Variational approach of coarse-grained lipid dynamics

Rolf Ryham (Fordham University), Szu-Pei (Peter) Fu (Fordham University), Yuan-Nan Young (NJIT)

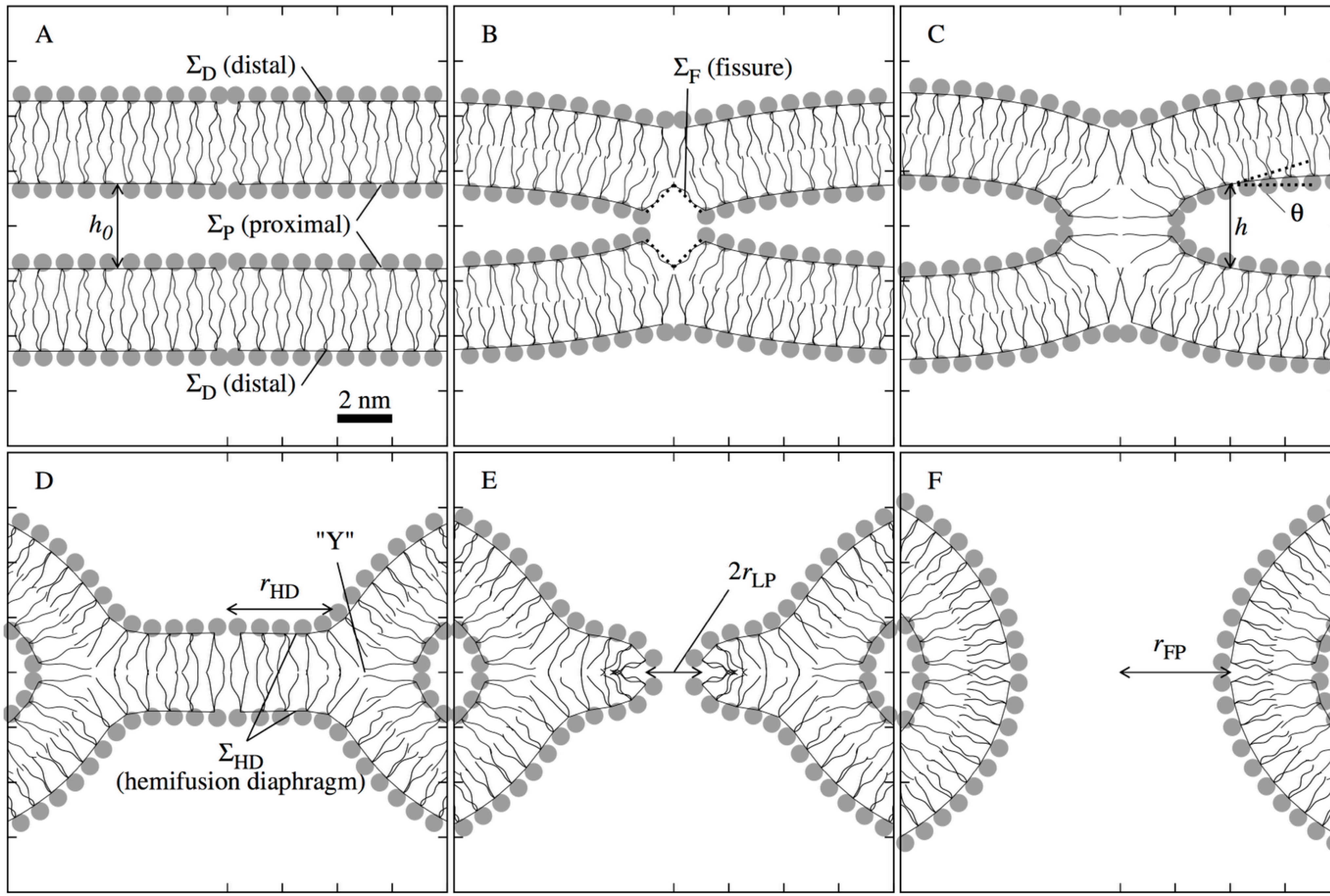
MS16, SIAM Conference on Life Sciences, Minneapolis 2018.

Continuum modeling: Helfrich Hamiltonian

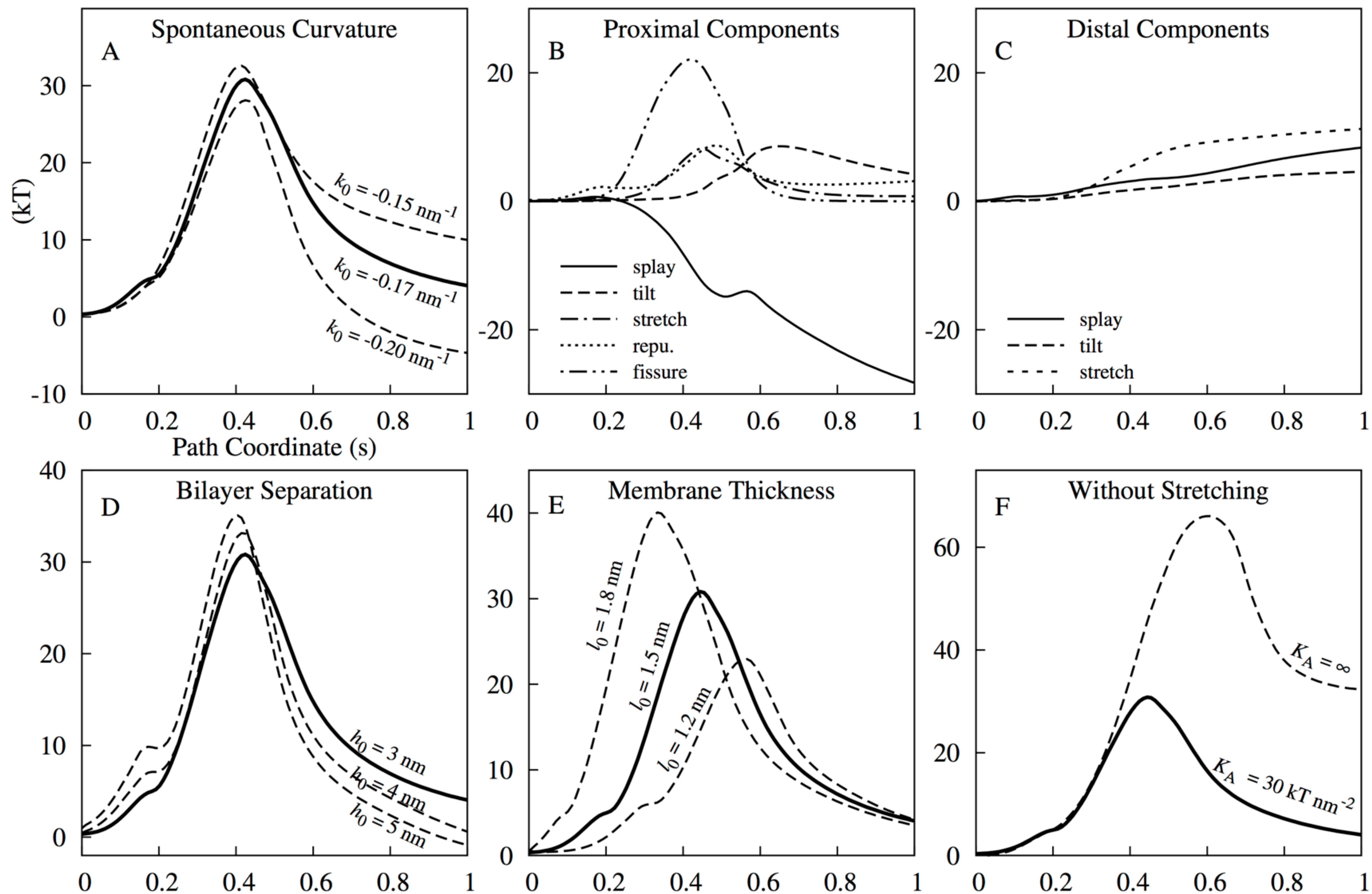
$$E = \int_\Sigma \frac{K_C}{2}\left[(\nabla\cdot\mathbf{d}+k_0)^2 - k_0^2\right] + \frac{K_\theta}{2}|\mathbf{d}\times\mathbf{n}|^2 + \frac{K_A}{2}\frac{(a-a_0)^2}{aa_0}\,dS$$
$$+ \int_\Sigma W(h,\theta)\,dS + \Phi(\Sigma_F)$$

Calculating Transition Energy Barriers and Characterizing Activation States for Steps of Fusion, RR, T. S
Klotz, L. Yao, and F. S. Cohen, Biophysical Journal 2016

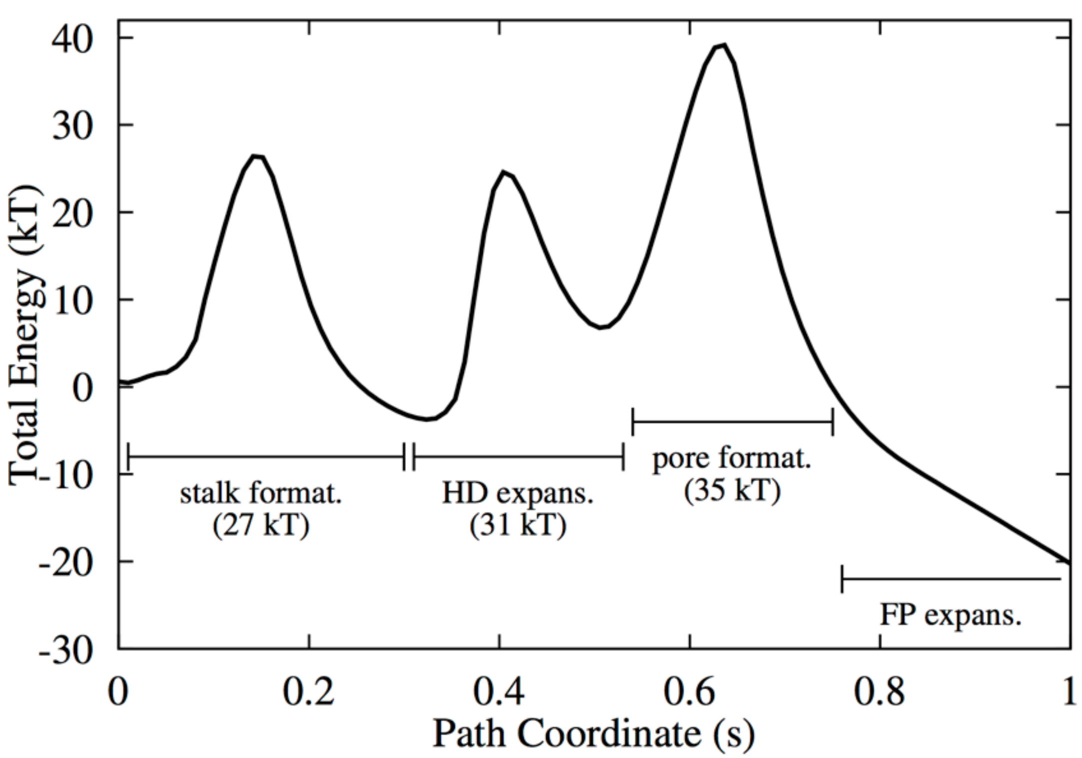
Energetics of Fusion Between Planar Bilayers

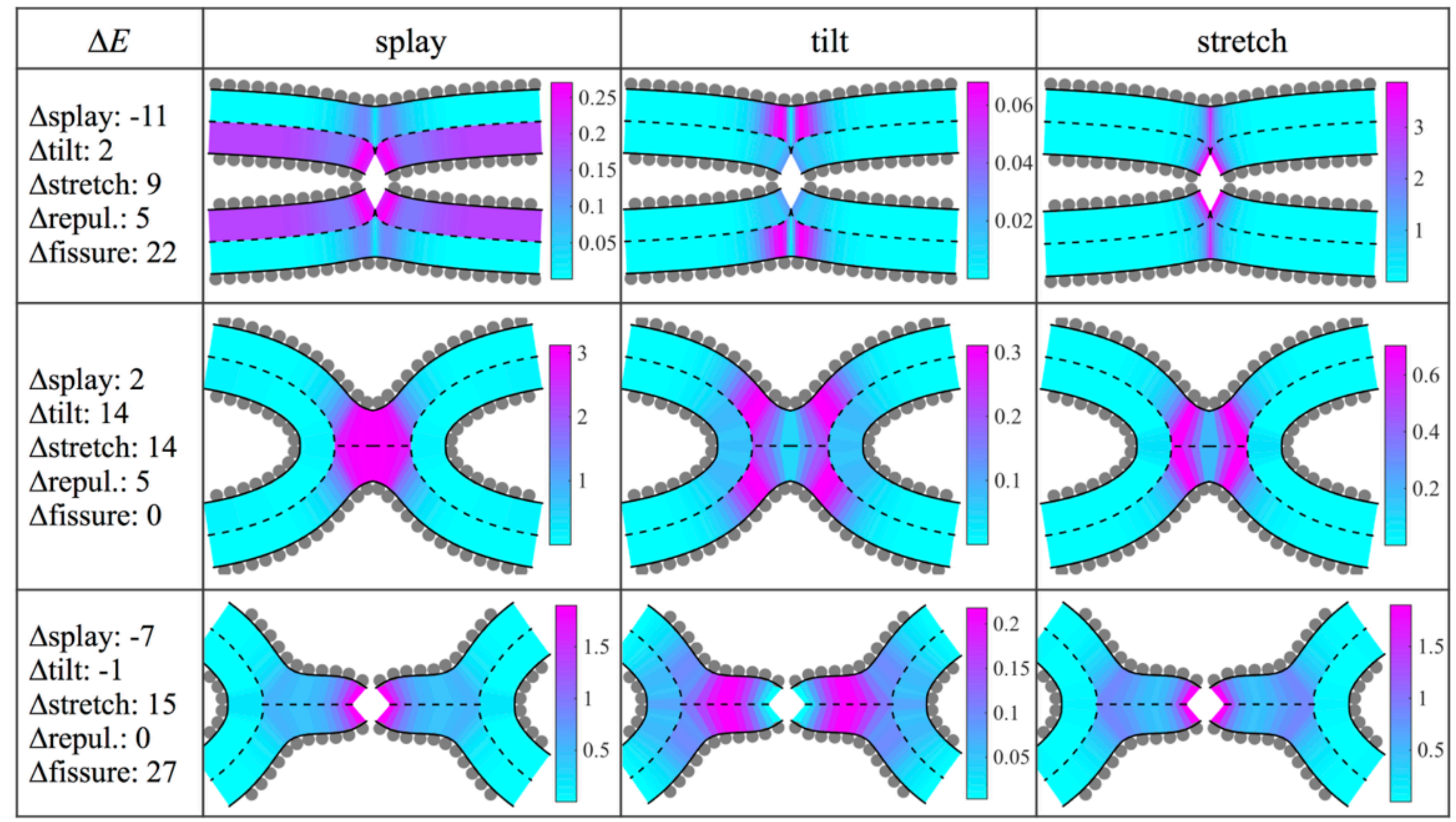


Energetics of Fusion



Energetics of Fusion





"For both DOPC and POPC, we measured E_a close to 30 k_BT. Such a low value [] remains consistent with recently published coarse-grained simulations (14, 16) in which there is no prior hypothesis concerning the fusion pathway [] Thus, these predictions [coarse-grained and continuum] are compatible with our experimental measurements and may closely reproduce the reality of the fusion process at a molecular scale."

Low energy cost for optimal speed and control of membrane fusion, C. François-Martin, J. E. Rothman, and F. Pincet, PNAS 2017

Summary

- Continuum and molecular approaches yield energies and forces in membranes that are close to experiment

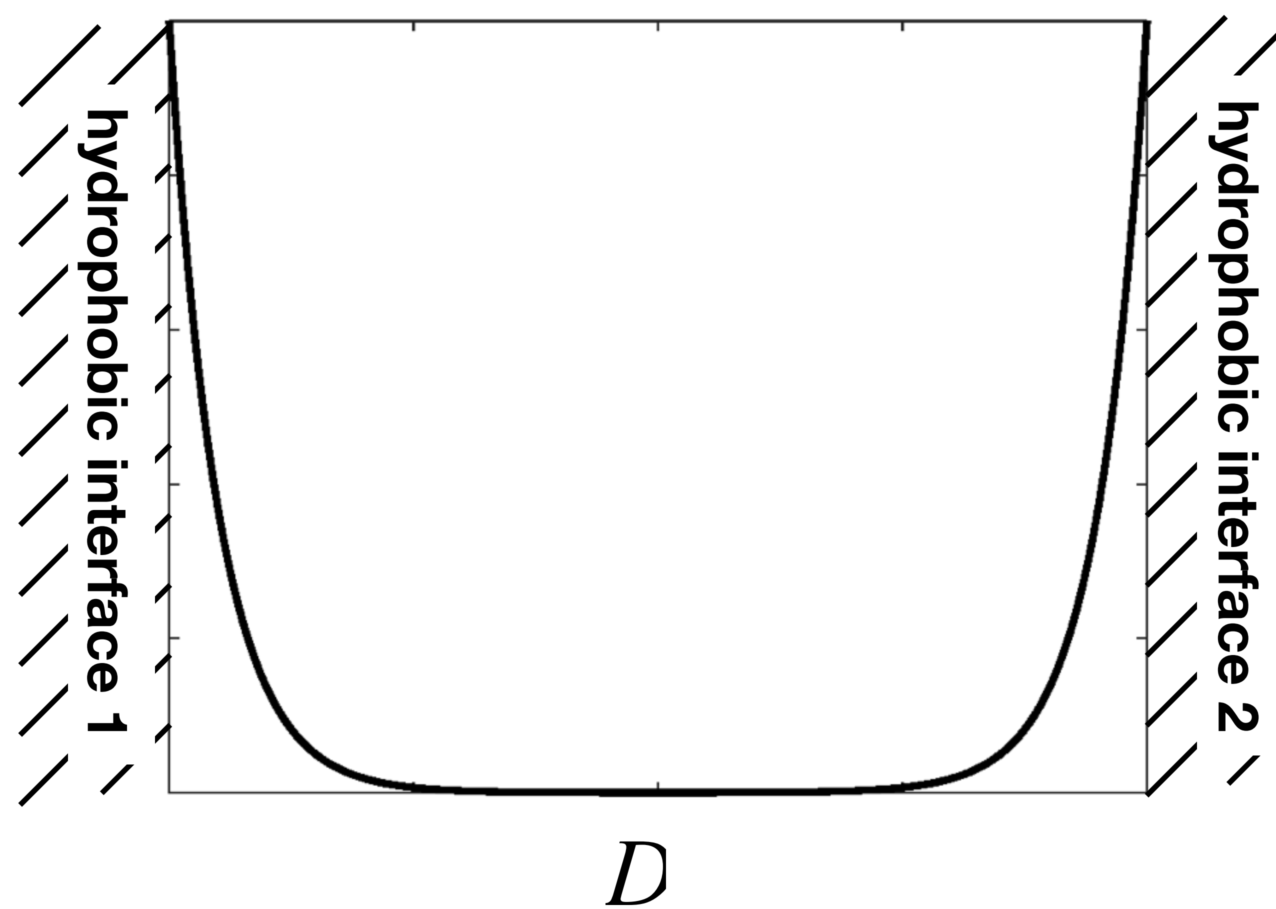
- In continuum modeling, however, the placement of surface interruptions done on a case-by-case basis

- Molecular approaches (coarse-grained or otherwise) make water explicit and/or assume pairwise potentials

- Is there a formalism that treats water as a continuum and gives expected lipid self assembly/energies?

1D Hydrophobic Attraction

$$\Phi(D) = \gamma 2A$$

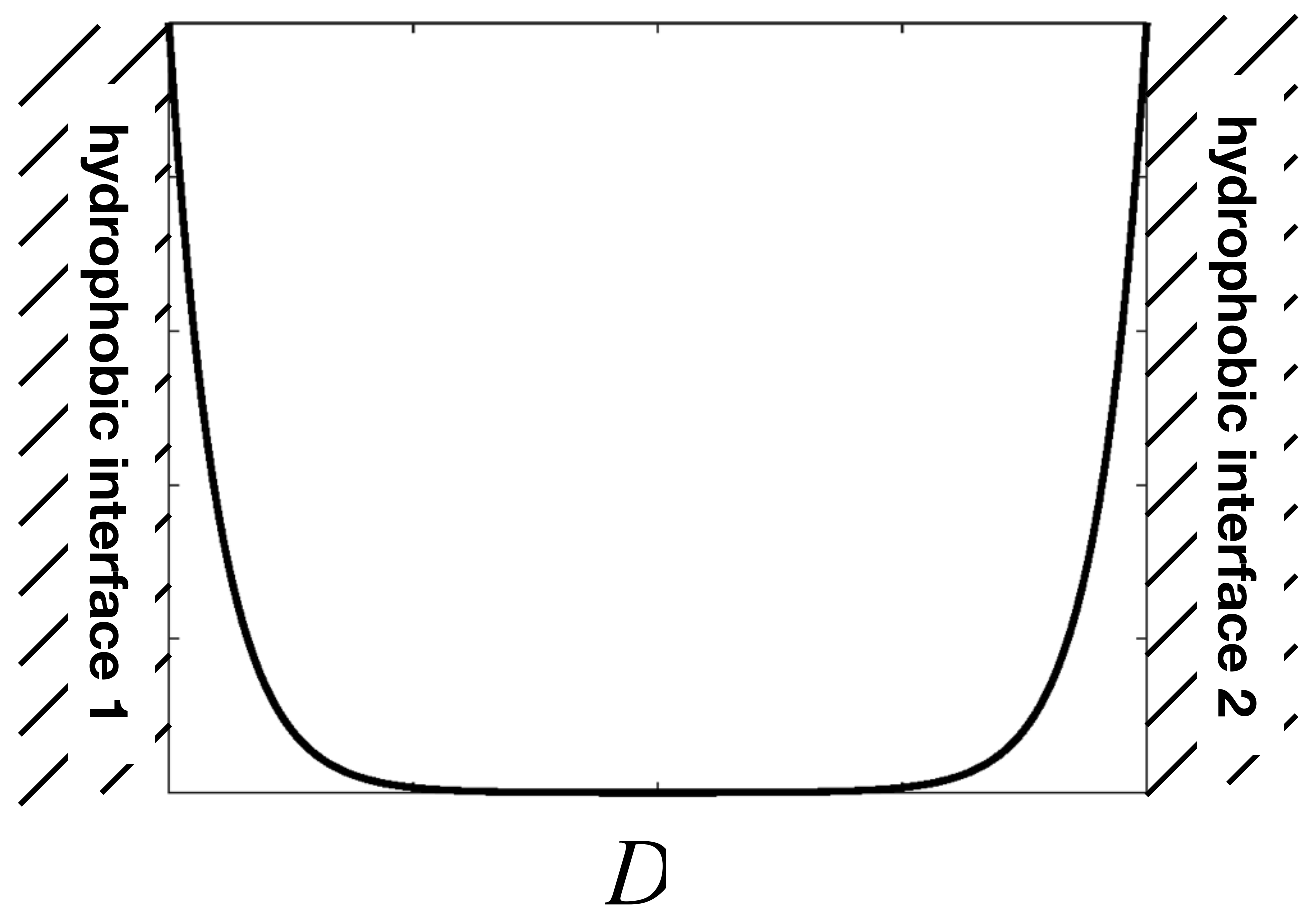


1D Hydrophobic Attraction

$$\Phi(D) = \min_u \gamma I[u], \quad I[u] = A\int_{-D/2}^{D/2} \rho(u')^2 + \rho^{-1}u^2\,dx$$

$$\begin{cases} -\rho^2 u'' + u = 0 \\ u(\pm D/2) = 1 \end{cases}$$

$$u(x) = \frac{\cosh(x/\rho)}{\cosh(D/2\rho)}$$

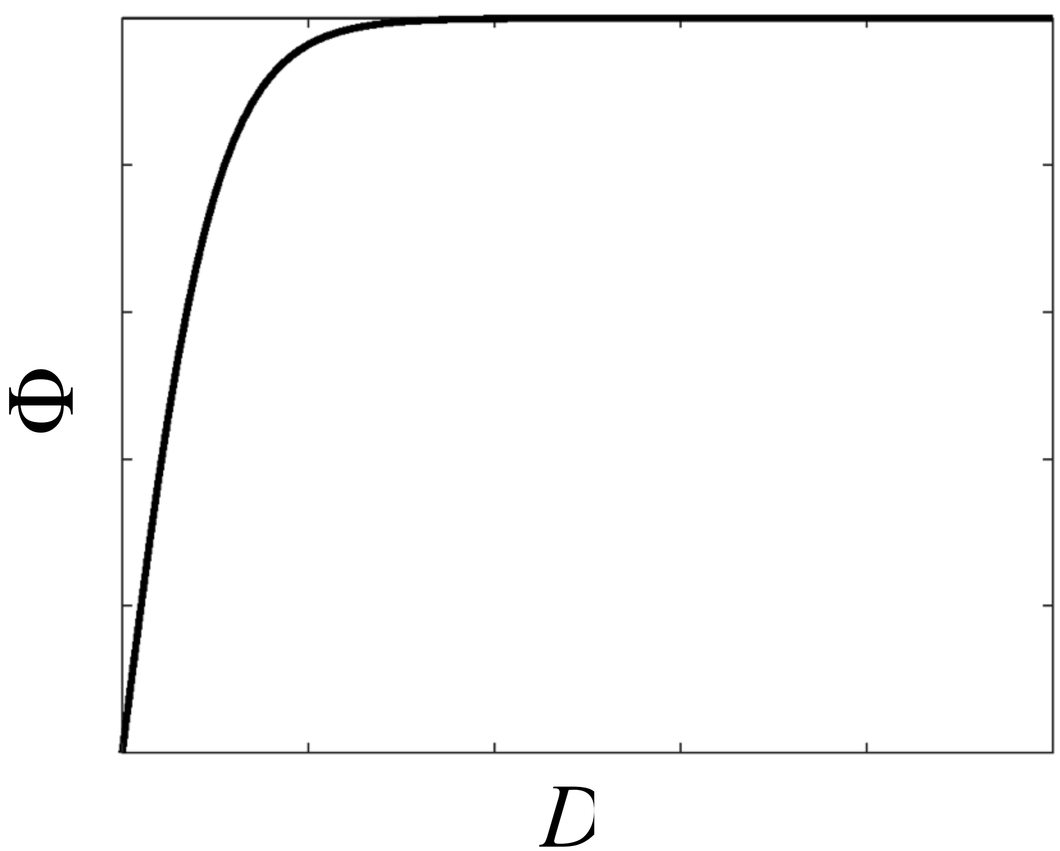


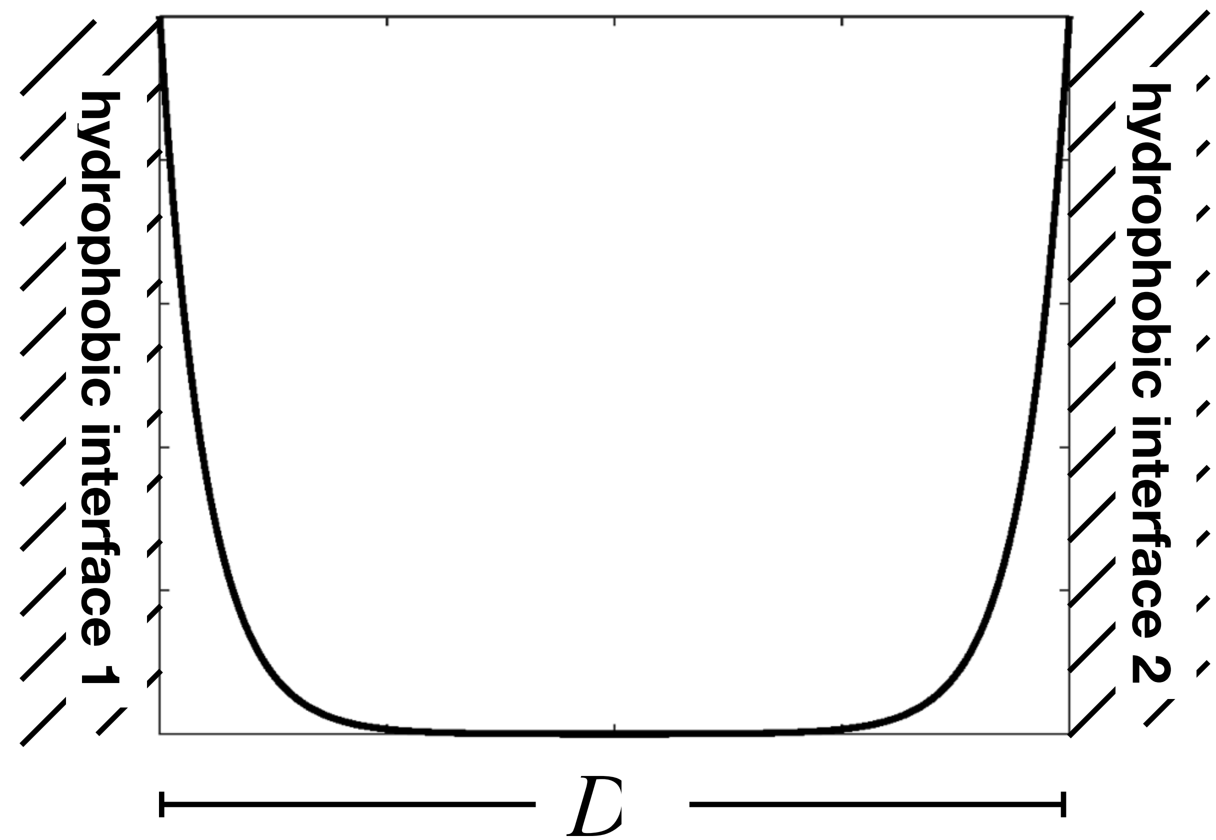
Structural contribution to solute-solute interaction, S. Marčelja, Croat. Chem. Acta., 1977

A phenomenological theory of long-range hydrophobic attraction forces based on a square-gradient variational approach, J. C. Ericksson, S. Ljunggren, P. M. Claesson, J. Chem. Soc., Faraday Trans., 1989

1D Hydrophobic Attraction

$$\cancel{\Phi(D) = \gamma 2A} \qquad \Phi(D) = 2\gamma A \tanh(D/\rho)$$





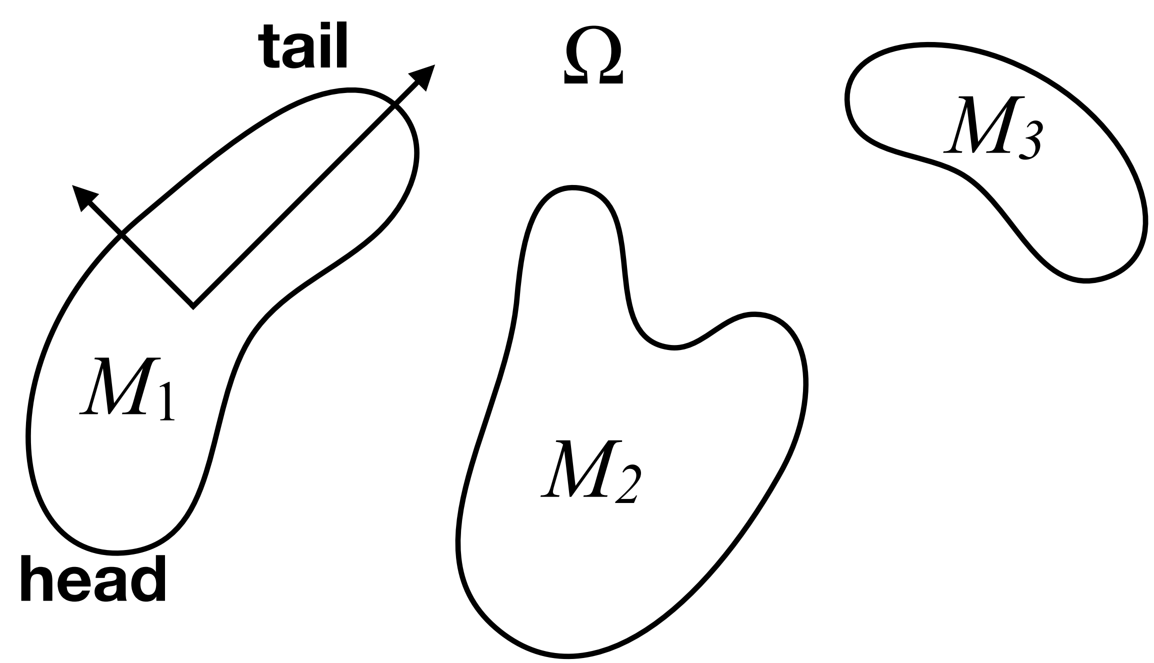
Hydrophobic Attraction Potential BVP

$$\Phi(\Omega, f) = \gamma \min_{\mathcal{A}} I[u], \text{ where } I[u] = \int_\Omega \rho|\nabla u|^2 + \rho^{-1}u^2 \, dx$$

$$\mathcal{A} = \{u \in H^1(\Omega) : u(x) = f_i(x), x \in M_i\}$$

For example:

$$f_i(x) = \cos^2(\theta_i(x)/2)$$



Amphiphilic Interaction and Dynamics of Lipid-like Particles by an Integral Equation Method, S.-P. Fu, RR, A. Klöckner, M. Wala, S. Jiang and Y.-N. Young, in preparation

Hydrophobic Attraction Potential BVP

$$\Phi(\Omega, f) = \gamma \min_{\mathcal{A}} I[u], \text{ where } I[u] = \int_{\Omega} \rho |\nabla u|^2 + \rho^{-1} u^2 \, dx$$

$$\Updownarrow$$

Screened Laplace Boundary Value Problem

$$\begin{cases} -\rho^2 \Delta u + u = 0 \text{ in } \Omega, \\ u(x) = f(x) \text{ on } \Sigma \text{ and } \lim\limits_{x \to \infty} u(x) = 0 \end{cases}$$

- Exterior problem: existence and uniqueness
- Solutions decay and other properties

Forces and torques

Hydrophobic stress tensor

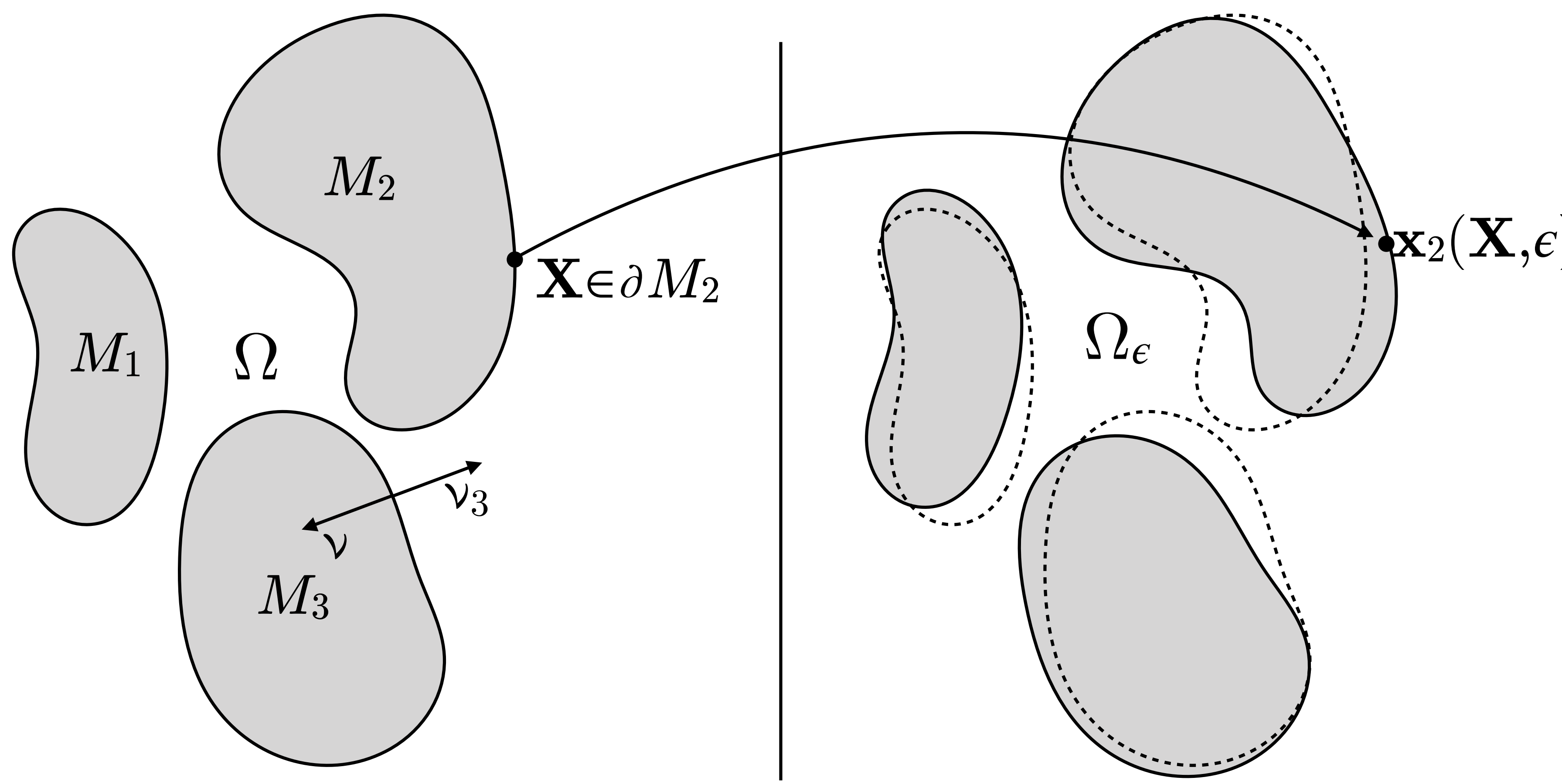
$$\mathbf{F}_i = \int_{\partial M_i} \mathbf{T} \cdot \nu_i \, dS, \quad \tau_i^0 = \int_{\partial M_i} \mathbf{r}_0 \times (\mathbf{T} \cdot \nu_i) \, dS$$

$$\mathbf{T} = \gamma \rho^{-1} u^2 \mathbf{I} + 2\rho\gamma\left(\tfrac{1}{2}|\nabla u|^2 \mathbf{I} - \nabla u \otimes \nabla u\right)$$

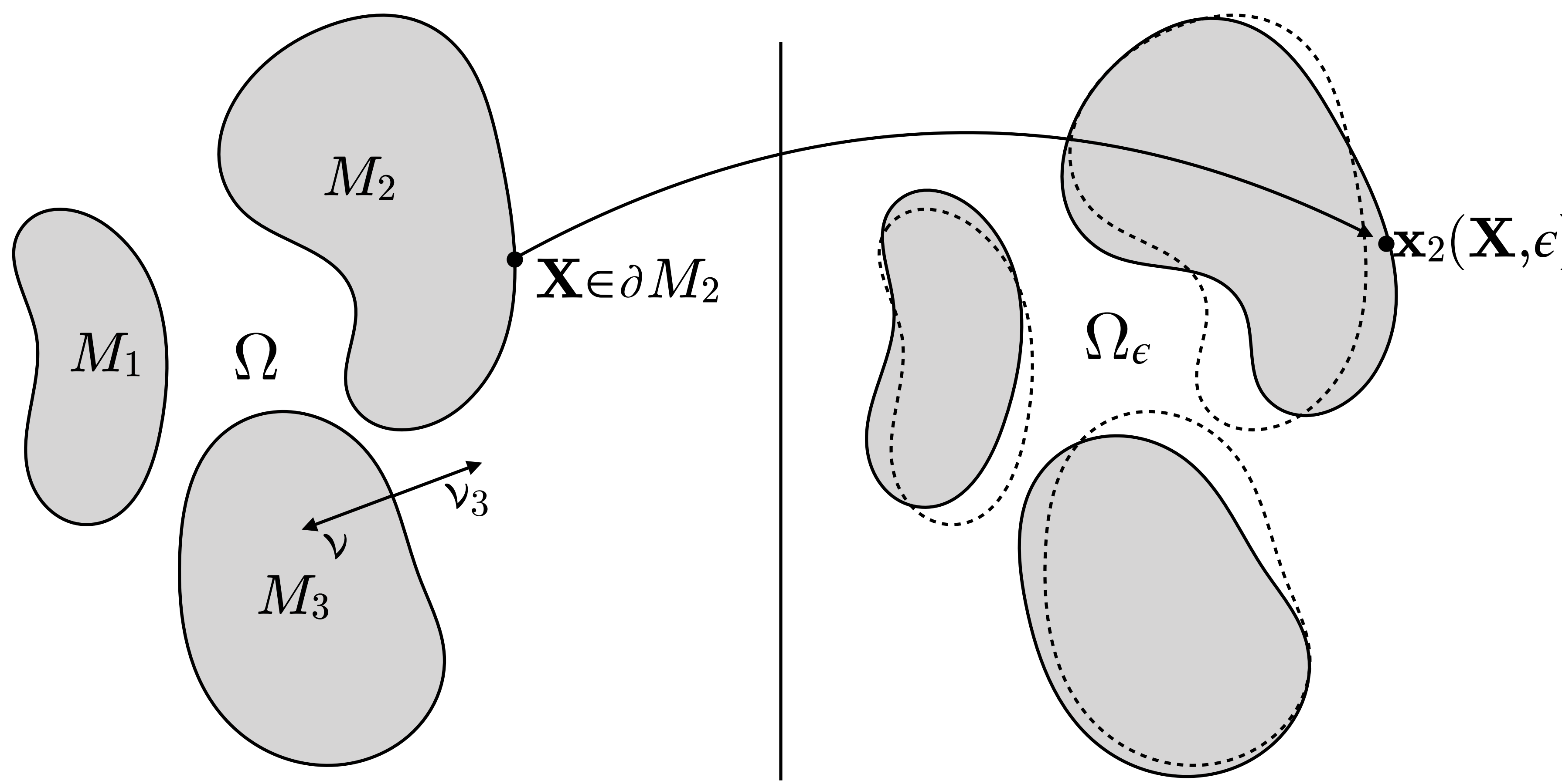
$$\Omega = \mathbb{R}^n \setminus \bigcup_{i=1}^{N} M_i, \quad \Sigma = \bigcup_{i=1}^{N} \partial M_i$$

$$\begin{cases} -\rho^2 \Delta u + u = 0 \text{ in } \Omega, \\ u(x) = f(x) \text{ on } \Sigma \text{ and } \lim_{x \to \infty} u(x) = 0 \end{cases}$$

Derivation: outline



$$\frac{d}{d\epsilon}\Phi(\Omega_\epsilon, f_\epsilon)\Big|_{\epsilon=0} = -\sum_{i=1}^{N}\left(\mathbf{c}_i'(0)\cdot\mathbf{F}_i + \mathbf{w}_i\cdot\tau_i^0\right)$$



$$\mathbf{x}_i(\mathbf{X}, \epsilon) = \mathbf{c}_i(\epsilon) + \mathbf{Q}_i(\epsilon)\mathbf{X}$$

$$\Omega_\epsilon = \mathbb{R}^n \setminus \bigcup_{i=1}^{N} \mathbf{x}_i(M_i, \epsilon), \quad \Sigma_\epsilon = \partial\Omega_\epsilon$$

$$f_\epsilon(\mathbf{x}_i(\mathbf{X}, \epsilon)) = f(\mathbf{X}), \quad \mathbf{X} \in \partial M_i$$

$$\begin{cases} -\rho^2 \Delta u_\epsilon + u_\epsilon = 0 \text{ in } \Omega_\epsilon \\ u_\epsilon = f_\epsilon \text{ in } \Sigma_\epsilon \end{cases}$$

- **Water activity u satisfies transport equation at molecular interface**

$$u' + \nabla u \cdot \mathbf{x}' = 0 \text{ on } \Sigma$$

- **Bulk values determined by PDE**

$$
\begin{aligned}
\frac{d}{d\epsilon}\Phi(\Omega_\epsilon, f_\epsilon)\Big|_{\epsilon=0} &= \gamma\frac{d}{d\epsilon}\left(\int_{\Omega_\epsilon}\rho|\nabla u_\epsilon|^2 + \rho^{-1}u_\epsilon^2\,dx\right)\Big|_{\epsilon=0} \\
&= \gamma\int_\Omega 2\rho\nabla u\cdot\nabla u' + 2\rho^{-1}uu'\,dx + \gamma\int_\Sigma \left(\rho|\nabla u|^2 + \rho^{-1}u^2\right)\mathbf{x}'\cdot\nu\,dS \\
&= \gamma\int_\Sigma \left(\rho|\nabla u|^2 + \rho^{-1}u^2\right)\mathbf{x}'\cdot\nu - 2\rho\nabla u\cdot\nu u'\,dS \\
&= \gamma\sum_{i=1}^N\int_{\partial M_i} -\left(\rho|\nabla u|^2 + \rho^{-1}u^2\right)\nu_i\cdot\mathbf{x}_i'(0) + 2\rho\nabla u\cdot\nu_i\nabla u\cdot\mathbf{x}_i'(0)\,dS \\
&= \gamma\sum_{i=1}^N\int_{\partial M_i}\mathbf{x}_i'(0)\cdot\left[-\rho^{-1}u^2\mathbf{I} + 2\rho(\nabla u\otimes\nabla u - \tfrac{1}{2}|\nabla u|^2\mathbf{I})\right]\cdot\nu_i\,dS \\
&= -\sum_{i=1}^N\int_{\partial M_i}(\mathbf{c}_i'(0) + \mathbf{Q}_i'(0)\mathbf{r}_0)\cdot\mathbf{T}\cdot\nu_i\,dS
\end{aligned}
$$

Overall strategy

Hydrophobic stress tensor

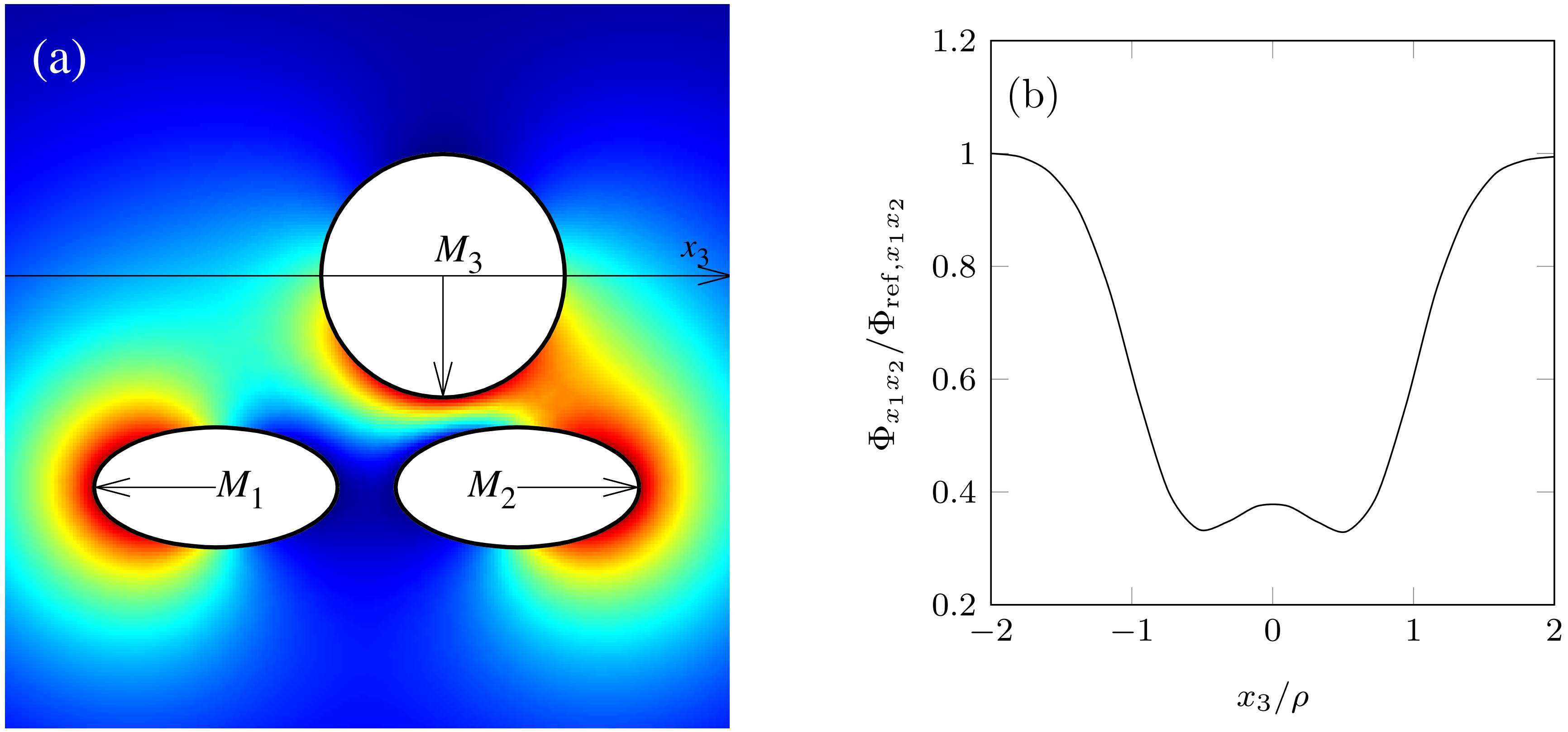
$$\mathbf{F}_i = \int_{\partial M_i} \mathbf{T} \cdot \nu_i \, dS, \quad \tau_i^0 = \int_{\partial M_i} \mathbf{r}_0 \times (\mathbf{T} \cdot \nu_i) \, dS$$

$$\mathbf{T} = \gamma \rho^{-1} u^2 \mathbf{I} + 2\rho\gamma \left(\tfrac{1}{2} |\nabla u|^2 \mathbf{I} - \nabla u \otimes \nabla u\right)$$

- Rapid solution of screened Laplace BVP (see MS54 on Thursday)
- Numerically integrate surface stresses
- Apply (particle-wise) rigid deformations—or—for flexible interfaces, balance with any other elastic stresses

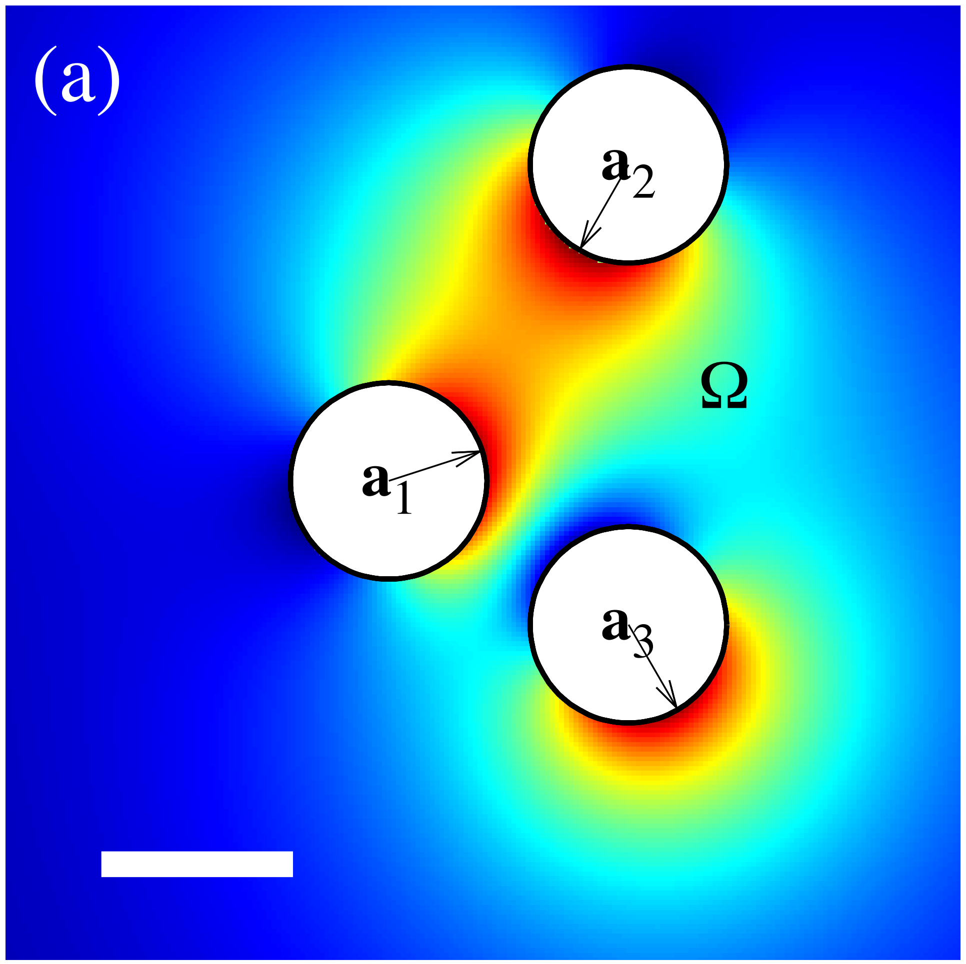
Can hydrophobic attraction be represented by pairwise interaction?

$$\Phi = \sum_{i=1}^{N} \sum_{j>i}^{N} \phi_{ij}(x_i, y_i, \theta_i, x_j, y_j, \theta_j)?$$



$$\frac{\partial \mathbf{F}_{1x}}{\partial x_2} = \frac{\partial^2 \Phi}{\partial x_2 \partial x_1} = \frac{\partial^2 \phi_{12}}{\partial x_2 \partial x_1}(x_1, y_1, \theta_1, x_2, y_2, \theta_2)$$

Validation



$$\mathbf{v} \cdot \mathbf{F}_i = -\frac{d}{d\epsilon}\Phi(\mathbf{a}_i + \epsilon\mathbf{v}, \theta_i)|_{\epsilon=0}$$
$$\approx -\frac{\Phi(\mathbf{a}_i + \epsilon\mathbf{v}, \theta_i) - \Phi(\mathbf{a}_i - \epsilon\mathbf{v}\theta_i)}{2\epsilon}$$
$$\omega\tau_i = -\frac{d}{d\epsilon}\Phi(\mathbf{a}_i, \theta_i + \omega\epsilon)|_{\epsilon=0}$$
$$\approx -\frac{\Phi(\mathbf{a}_i\theta_i + \omega\epsilon) - \Phi(\mathbf{a}_i, \theta_i - \omega\epsilon)}{2\epsilon}$$

Centered Difference		Variation	
$\mathbf{F}_i$	τ_i	$\mathbf{F}_i$	τ_i
$\langle -0.94496, +1.37954 \rangle$	$+0.90685$	$\langle -0.83884, +1.35038 \rangle$	$+0.92534$
$\langle -0.28603, -0.46196 \rangle$	$+0.02815$	$\langle -0.26879, -0.43257 \rangle$	$+0.02923$
$\langle +1.17189, -0.90103 \rangle$	-0.23972	$\langle +1.20538, -0.91928 \rangle$	-0.23962

Particle Dynamics

- 2-dimensional problem (line tension)
- Assume Janus-like particles—oriented disks
- Include repulsive force to prevent particles coming into contact

$$\xi_x \frac{d\mathbf{a}_i}{dt} = \mathbf{F}_i + \sum_{j \neq i} \mathbf{F}_{ij}^{\mathrm{rep}}$$

$$\xi_\theta \frac{d\theta_i}{dt} = \tau_i^0 - \mathbf{a}_i \times \mathbf{F}_i, \quad i = 1, \ldots, N$$

$$\Phi^{\mathrm{rep}} = \sum_{i=1}^{N} \sum_{j \neq i} \frac{c_0}{4(x_{ij} - 2a)^2}$$

Particle Dynamics

<u>Properties</u>

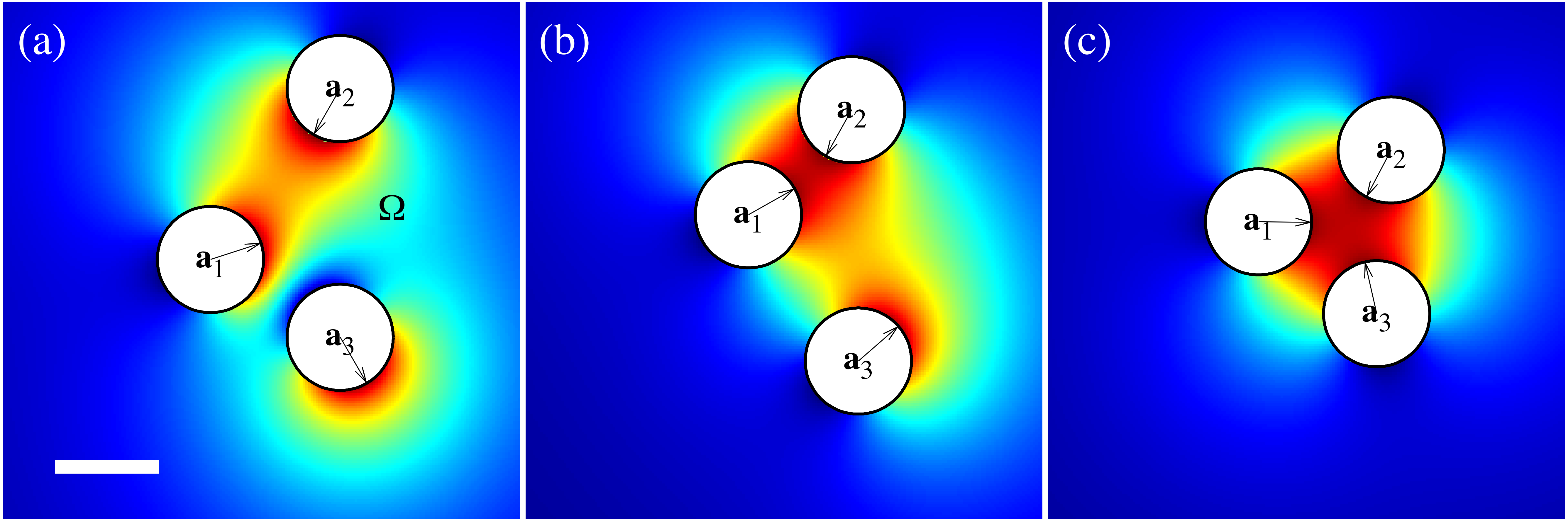
- Net force and torque is zero

$$\sum_{i=1}^{N} \mathbf{c}'(0) \cdot \mathbf{F}_i + \mathbf{w} \cdot \tau_i^0 = -\frac{d}{d\epsilon}\Phi(\Omega_\epsilon, f_\epsilon)\Big|_{\epsilon=0} = -\frac{d}{d\epsilon}\Phi(\Omega, f)\Big|_{\epsilon=0} = 0$$

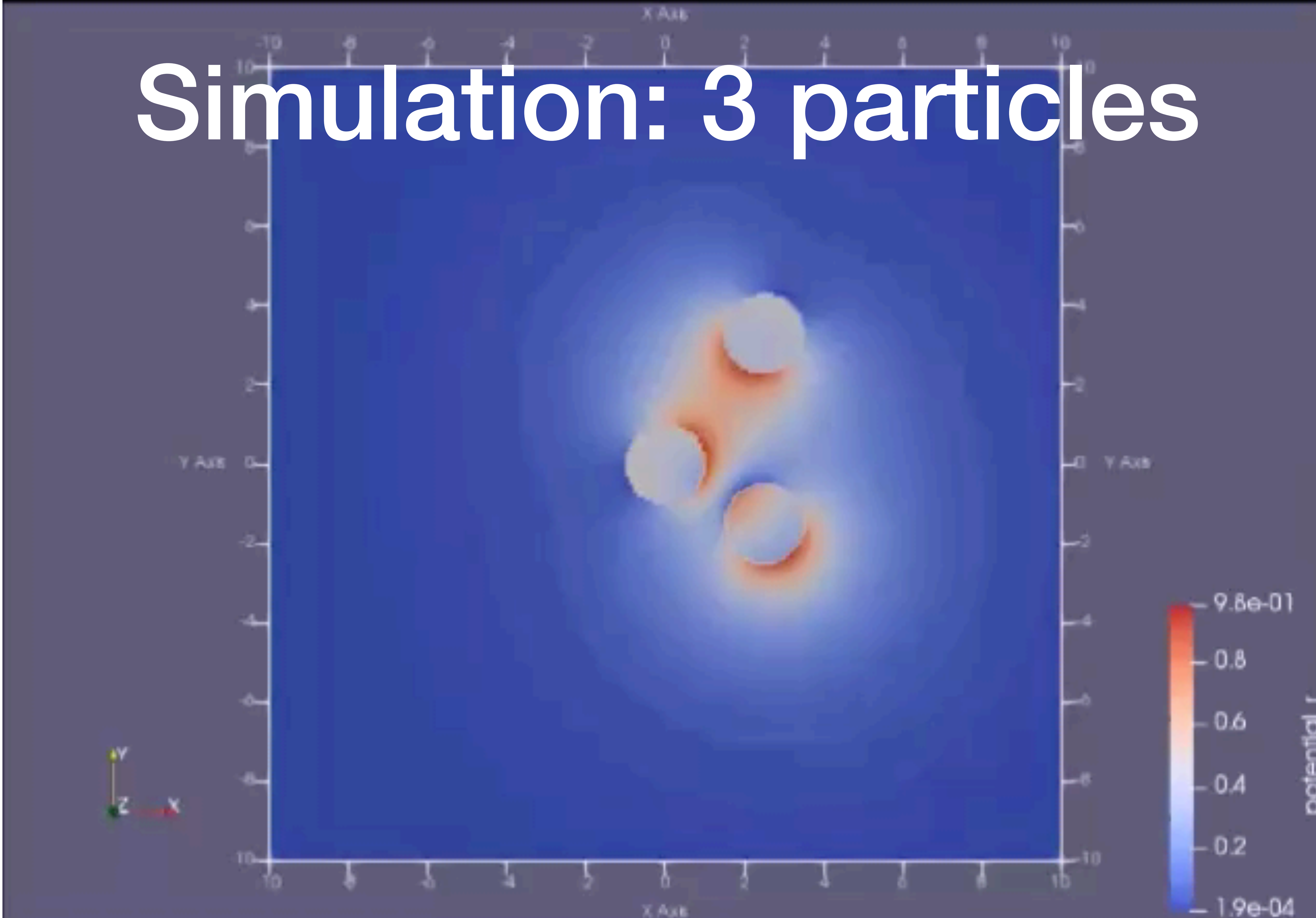
- Total energy is non-increasing

$$\frac{d}{dt}\left(\Phi(\Omega, h) + \Phi^{\mathrm{rep}}\right) = -\sum_{i=1}^{N}\left[\left(\mathbf{F}_i + \sum_{j\neq i}\mathbf{F}_{ij}^{\mathrm{rep}}\right) \cdot \frac{d\mathbf{a}_i}{dt} + \tau_i \frac{d\theta_i}{dt}\right] \leq 0$$

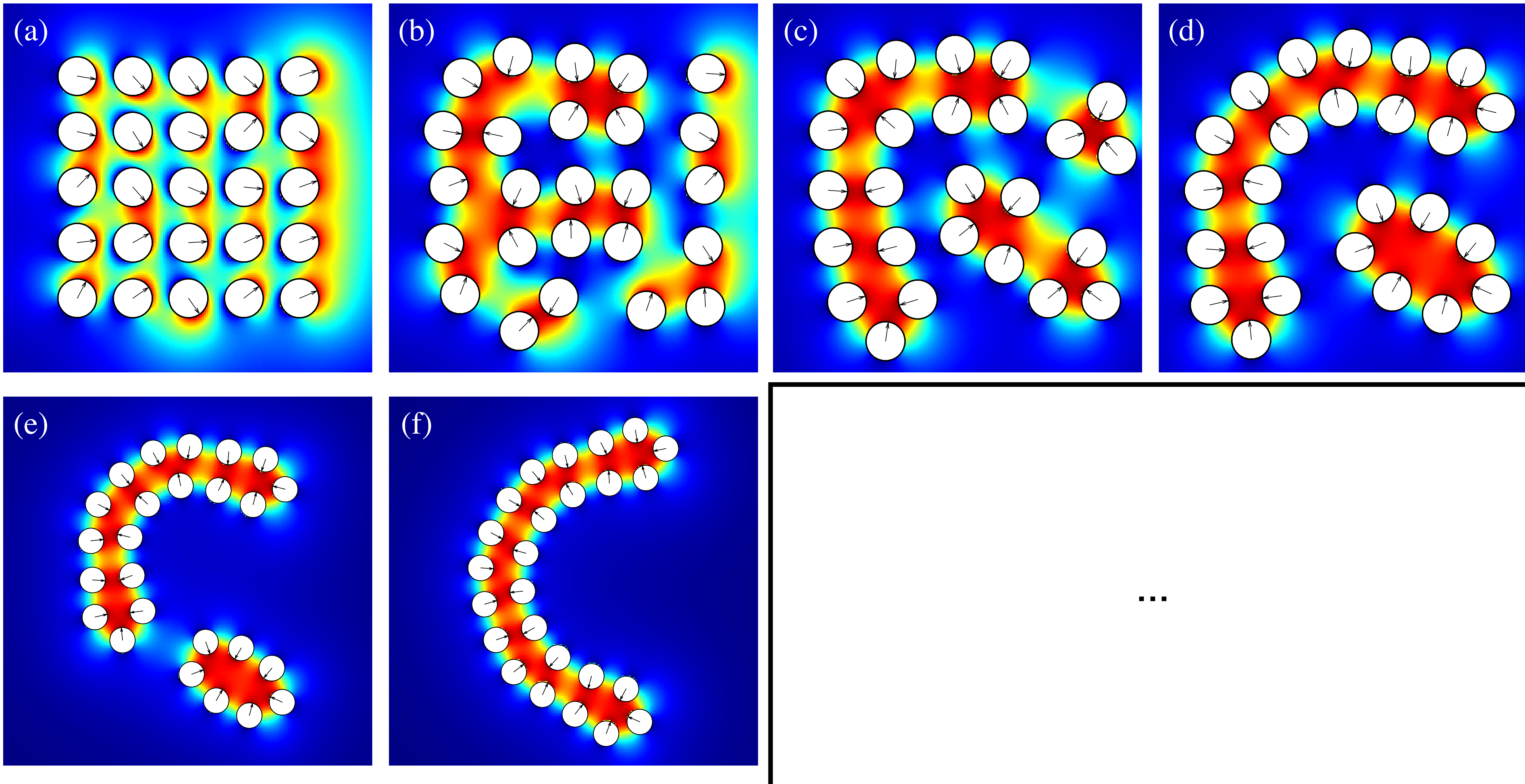
Simulation: 3 particles



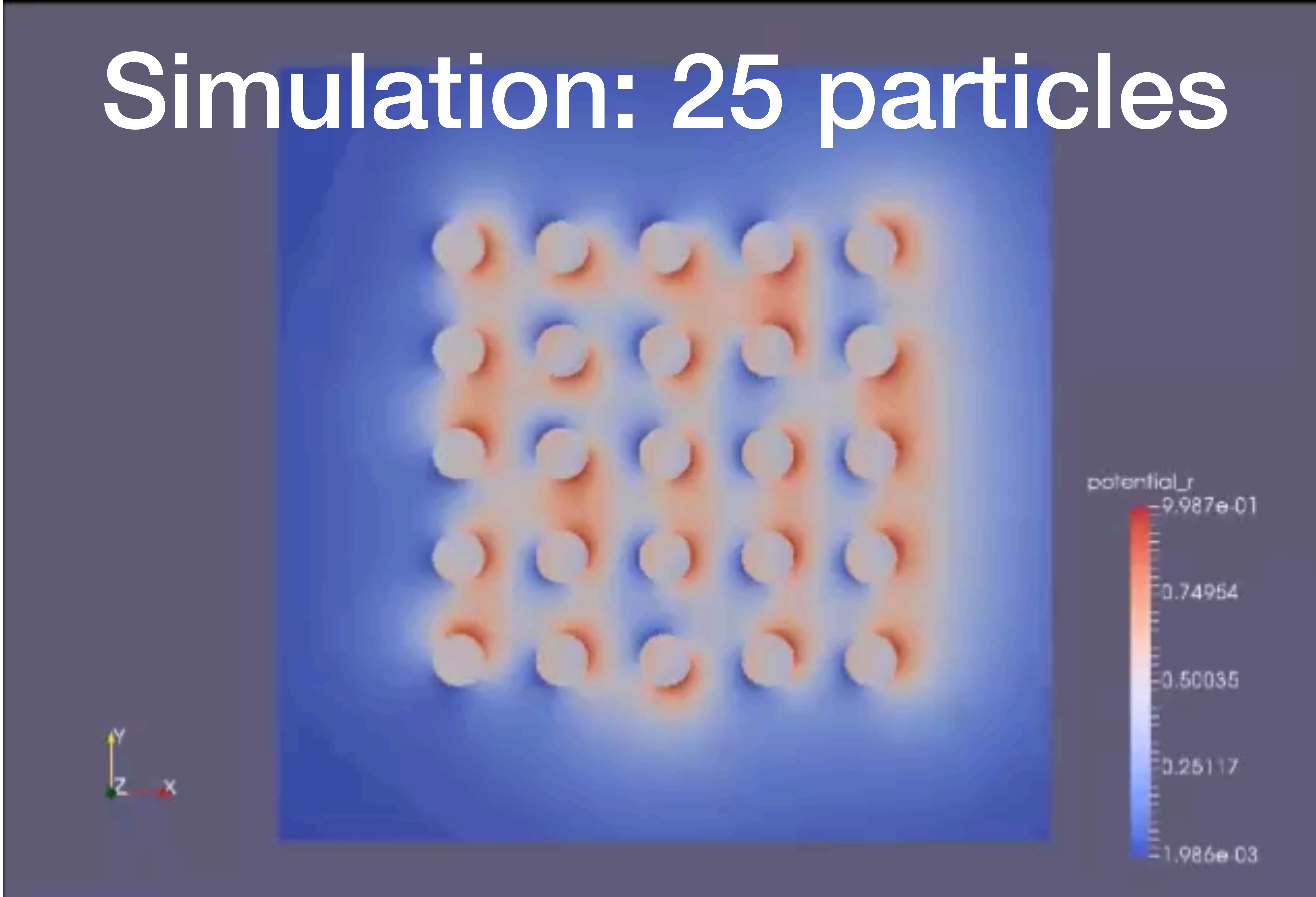
Simulation: 3 particles



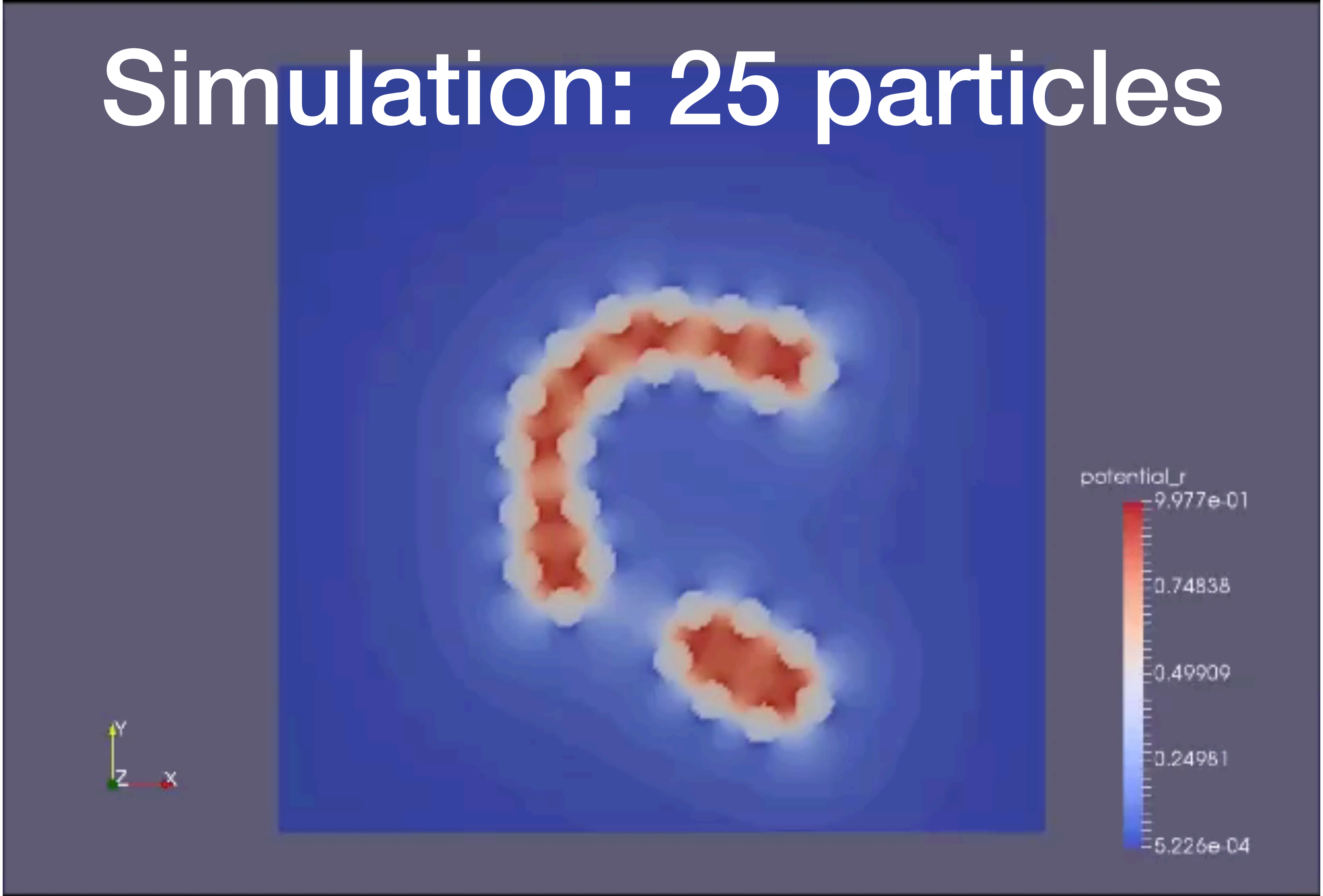
Simulation: 25 particles



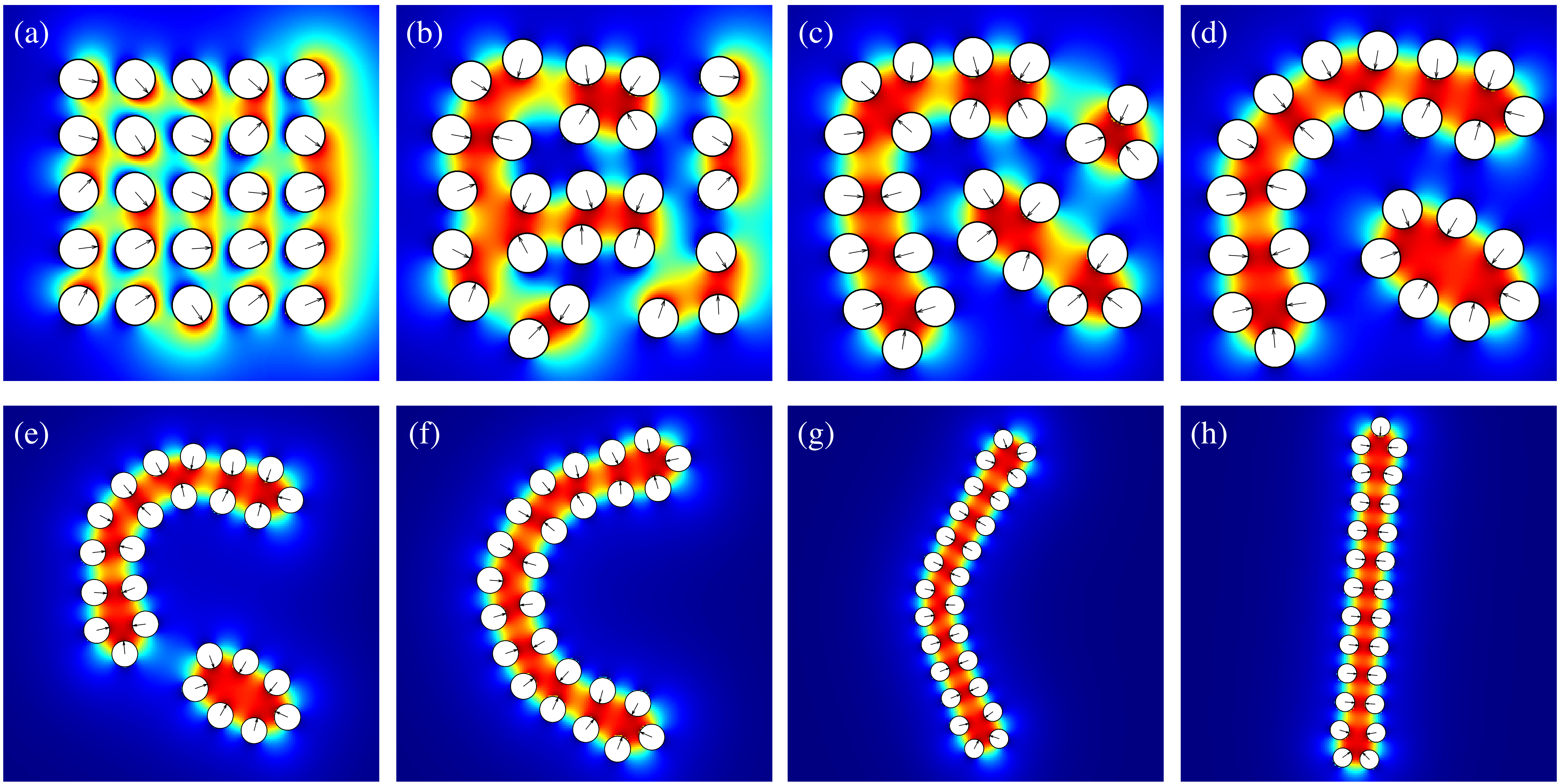
Simulation: 25 particles



Simulation: 25 particles



Simulation: 25 particles



Conclusion

- Given challenges with continuum and molecular models, we use formalism for long-range hydrophobic attraction to model amphiphilic molecules
- Hydrophobic attraction has an associated stress tensor, which we derive explicitly by domain variation
- The flexible approach yields expected lipid self-assembly, e.g. micelles and bilayers, with practical computational times
- In future works, we must evaluate how Φ connects to the traditional Helfrich hamiltonian—include realistic hydrodynamic interaction