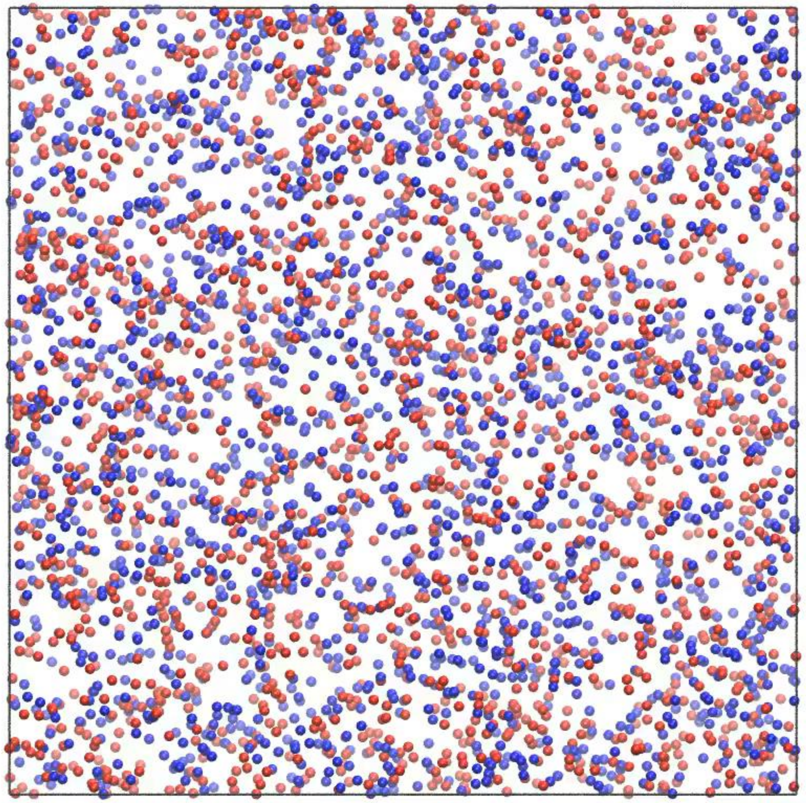
Producer+consumer:

aggregation into cluster with defined stoichiometry
→ shape-instability towards self-propelled state

$$\tilde{\alpha} = (1, -2)$$
$$\tilde{\mu} = (1,3)$$
$$N = (2000,2000)$$

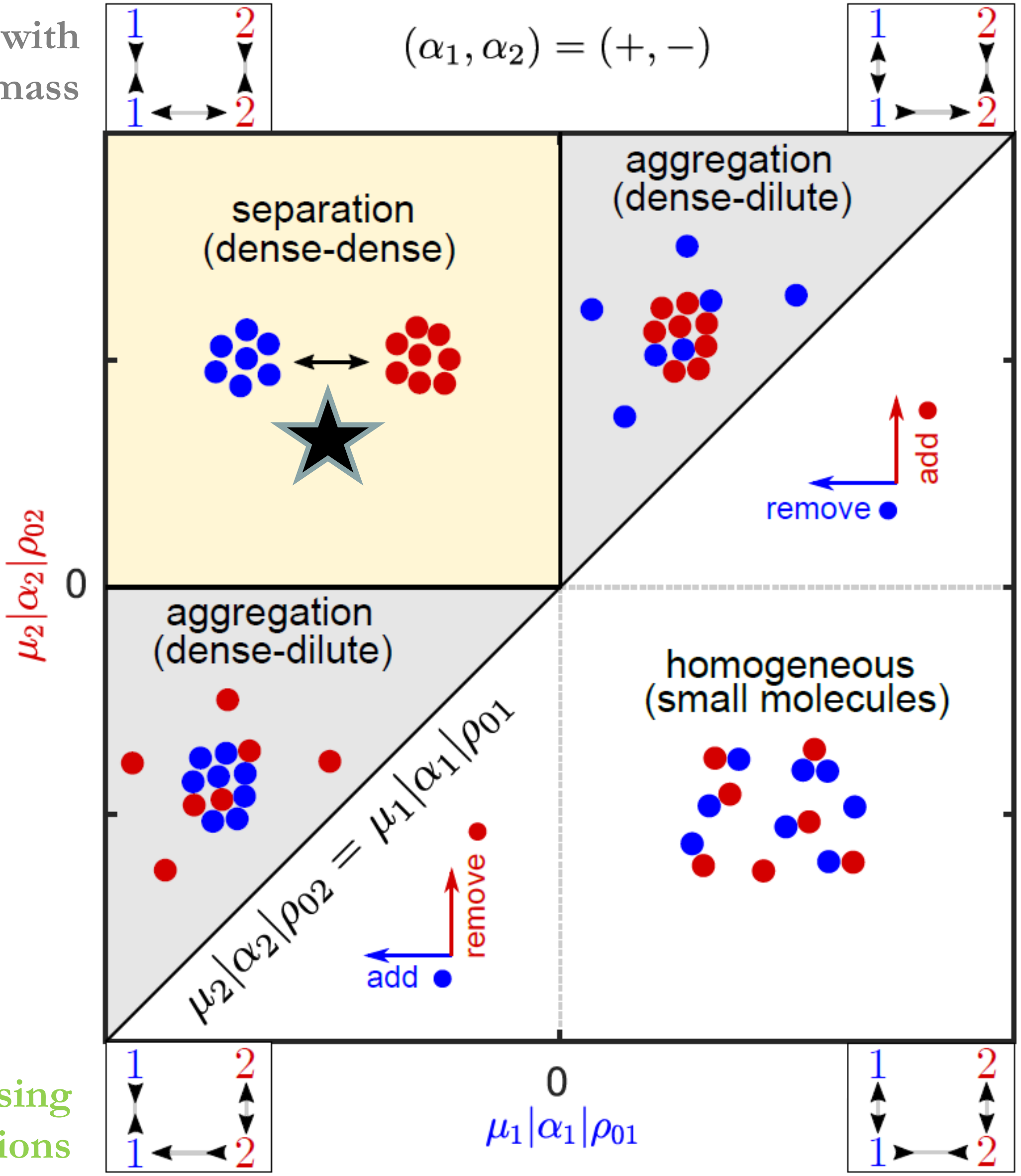
Stable self-propelled state





► **Morphogenesis and collective migration: small changes in a subpopulation can trigger collective self-propulsion**

Producer+consumer:
separation into two collapsed clusters



~ gravity with negative mass

chasing interactions

chasing interactions

~opposite-charge electrostatics

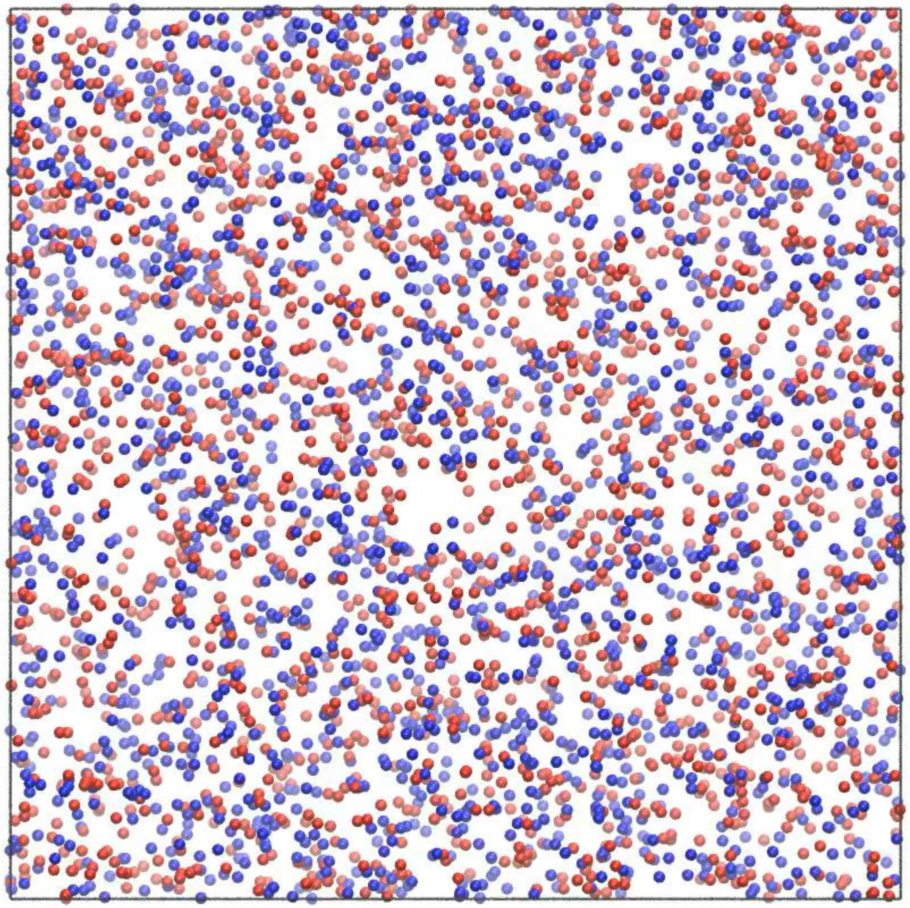
[Soto & Golestanian PRL 112, 068301 (2014), PRE 91, 052304 (2015)]

Producer+consumer:
separation into two collapsed clusters

$\tilde{\alpha} = (1, -1)$

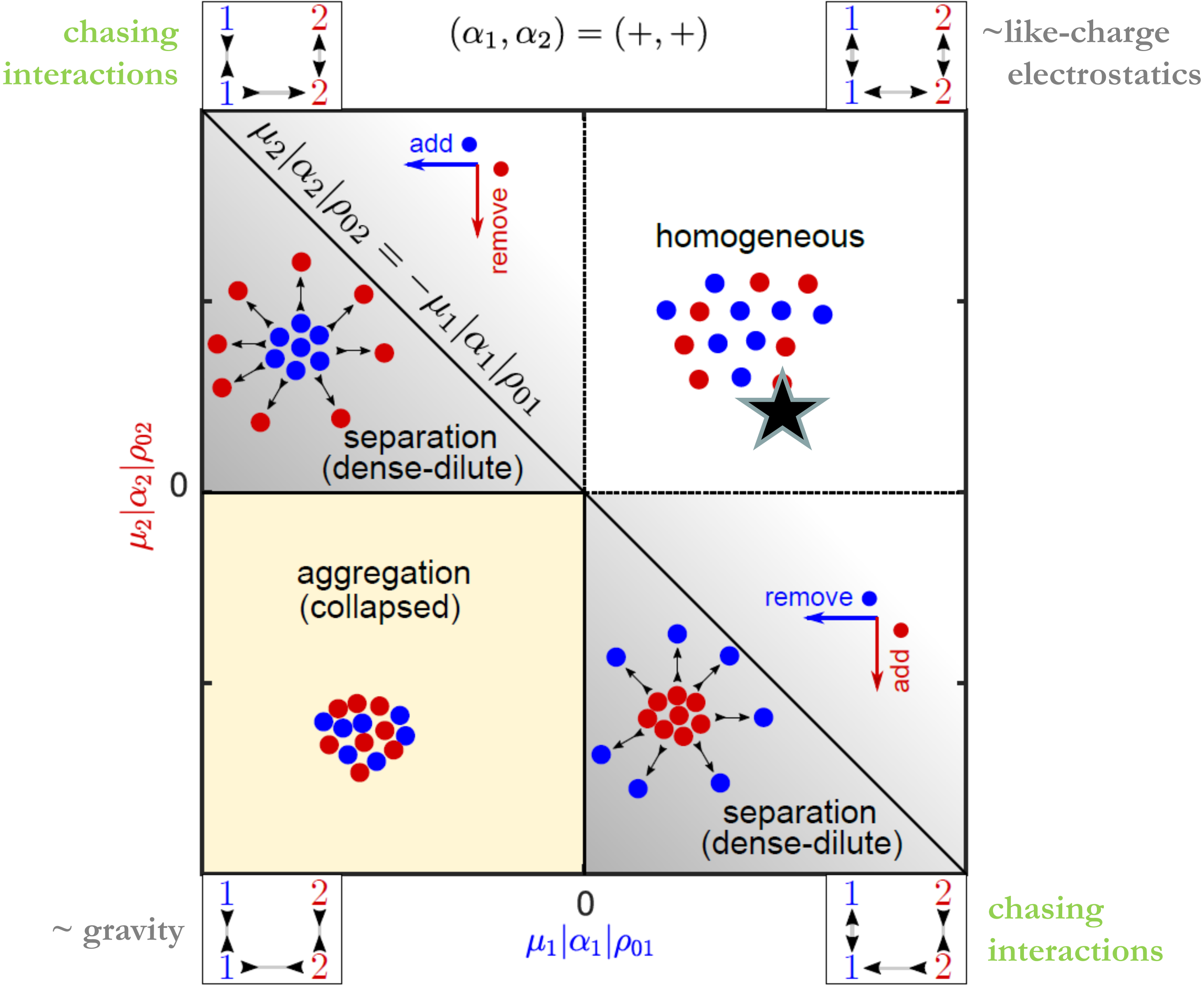
$\tilde{\mu} = (-1, 2)$

$N = (2000, 2000)$



Two producers:

homogeneous state without molecule formation



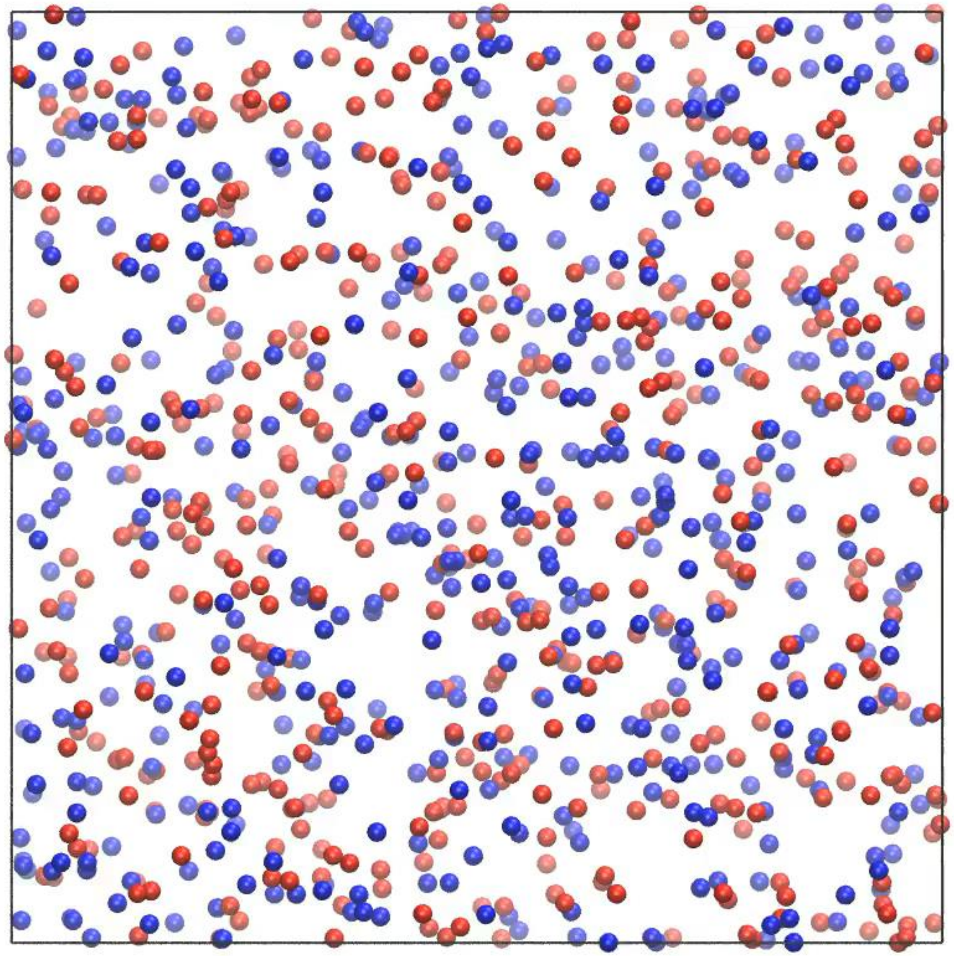
Two producers:

homogeneous state without molecule formation

$\tilde{\alpha} = (1,1)$

$\tilde{\mu} = (1,1/2)$

$N = (500,500)$

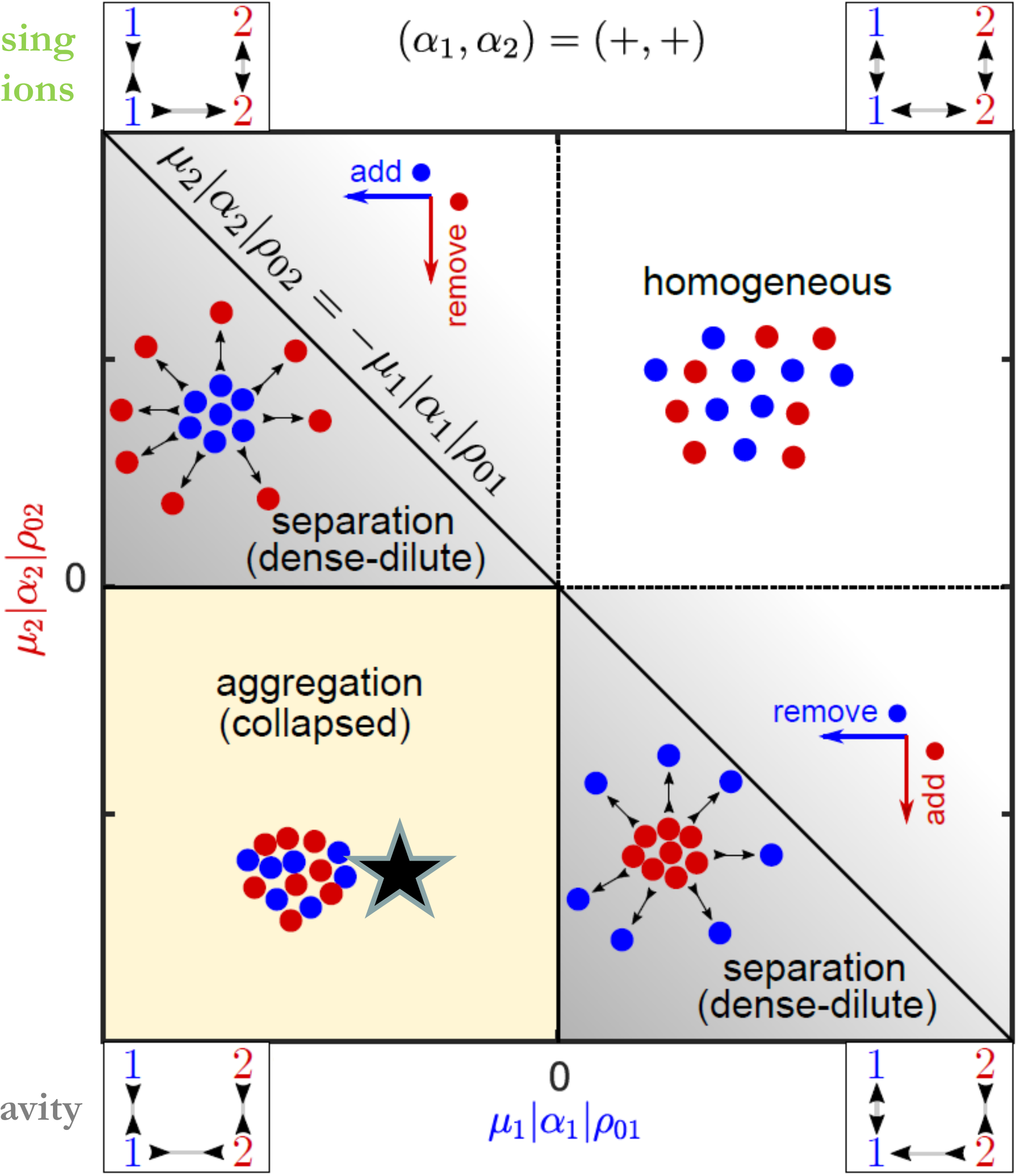


Two producers:

aggregation into a collapsed cluster

chasing interactions

~like-charge electrostatics



~ gravity

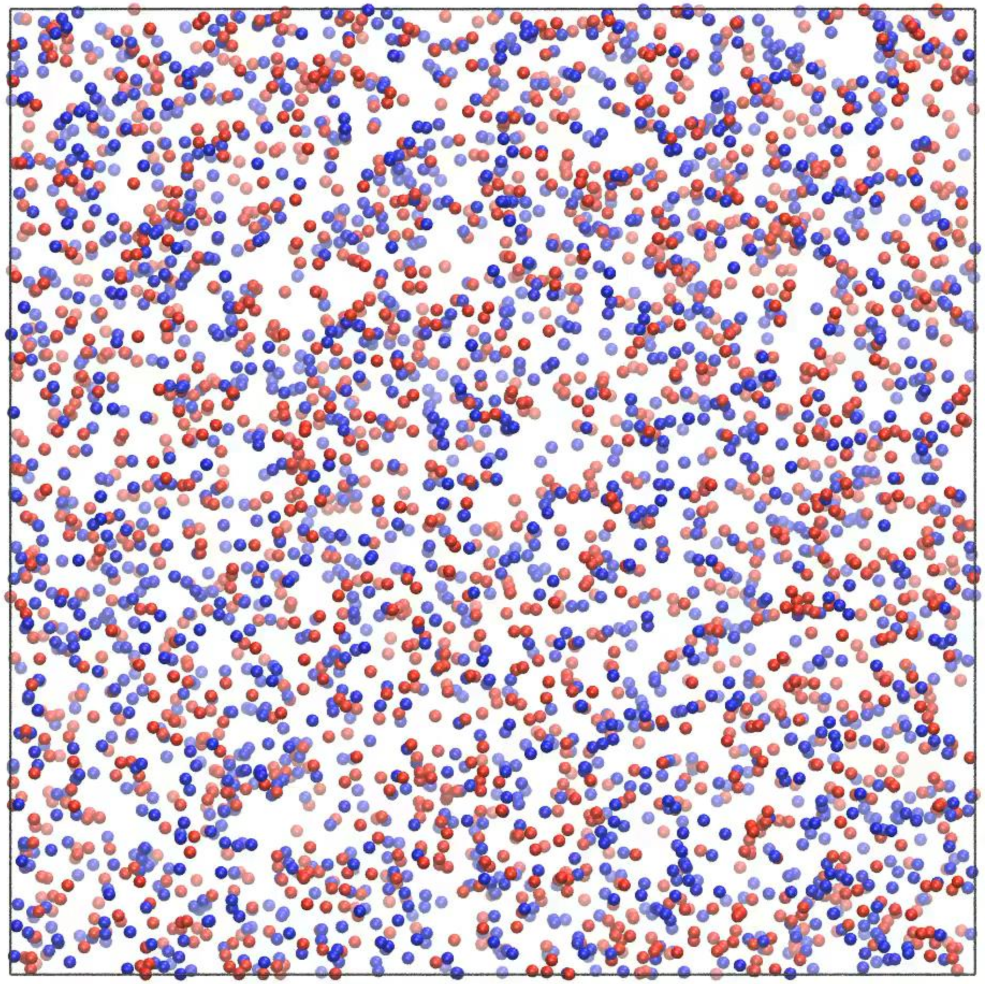
chasing interactions

Two producers:
aggregation into a collapsed cluster

$\tilde{\alpha} = (1,1)$

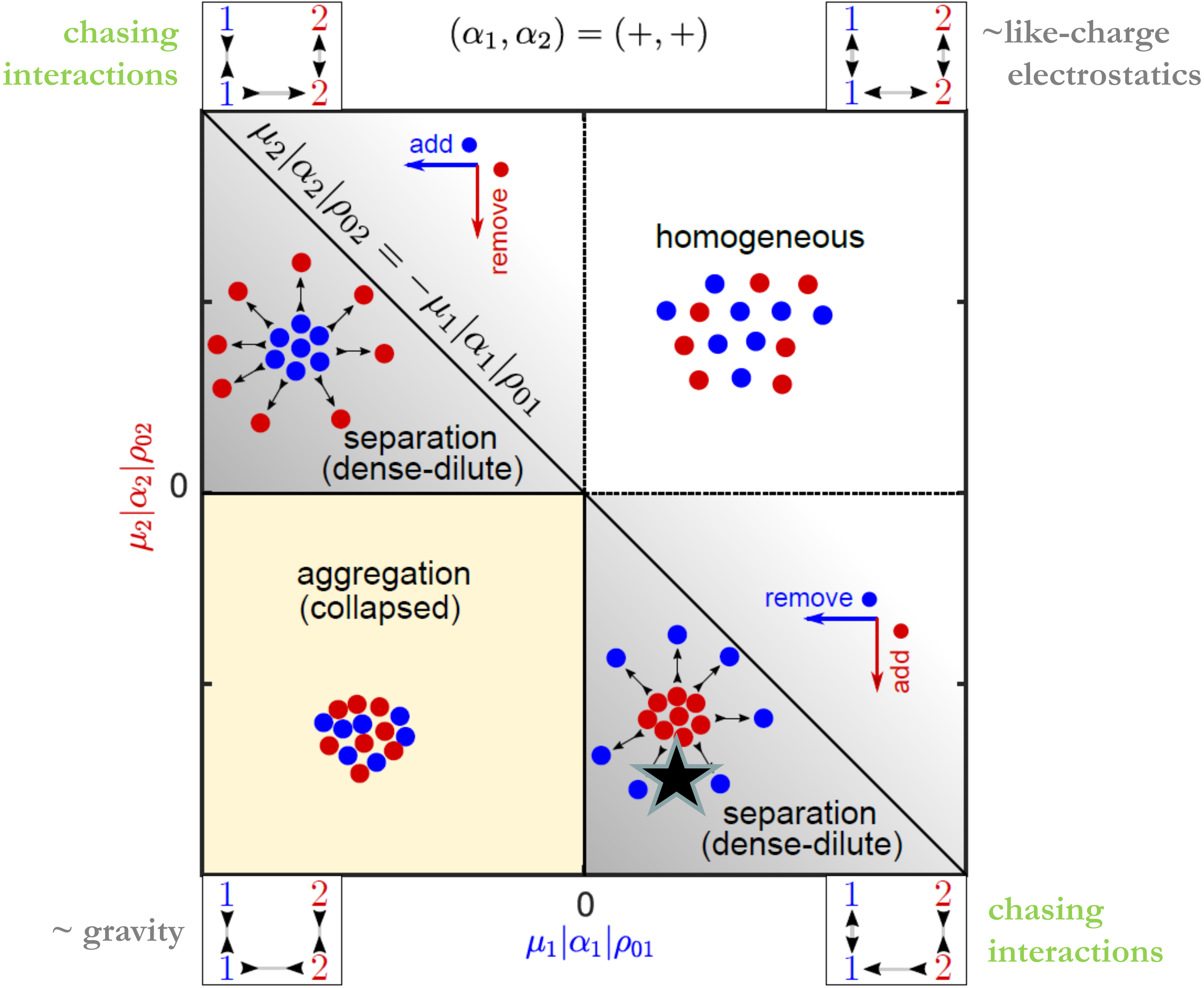
$\tilde{\mu} = (-1,-2)$

$N = (2000,2000)$



Two producers:

separation into cluster and repelled dilute phase



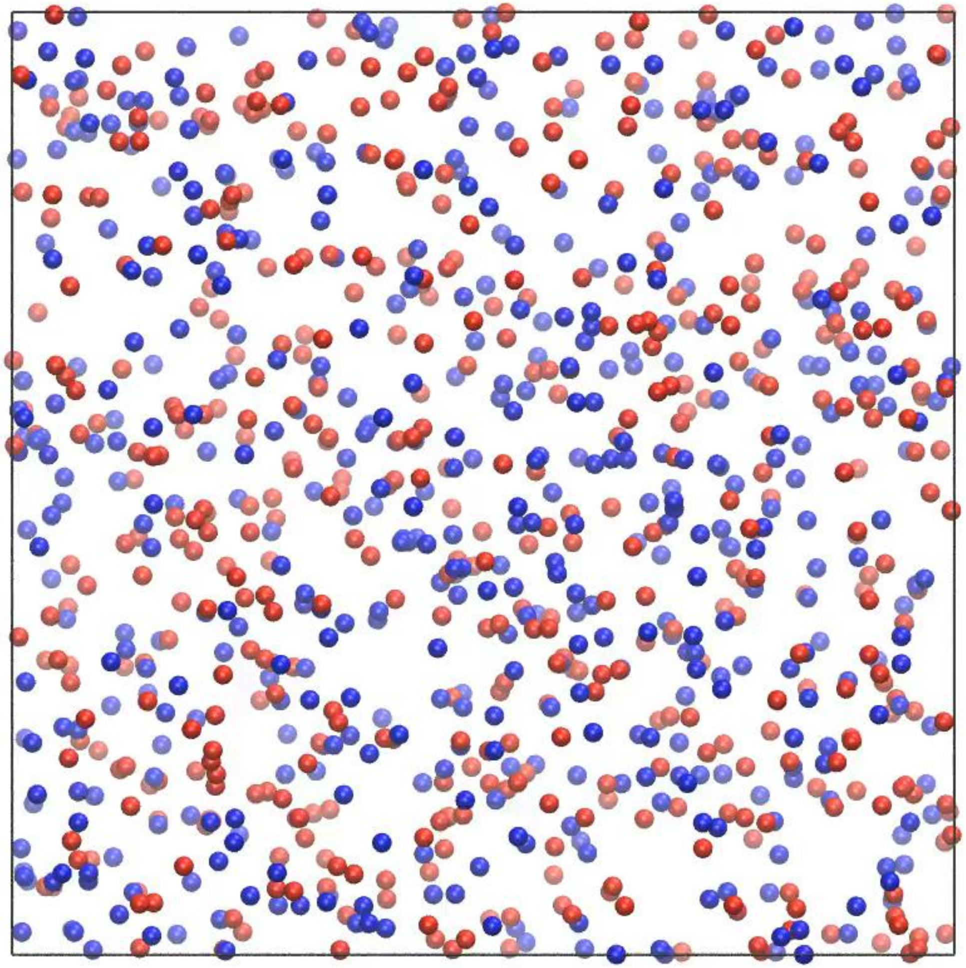
Two producers:

separation into cluster and repelled dilute phase

$\tilde{\alpha} = (1,1)$

$\tilde{\mu} = (1,-2)$

$N = (500,500)$



Beyond binary mixtures:
phase separation triggered by active "doping agent"

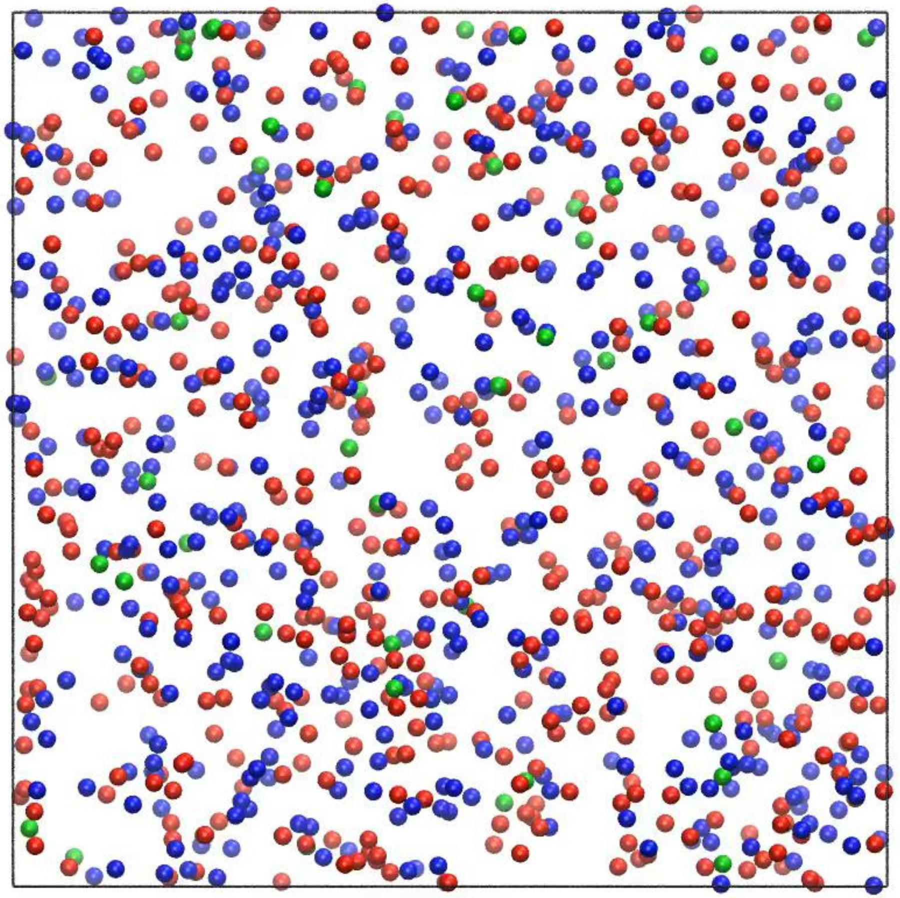
$\tilde{\alpha} = (1, -1, -5)$

$\tilde{\mu} = (1, 1/2, 2)$

$N = (500, 500, 50)$

Addition of just a few particles of a 3rd type triggers phase separation in an otherwise homogeneous mixture (cf. first movie)

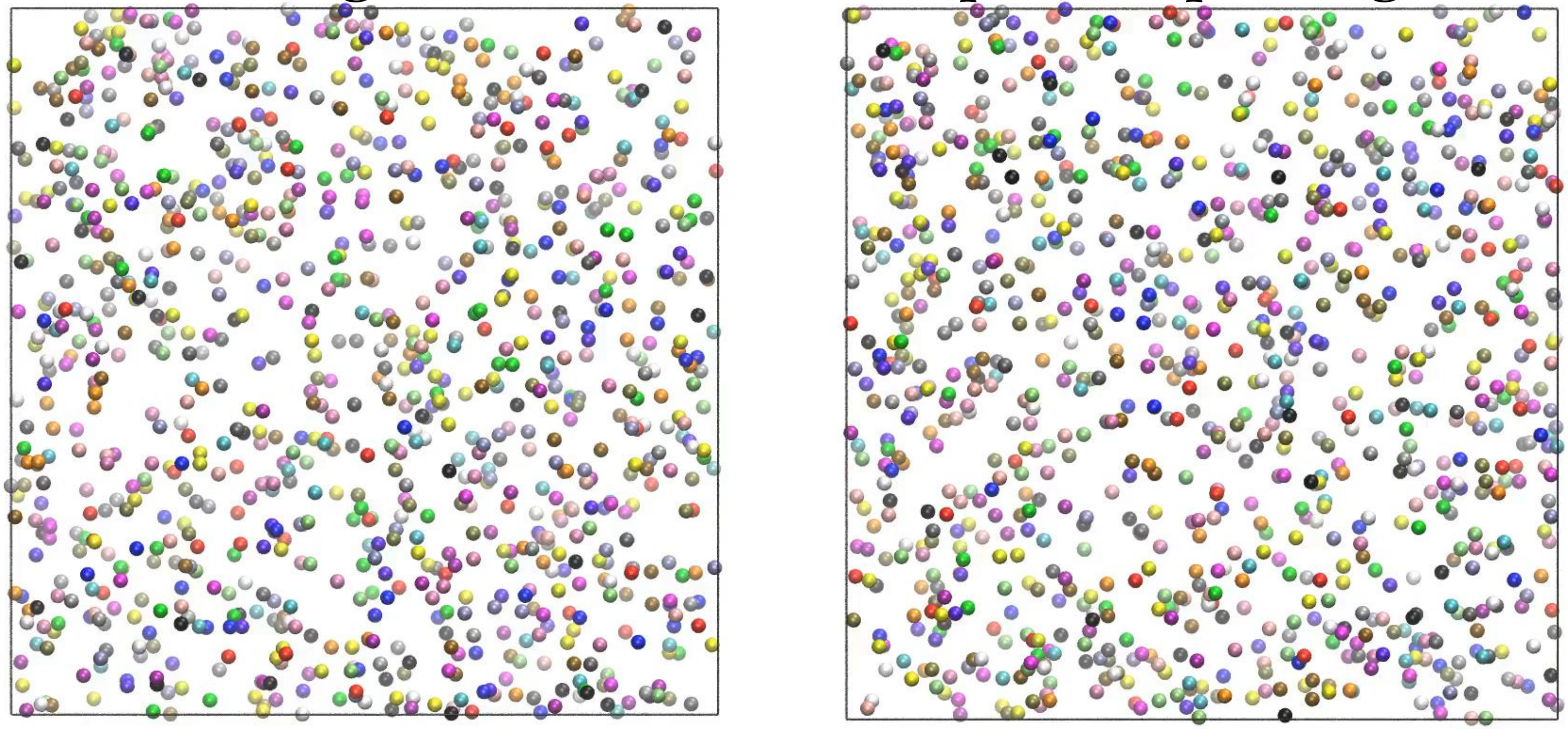
$$\boxed{\sum_i \mu_i \alpha_i \rho_{0i} < 0}$$



Beyond binary mixtures:
phase separation in highly polydisperse mixtures

- Randomly-generated mixtures with 20 different species

homogeneous **phase-separating**

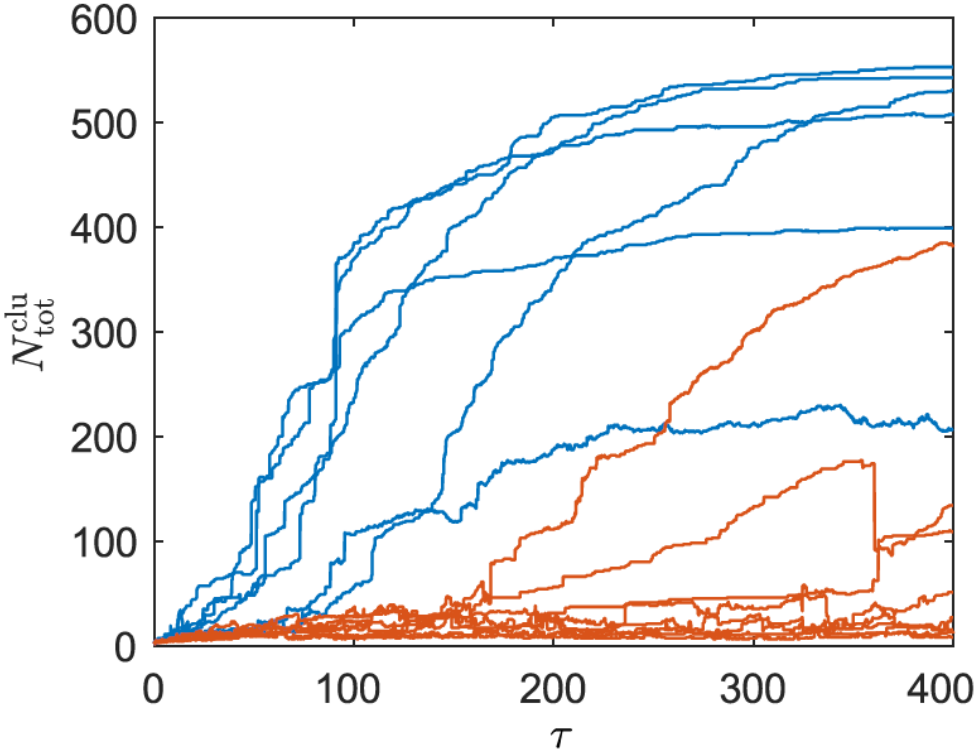


Beyond binary mixtures:
phase separation in highly polydisperse mixtures

- Randomly-generated mixtures with 20 different species

Instability condition:

$$\boxed{\sum_i \mu_i \alpha_i \rho_{0i} < 0}$$



All linearly unstable mixtures undergo phase separation, but some linearly stable mixtures too

→ nucleation-and-growth mechanism?

Summary II:

- Theory for **arbitrary mixtures** (*N* species) of chemically-interacting particles shows **wide variety** of phase separation phenomena
- Linked to **active, nonreciprocal** nature of the interactions
- Minimal model applicable to catalytic **enzymes** (metabolon formation), heterogeneous populations of **cells and bacteria** (morphogenesis, migration), catalytic phoretic **colloids** (self-assembly of active materials)

[Agudo-Canalejo, J., & Golestanian, R. (2019). Active phase separation in mixtures of chemically interacting particles. *Physical Review Letters*, *123*, 018101.]