

Advances in the Hybrid Particle-Field Approach

Towards Biological Systems

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PhD lecture, Oslo, 27 March 2020

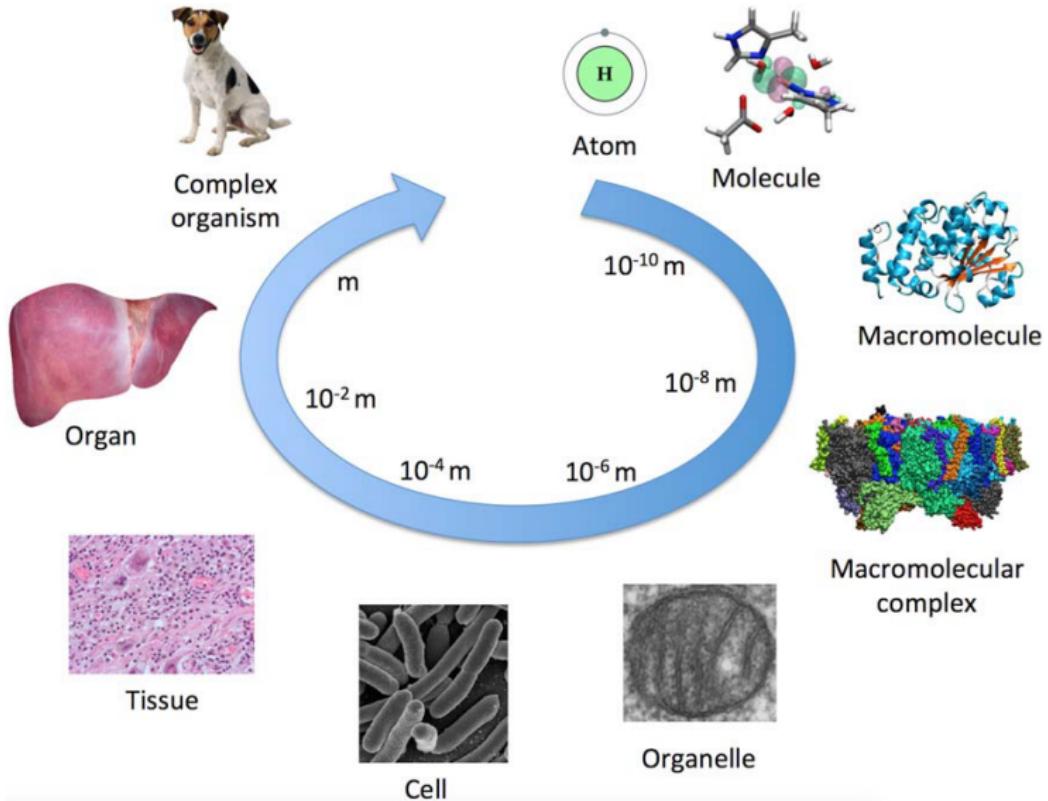


UiO : University of Oslo

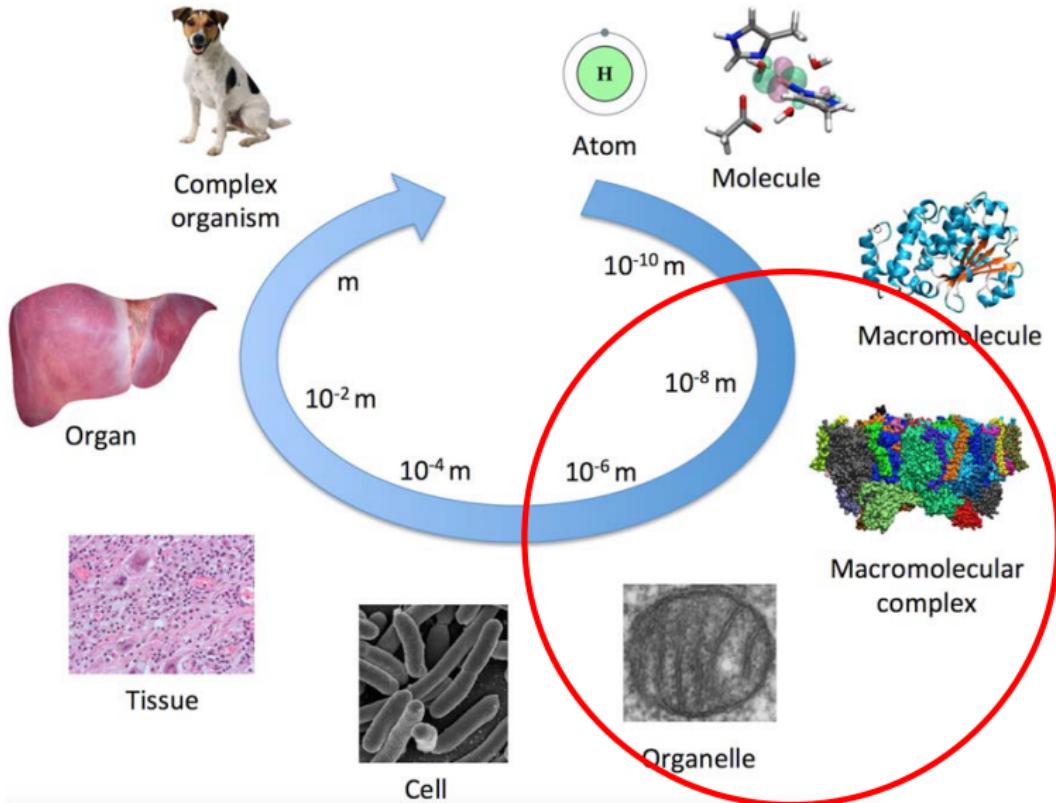


Hylleraas

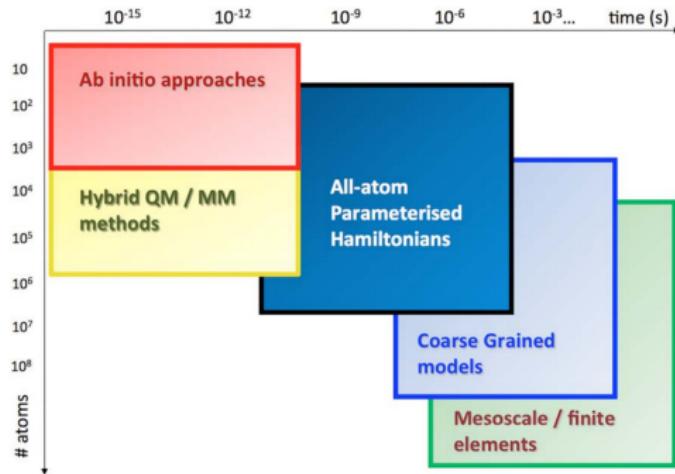
Scope of the work



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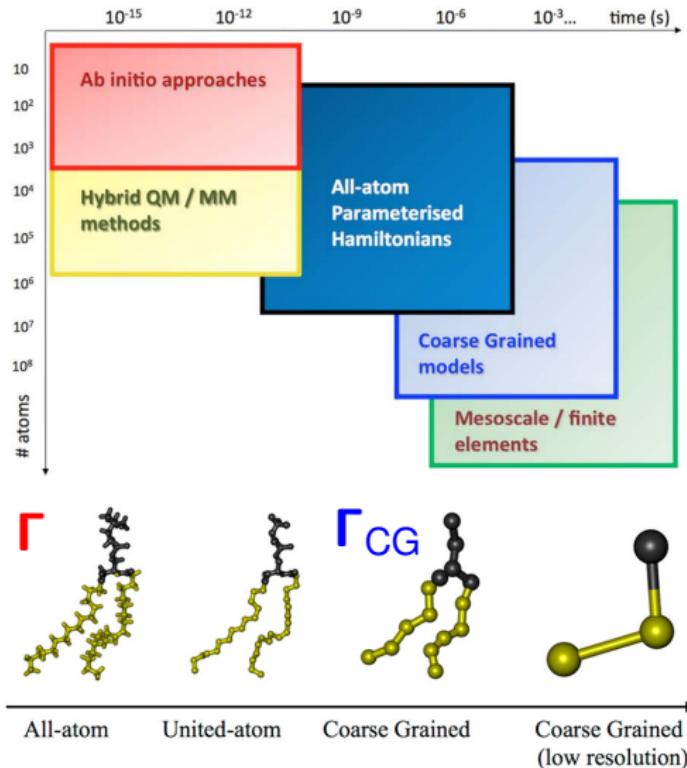
Coarse-grained methods



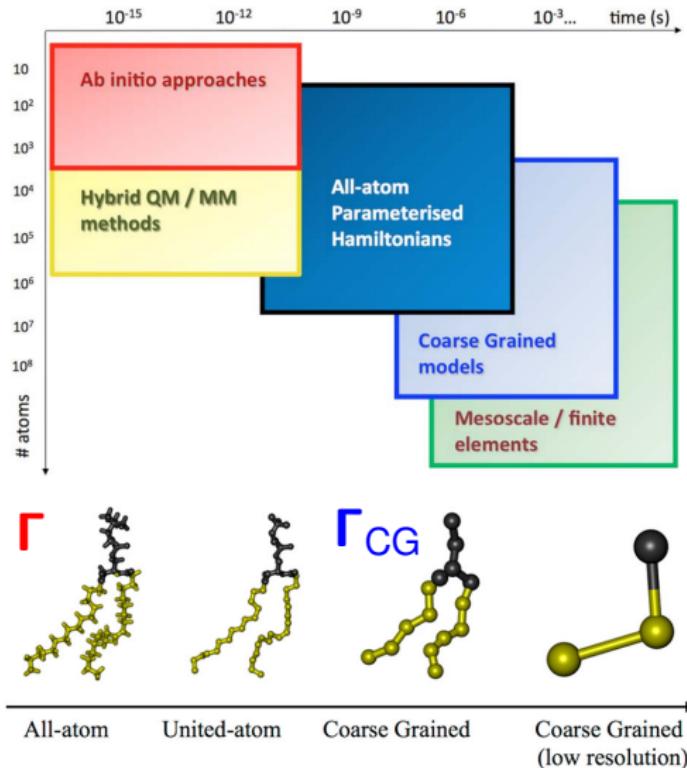
M. Cascella and S. Vanni, Chem. Modell. 12, 1–52 (2016)

T.A. Soares et al., J. Phys. Chem. Lett. 8, 3586–3594 (2017)

Coarse-grained methods



Coarse-grained methods

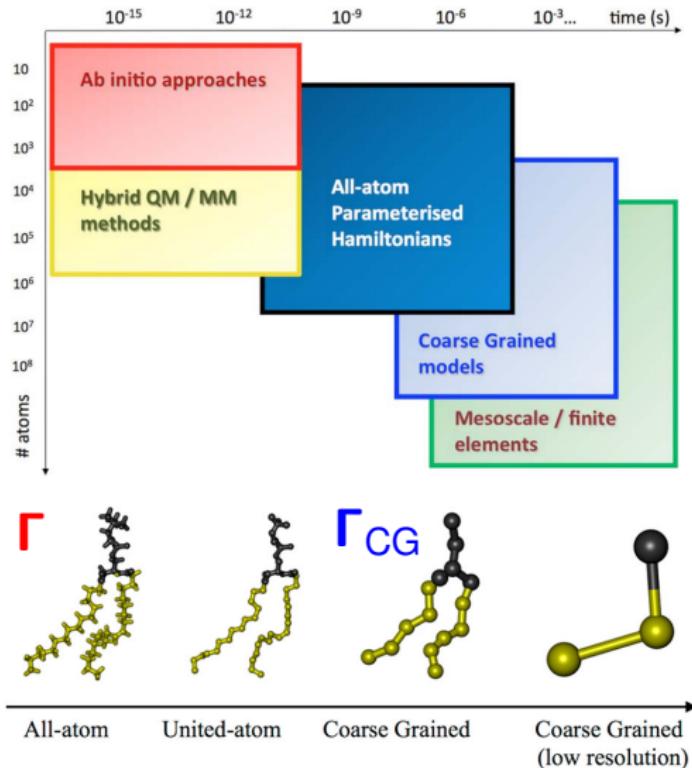


$$Z = \int d\Gamma e^{-\beta H(\Gamma)}$$

↓

$$Z \simeq \int d\Gamma_{CG} e^{-\beta H(\Gamma_{CG})}$$

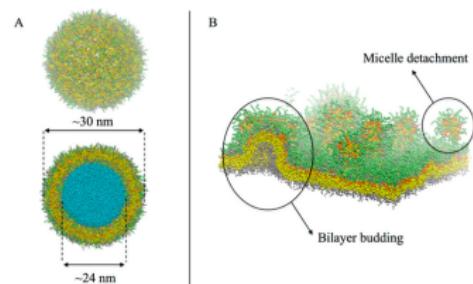
Coarse-grained methods



$$Z = \int d\Gamma e^{-\beta H(\Gamma)}$$

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$$Z \simeq \int d\Gamma_{CG} e^{-\beta H(\Gamma_{CG})}$$



Large systems and
long time scales!

The hybrid particle-field method

$$H(\{\mathbf{r}\}) = \sum_{m=1}^{N_{\text{mol}}} \underbrace{H_0(\{\mathbf{r}_m\})}_{\text{Intramolecular}} + \underbrace{W[\{\phi(\mathbf{r})\}]}_{\text{Intermolecular}}$$

($\{\mathbf{r}\} \equiv \{\mathbf{r}_1, \dots, \mathbf{r}_N\}$, *particle positions*)

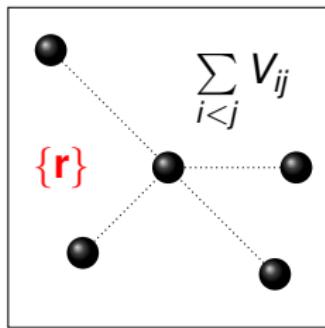
($\{\phi\} \equiv \{\phi_1, \dots, \phi_M\}$, *particle-type number densities*)

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Intermolecular interactions

Particle-particle



($\{\mathbf{r}\} \equiv \{\mathbf{r}_1, \dots, \mathbf{r}_N\}$, *particle positions*)

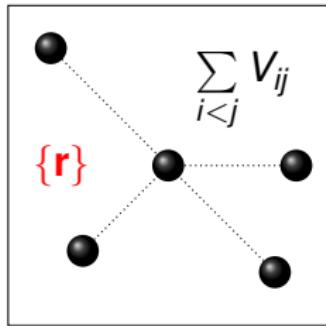
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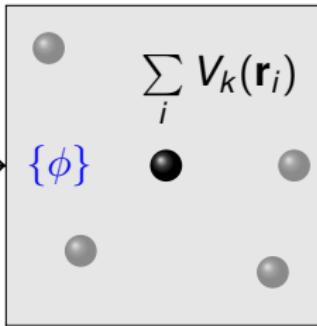
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Intermolecular interactions

Particle-particle



Particle-field



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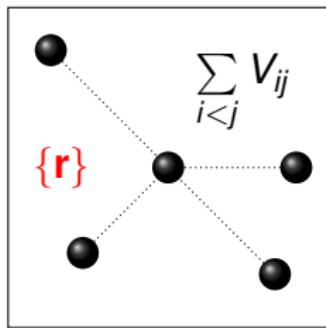
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The hybrid particle-field method

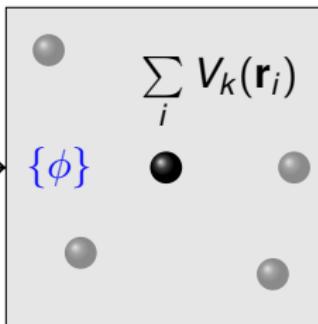
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Intermolecular interactions

Particle-particle



Particle-field



$$V_k(\mathbf{r}) = \frac{\delta W[\{\phi\}]}{\delta \phi_k(\mathbf{r})}$$

$$\mathbf{F}_i = -\nabla_i V_k(\mathbf{r}_i)$$

($\{\mathbf{r}\} \equiv \{\mathbf{r}_1, \dots, \mathbf{r}_N\}$, *particle positions*)

($\{\phi\} \equiv \{\phi_1, \dots, \phi_M\}$, *particle-type number densities*)

Interaction energy from polymer theory

$$W[\phi] = \int d\mathbf{r} \frac{1}{\rho_0} \left(\sum_{k\ell} \frac{\tilde{\chi}_{k\ell}}{2} \phi_k(\mathbf{r}) \phi_\ell(\mathbf{r}) + \frac{1}{\kappa} \left(\sum_\ell \phi_\ell(\mathbf{r}) - \rho_0 \right)^2 \right)$$

(ρ_0 : Density parameter related to the volume per bead)

Interaction energy from polymer theory

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$\tilde{\chi}_{k\ell} > 0 \rightarrow$ Likes not to mix

$\tilde{\chi}_{k\ell} \leq 0 \rightarrow$ Likes to mix

(ρ_0 : Density parameter related to the volume per bead)

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$\tilde{\chi}_{k\ell} > 0 \rightarrow$ Likes not to mix

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$\kappa \sim 0 \rightarrow$ incompressible

$\kappa \gg 0 \rightarrow$ very compressible

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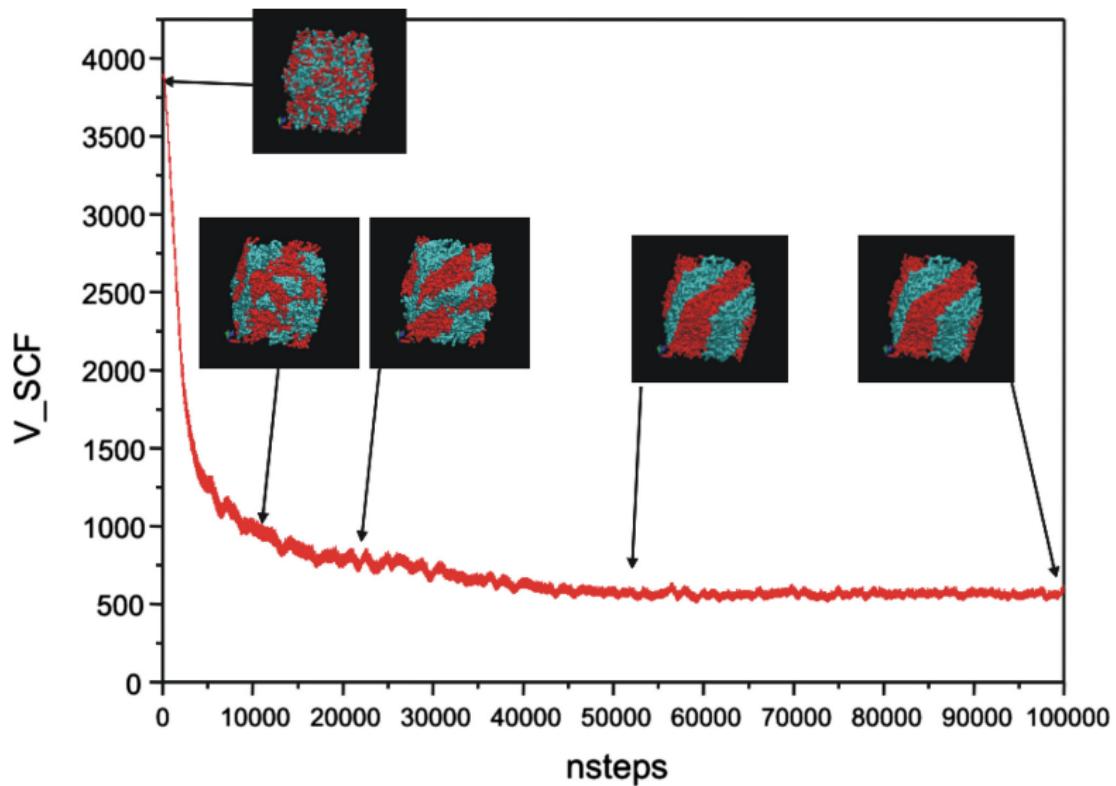
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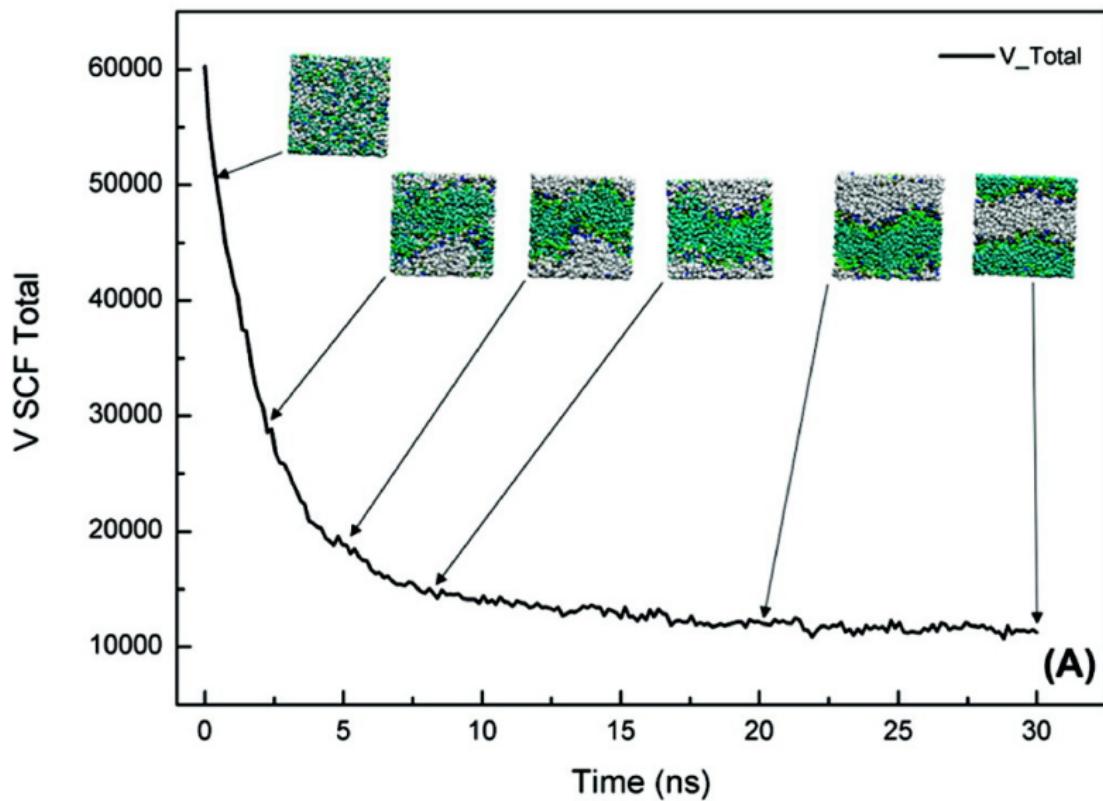
Net effect $V_k(\mathbf{r}) = \frac{1}{\rho_0} \left(\sum_\ell \tilde{\chi}_{k\ell} \phi_\ell(\mathbf{r}) + \frac{1}{\kappa} \left(\sum_\ell \phi_\ell(\mathbf{r}) - \rho_0 \right) \right)$

(ρ_0 : Density parameter related to the volume per bead)

Prototypic applications: Relaxation of polymer melts



Prototypic applications: Phospholipid aggregation



Research Goals

Overall objective:

- ▶ *Develop new hPF methods and models that can be used in the study of macromolecular biological systems*

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Extend the capability of hPF simulations to representing:

- ▶ Proteins
- ▶ Electrostatics
- ▶ Multiphase electrolytes
- ▶ Constant-pressure simulations

Papers included in the thesis

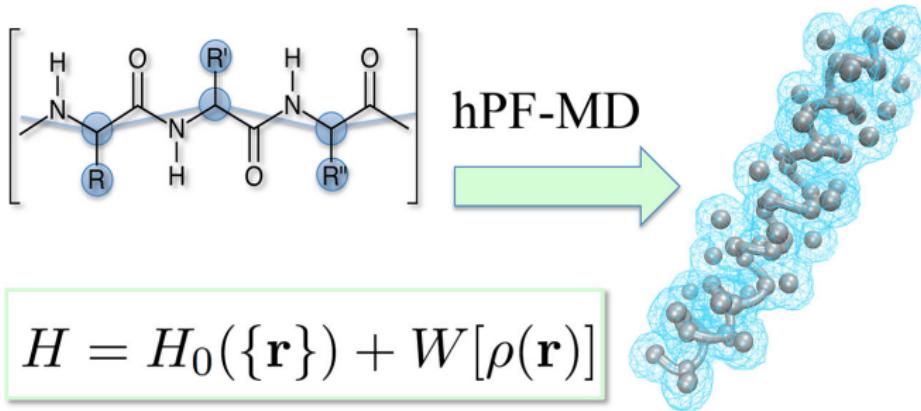
- I: *Hybrid Particle-Field Model for Conformational Dynamics of Peptide Chains* **Sigbjørn Løland Bore** et al. JCTC **14**, 1120–1130 (2018)
- II: *Hybrid Particle-Field Molecular Dynamics Simulations of Charged Amphiphiles in Aqueous Environment* Hima Bindu Kolli et al. JCTC **14**, 4928–4937 (2018)
- III: *Mesoscale Electrostatics Driving Particle Dynamics in Nonhomogeneous Dielectrics* **Sigbjørn Løland Bore** et al. JCTC **15**, 2033-2041 (2019)
- IV: *Aggregation of Lipid A Variants: a Hybrid Particle-Field Model* Antonio De Nicola et al. BBA, in press (2020)
- V: *Beyond the Molecular Packing Model: Understanding Morphological Transitions of Charged Surfactant Micelles* Ken Schäfer et al. (Submitted for peer-review)
- VI: *Hybrid Particle-Field Molecular Dynamics Under Constant Pressure* **Sigbjørn Løland Bore** et al. JCP, in press (2020)

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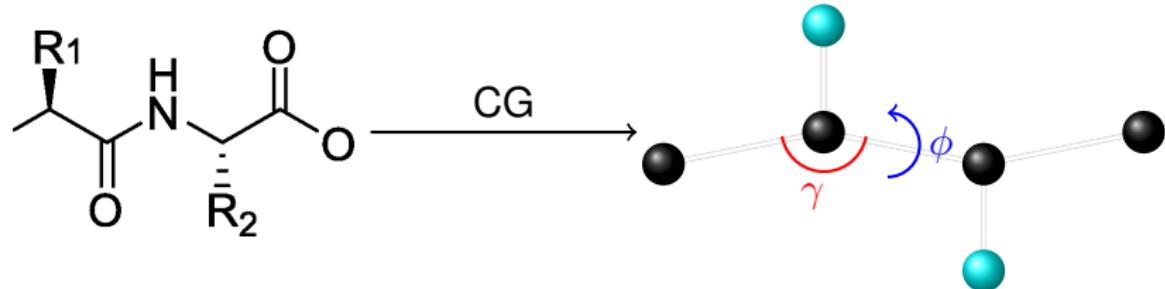
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Proteins, Electrostatics, Multiphase electrolytes, Constant-pressure

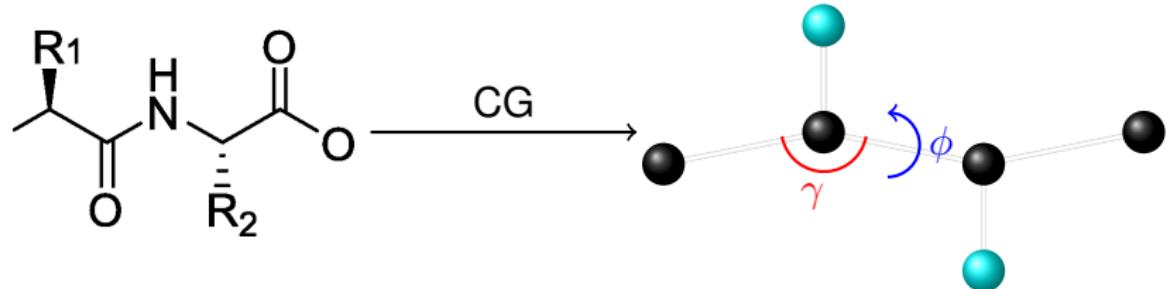
Hybrid Particle-Field Model for Proteins



Underlying model

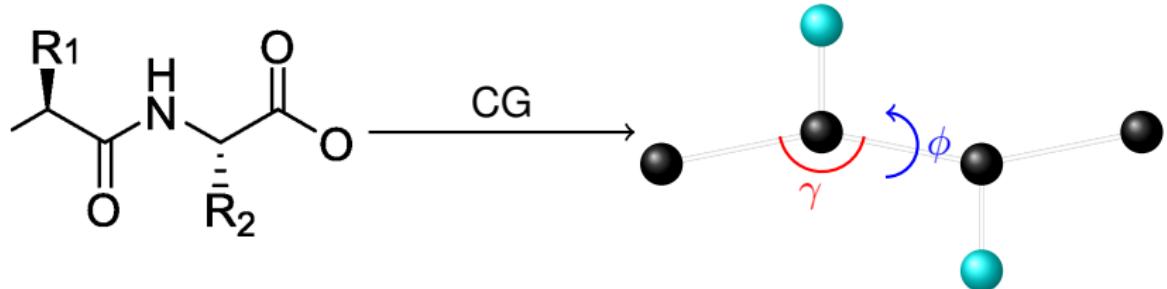


Underlying model



$$V(\gamma, \phi) = \frac{1}{2}k(\gamma - \gamma_0(\phi))^2 + V_{\text{propensity}}(\phi, \lambda)$$

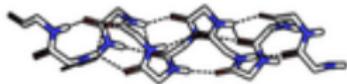
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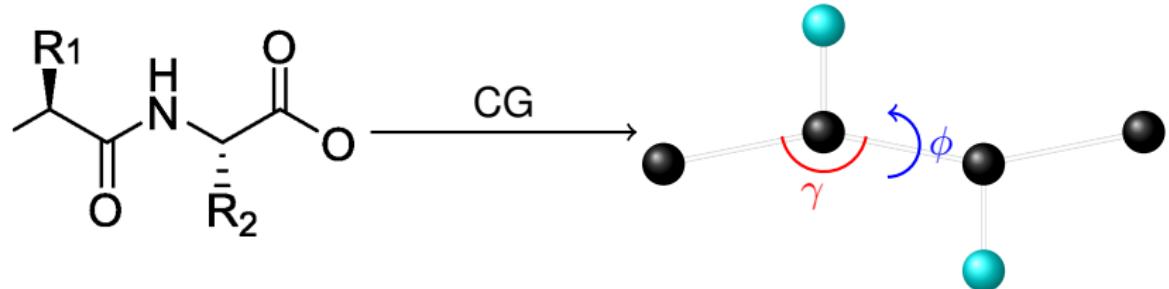
$$V(\gamma, \phi) = \frac{1}{2}k(\gamma - \gamma_0(\phi))^2 + V_{\text{propensity}}(\phi, \lambda)$$

$$\lambda = -1$$

Helical



Underlying model



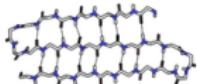
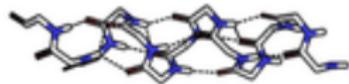
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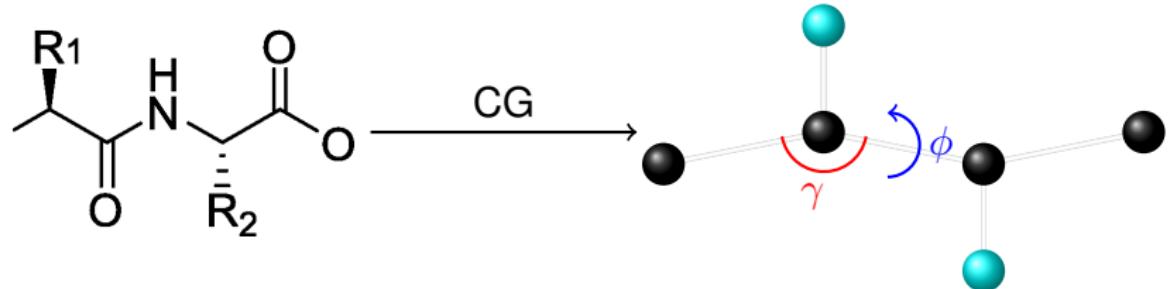
Helical

$$\lambda = 1$$

Extended



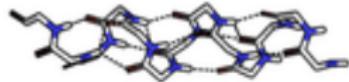
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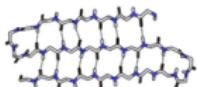
$$\lambda = -1$$

Helical



$$\lambda = 1$$

Extended



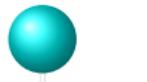
$$\lambda = 0$$

Random



Extension of model: χ_{kl} -interactions

Hydrophobic



Polar

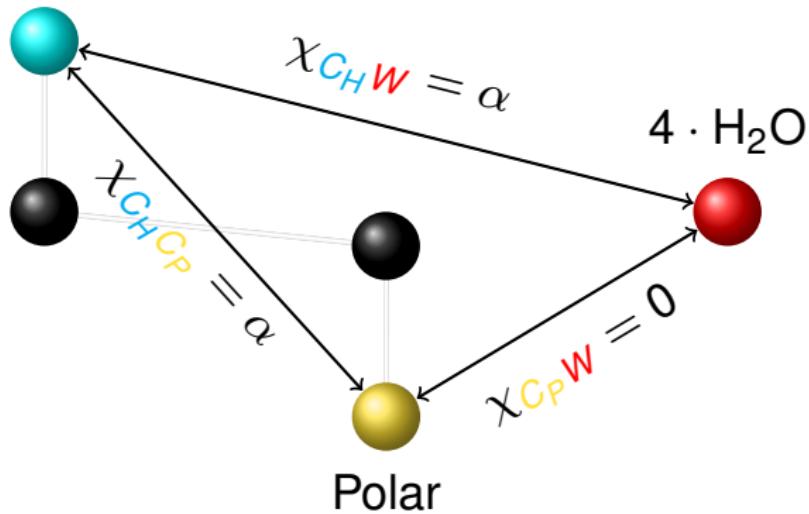
$4 \cdot \text{H}_2\text{O}$



$$V_k(\mathbf{r}) = \frac{1}{\rho_0} \left(\sum_{\ell} \tilde{\chi}_{k\ell} \phi_{\ell}(\mathbf{r}) + \frac{1}{\kappa} \left(\sum_{\ell} \phi_{\ell}(\mathbf{r}) - \rho_0 \right) \right)$$

Extension of model: χ_{kl} -interactions

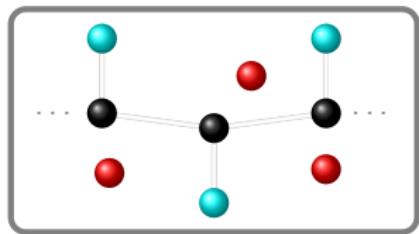
Hydrophobic



Polar

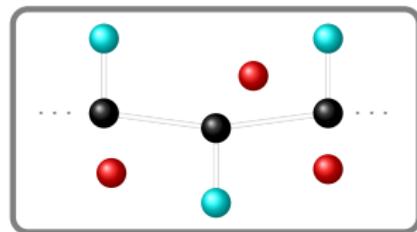
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Phase-diagram: Solvated homo-poly-peptide



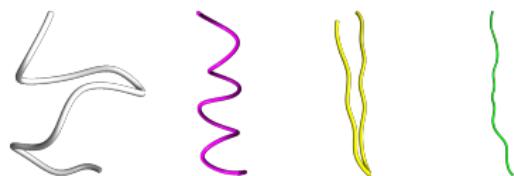
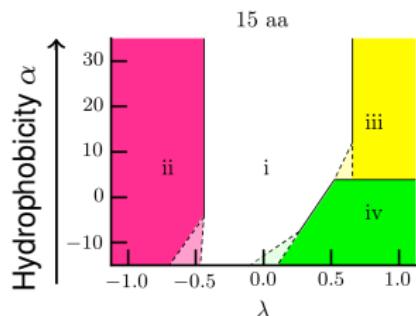
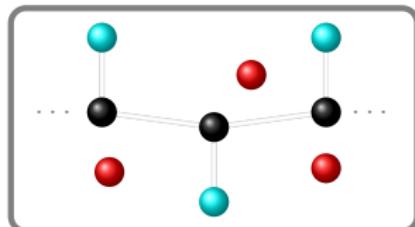
Phase-diagram: Solvated homo-poly-peptide

$\tilde{\chi}_{kl}$	CB	$4 \cdot H_2O$
CB	0	α
$4 \cdot H_2O$	α	0



Phase-diagram: Solvated homo-poly-peptide

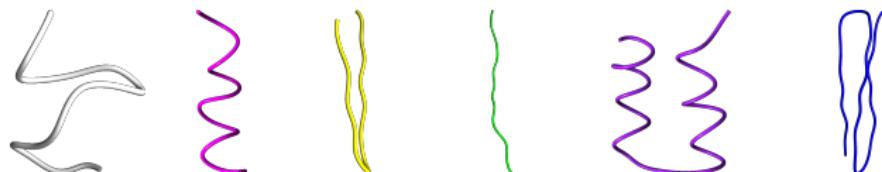
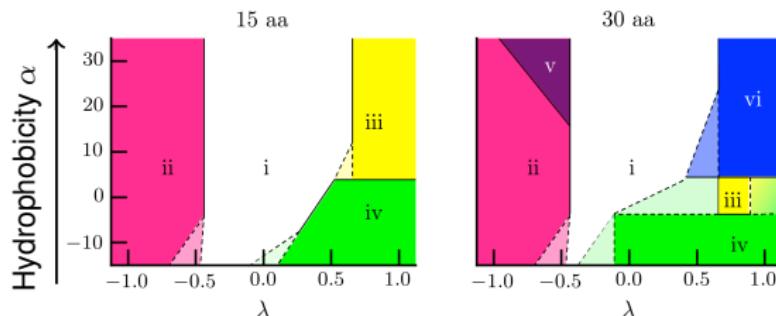
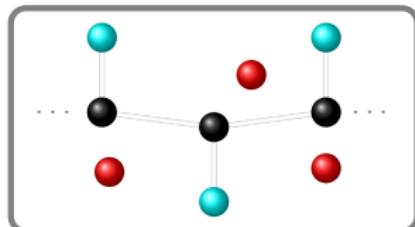
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i: Random coil ii: α -helix iii: β -hairpin iv: Extended

Phase-diagram: Solvated homo-poly-peptide

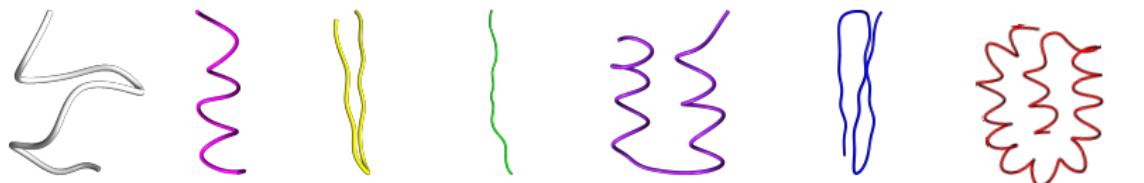
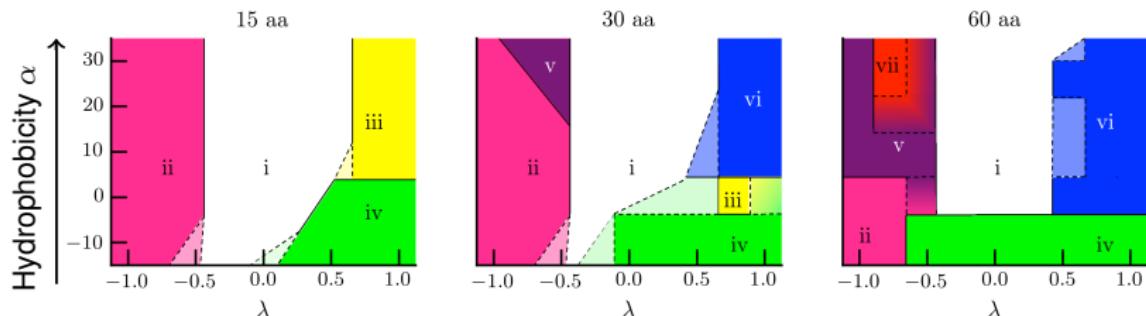
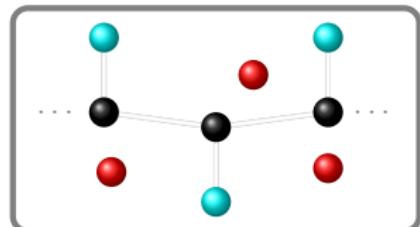
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i: Random coil ii: α -helix iii: β -hairpin iv: Extended v: Helix-coil-helix vi: β -floor/helix

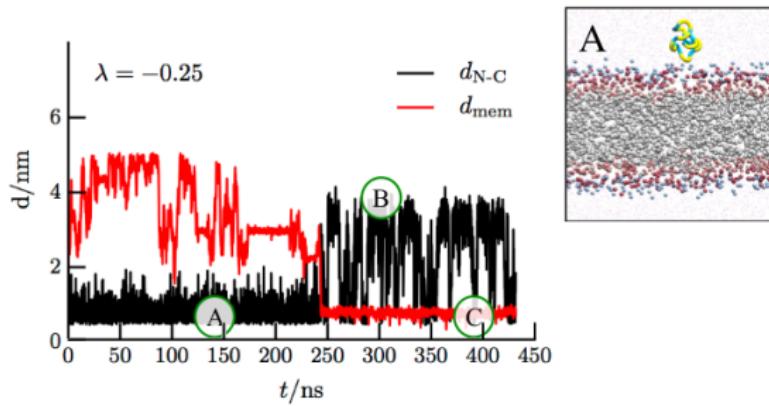
Phase-diagram: Solvated homo-poly-peptide

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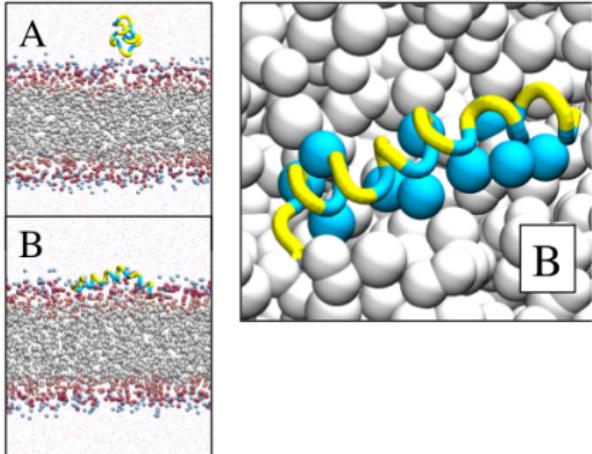
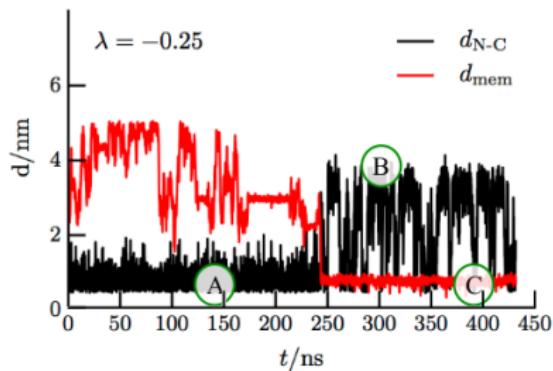


i: Random coil ii: α -helix iii: β -hairpin iv: Extended v: Helix-coil-helix vi: β -floor/helix vii: Helical bundle

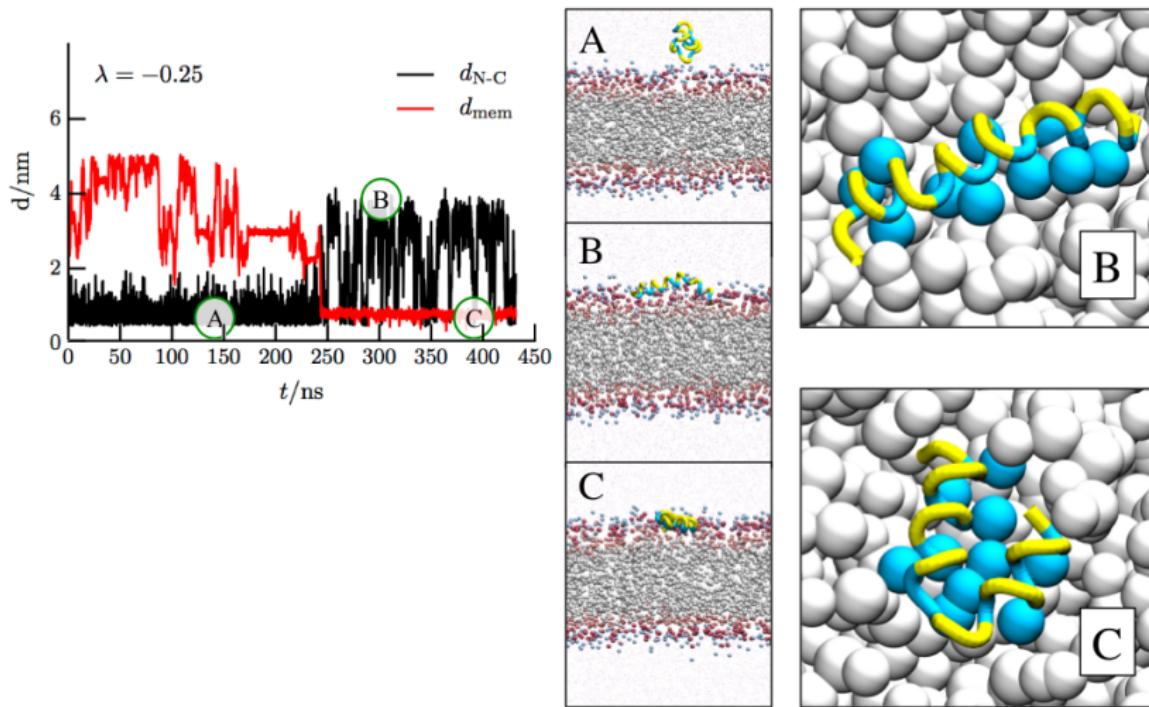
HP-polymer interacting with membrane



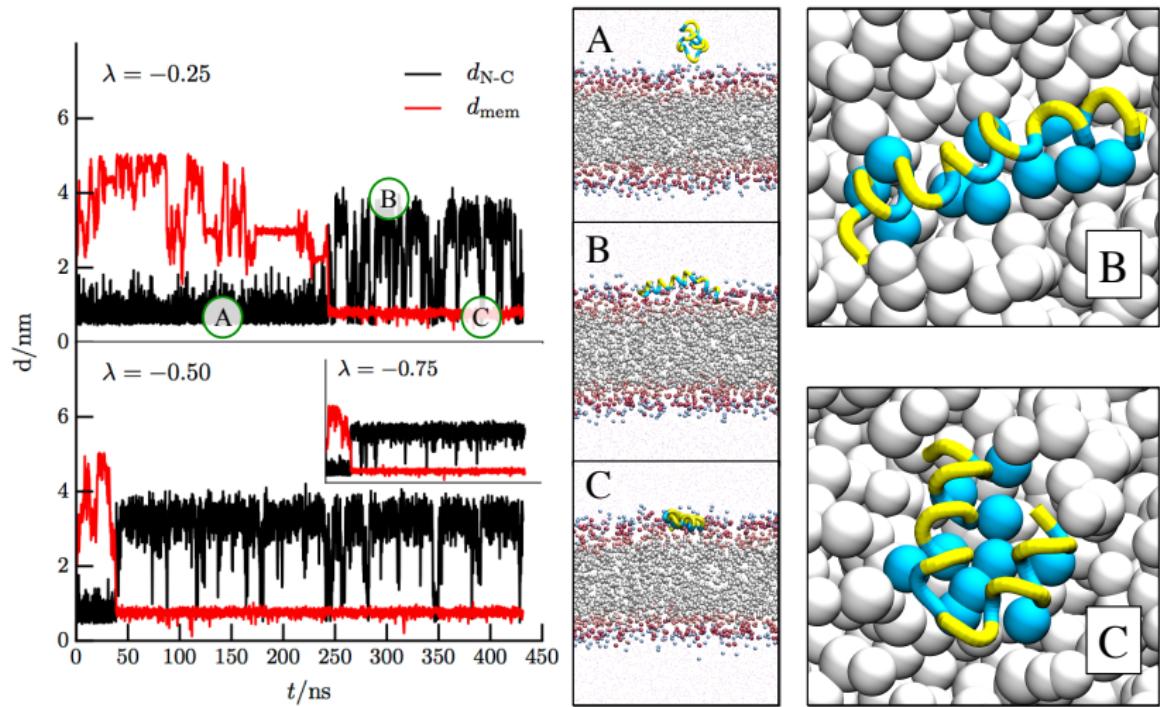
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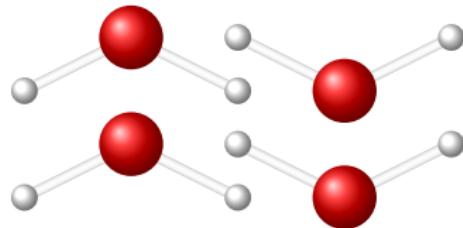


HP-polymer interacting with membrane



Electrostatics Coarse-Grained Simulations

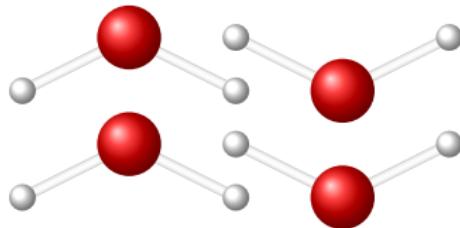
All-atom molecular dynamics:



Electrostatics Coarse-Grained Simulations

All-atom molecular dynamics:

- ▶ *Charges are resolved*
- ▶ *Screening is modeled directly*



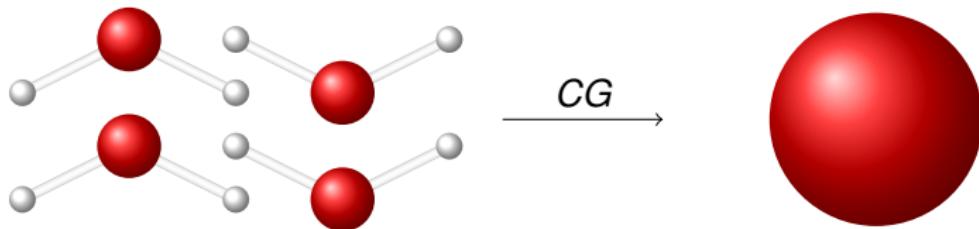
Electrostatics Coarse-Grained Simulations

All-atom molecular dynamics:

- ▶ *Charges are resolved*
- ▶ *Screening is modeled directly*

Coarse-grained molecular dynamics:

- ▶ *Charge resolution is lost*
- ▶ *Dielectric screening modeled modelled indirectly*



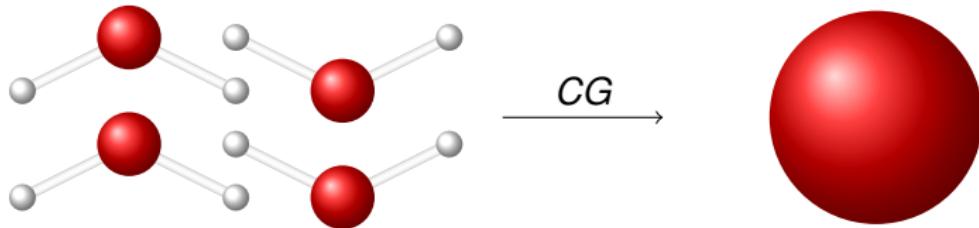
Electrostatics Coarse-Grained Simulations

All-atom molecular dynamics:

- ▶ *Charges are resolved*
- ▶ *Screening is modeled directly*

Coarse-grained molecular dynamics:

- ▶ *Charge resolution is lost*
- ▶ *Dielectric screening modeled modelled indirectly*



How do we model electrostatics?

Constant dielectrics approach

Model of paper II:

$$\epsilon \nabla^2 \psi = -\rho(\mathbf{r})$$

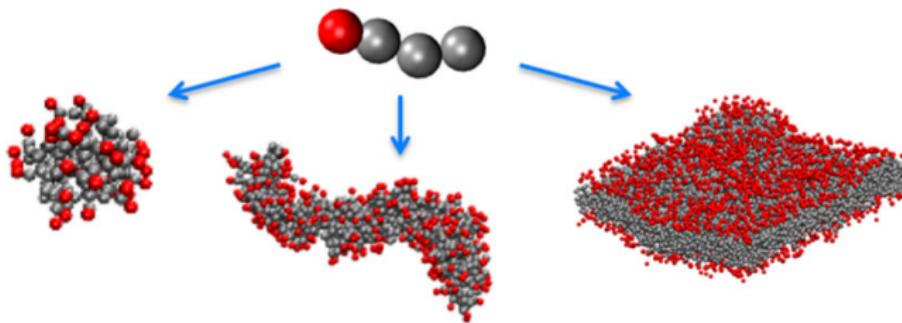
Solution for ψ :

Particle-Mesh-Ewald by FFT

External potential:

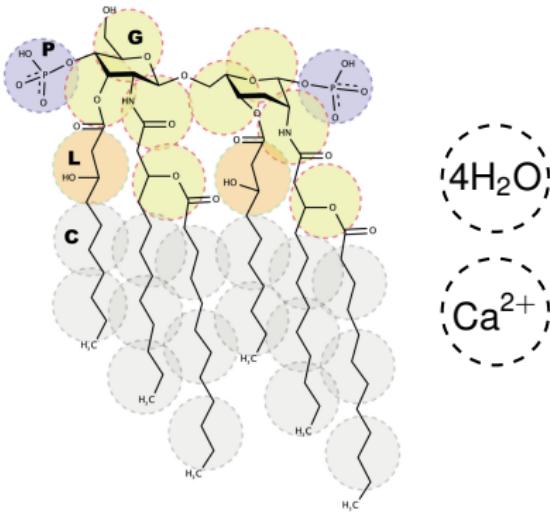
$$V_K(\mathbf{r}) = q_K(\psi_S(\mathbf{r}) + \psi_L(\mathbf{r}))$$

hPF-MD + electrostatics



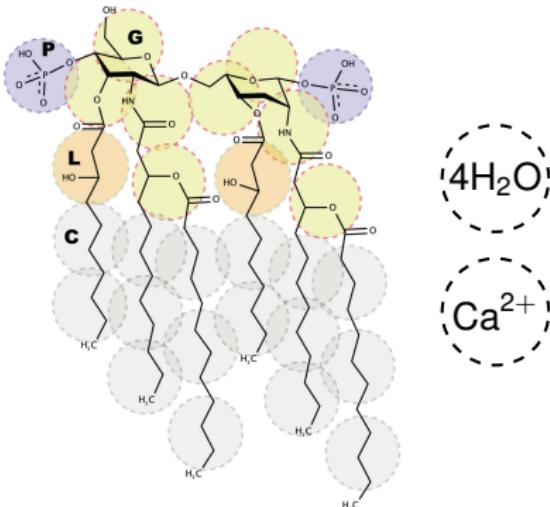
Application: Hybrid particle-field model for lipid A

CG-Representation



Application: Hybrid particle-field model for lipid A

CG-Representation



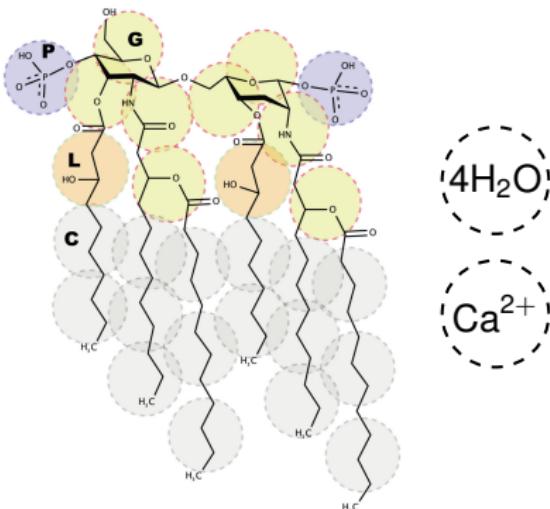
Free parameters:

$$\epsilon \nabla^2 \psi = -\rho(\mathbf{r})$$

$$V_k(\mathbf{r}) = \frac{1}{\rho_0} \sum_{\ell} \left(\tilde{\chi}_{k\ell} + \frac{1}{\kappa} \right) \phi_{\ell}(\mathbf{r})$$

Application: Hybrid particle-field model for lipid A

CG-Representation



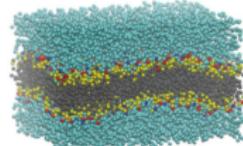
Free parameters:

$$\epsilon \nabla^2 \psi = -\rho(\mathbf{r})$$

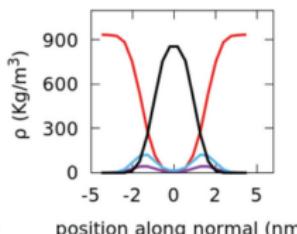
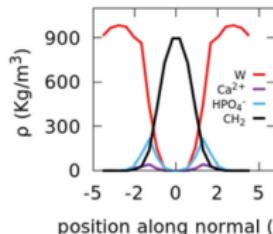
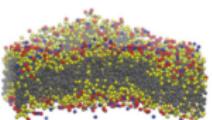
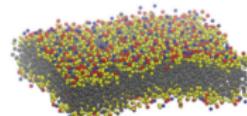
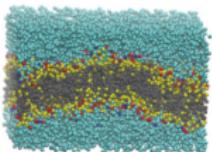
$$V_k(\mathbf{r}) = \frac{1}{\rho_0} \sum_{\ell} \left(\tilde{\chi} k e + \frac{1}{\kappa} \right) \phi_{\ell}(\mathbf{r})$$

Parameterization

all-atom



$$\epsilon_r = 15$$



Tuning of ϵ_r and χ

Lipid A aggregation

Variable dielectrics approach

Model of paper III:

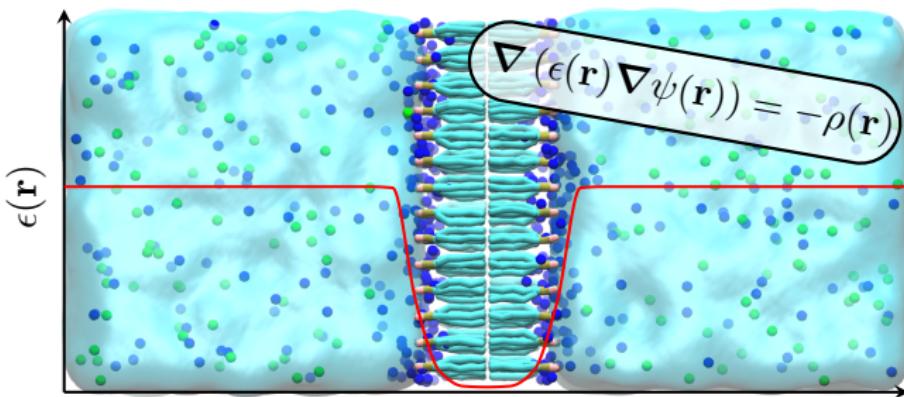
$$\nabla \cdot (\epsilon(\mathbf{r}) \nabla \psi(\mathbf{r})) = -\rho(\mathbf{r})$$

Solution for ψ :

Successive Over-Relaxation

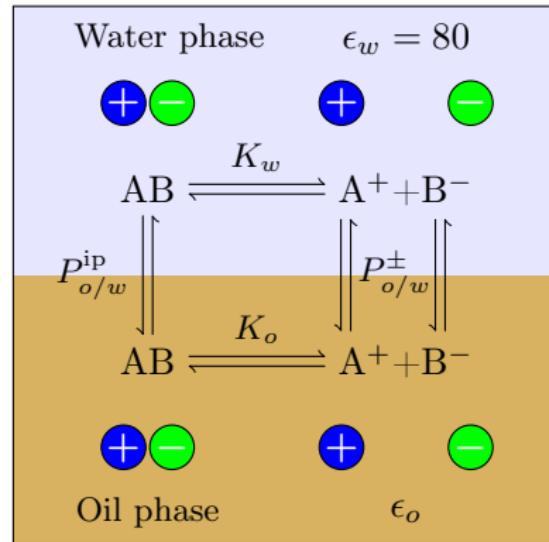
External potential:

$$V_K(\mathbf{r}) = q_K \psi(\mathbf{r}) - \frac{1}{2} \frac{\partial \epsilon(r)}{\partial \phi_k} |\nabla \psi(\mathbf{r})|^2$$



Application in paper III: Partitioning of ions (1)

Ions in a phase separated oil/water mixture of ϵ_o and ϵ_w . ($RT \times \chi_{ow} = 30 \text{ kJ mol}^{-1}$)



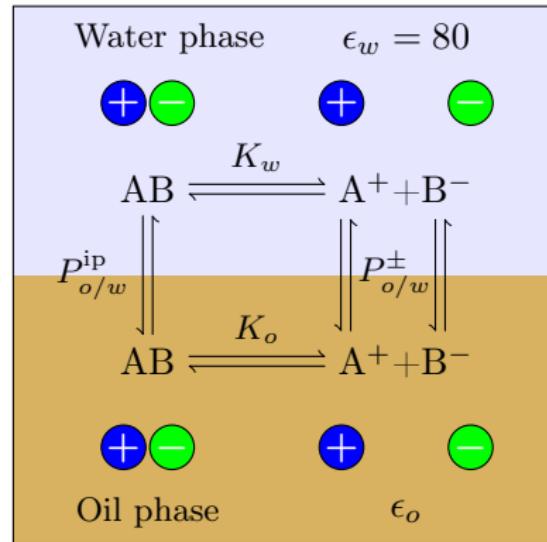
Application in paper III: Partitioning of ions (1)

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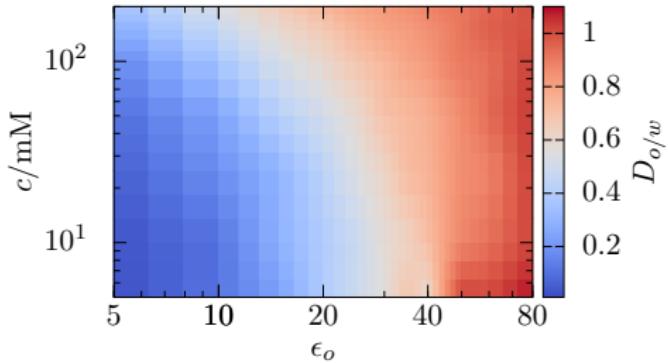
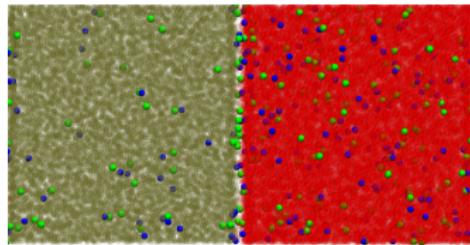
Distribution coefficient:

$$D_{o/w} = \frac{c_o}{c_w}$$

(c_o and c_w : concentration of ions within each phase)



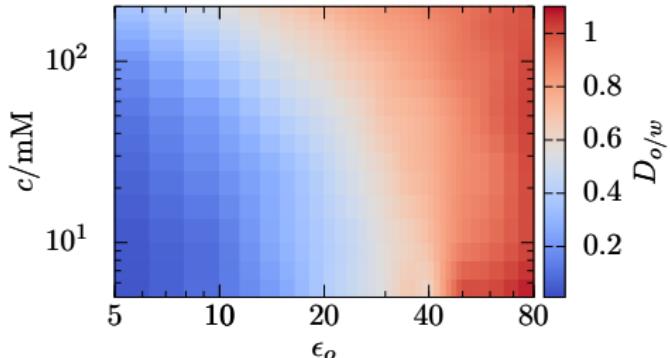
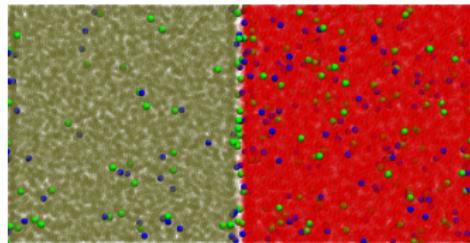
Application in paper III: Partitioning of ions (1))



$$D_{o/w} = f(c, P_{o,w}^\pm, P_{o,w}^{\text{ip}}, K_w)$$

c: concentration of ions.

Application in paper III: Partitioning of ions (1))

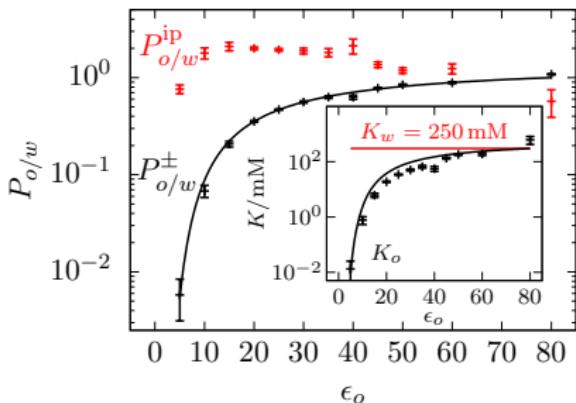


$$D_{o/w} = f(c, P_{o,w}^\pm, P_{o,w}^{\text{ip}}, K_w)$$

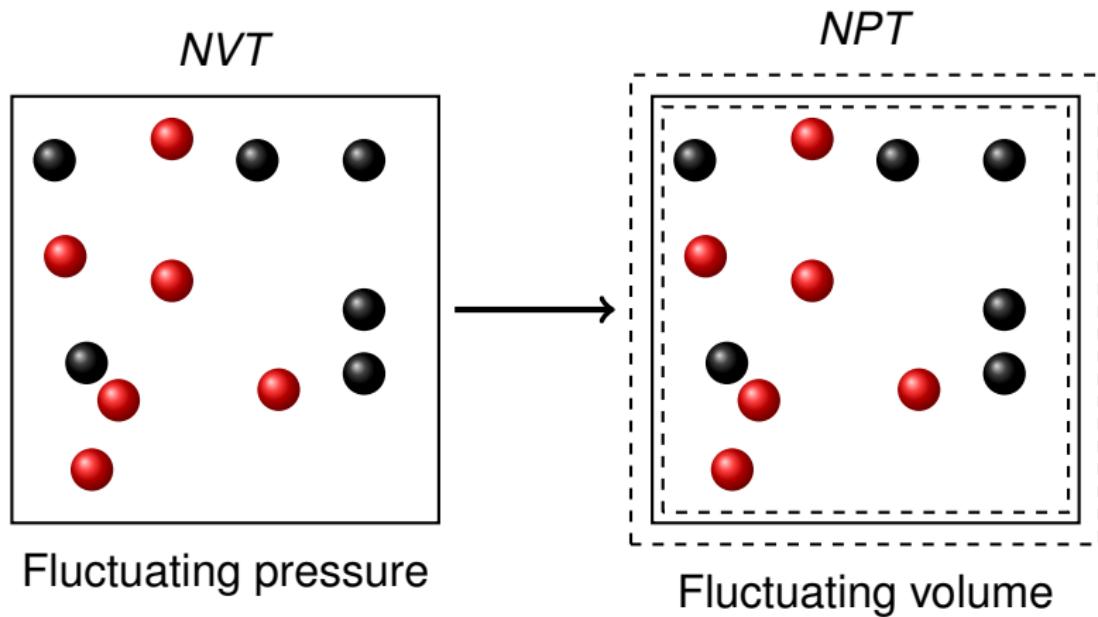
c : concentration of ions.

Born theory of ions:

$$\log P_{o/w}^\pm = \gamma \left(\frac{1}{\epsilon_w} - \frac{1}{\epsilon_o} \right)$$



Constant-Pressure Simulations



Pressure for particle-field

Hybrid particle field interaction-energy:

$$W_0[\phi] = \int d\mathbf{r} \frac{1}{\rho_0} \left(\sum_{k\ell} \frac{\tilde{\chi}_{k\ell}}{2} \phi_k(\mathbf{r}) \phi_\ell(\mathbf{r}) + \frac{1}{\kappa} \left(\sum_\ell \phi_\ell(\mathbf{r}) - a \right)^2 \right)$$

(a : equation of state parameter.)

Pressure for particle-field

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We use $P_\mu = -\frac{1}{V} \left\langle L_\mu \frac{\partial W}{\partial L_\mu} \right\rangle_{T,N}$:

(a : equation of state parameter.)

Pressure for particle-field

Hybrid particle field interaction-energy:

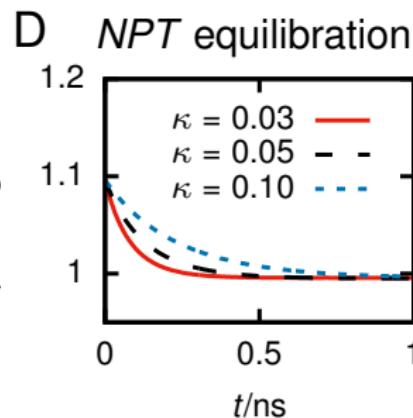
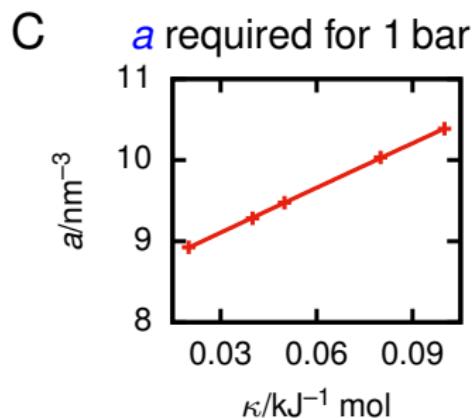
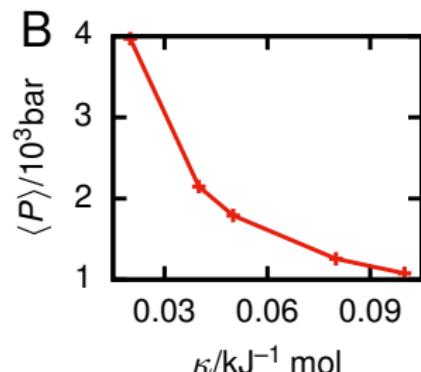
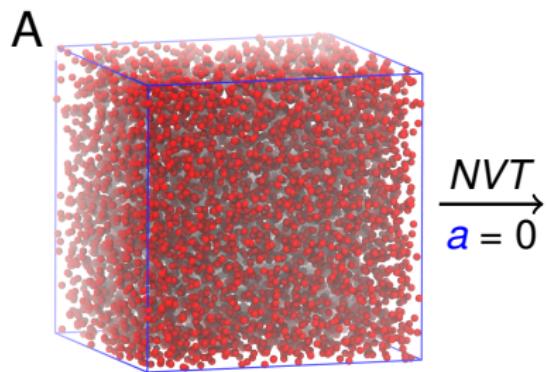
$$W_0[\phi] = \int d\mathbf{r} \frac{1}{\rho_0} \left(\sum_{k\ell} \frac{\tilde{\chi}_{k\ell}}{2} \phi_k(\mathbf{r}) \phi_\ell(\mathbf{r}) + \frac{1}{\kappa} \left(\sum_\ell \phi_\ell(\mathbf{r}) - a \right)^2 \right)$$

We use $P_\mu = -\frac{1}{V} \left\langle L_\mu \frac{\partial W}{\partial L_\mu} \right\rangle_{T,N}$:

$$P_{0,\mu} = \frac{1}{V} \int d\mathbf{r} \frac{1}{\rho_0} \left(\sum_{k\ell} \frac{\tilde{\chi}_{k\ell}}{2} \phi_k(\mathbf{r}) \phi_\ell(\mathbf{r}) + \frac{1}{2\kappa} \left(\phi(\mathbf{r})^2 - a^2 \right) \right),$$

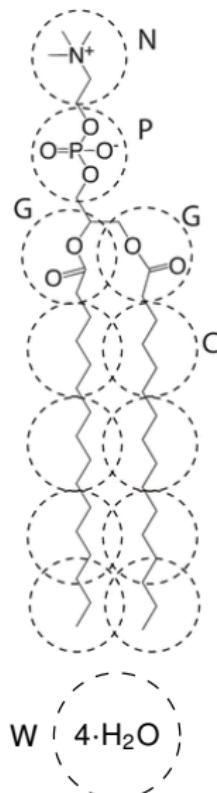
(a : equation of state parameter.)

Parameterization of water model



Model for DPPC lipids

CG mapping



Intramolecular Hamiltonian

$$H_0 = \sum \frac{m_i \dot{r}_i^2}{2} + \sum \frac{k_r(r_{ij} - r_0)^2}{2} + \sum \frac{k_\theta(\cos(\theta_{ijk}) - \cos(\theta_0))^2}{2}$$

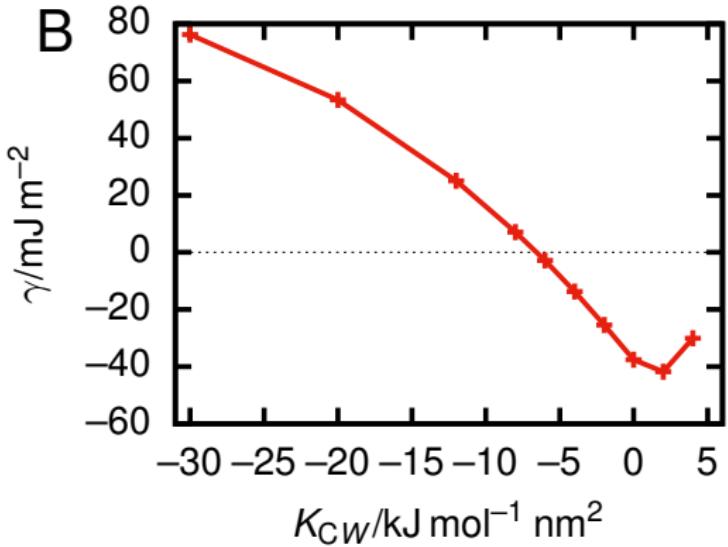
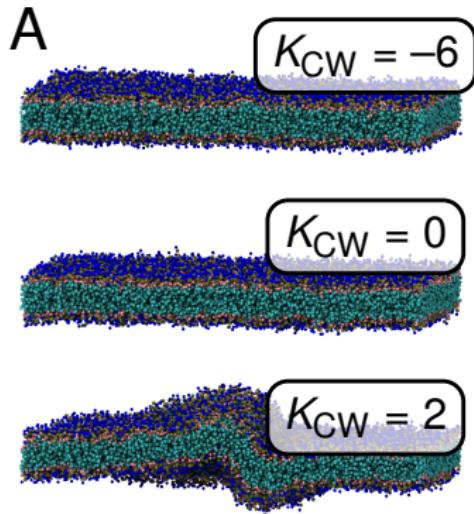
W_0 -interactions

G	P	C	W	
-1.50	6.30	9.00	-8.10	N
	4.50	13.50	-3.60	P
$\tilde{\chi}_{ke}$ /kJ mol ⁻¹		6.30	4.50	G
			33.75	C

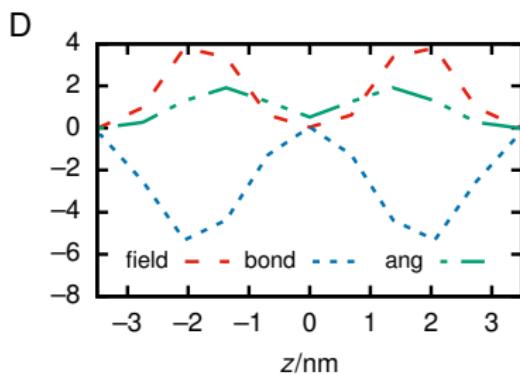
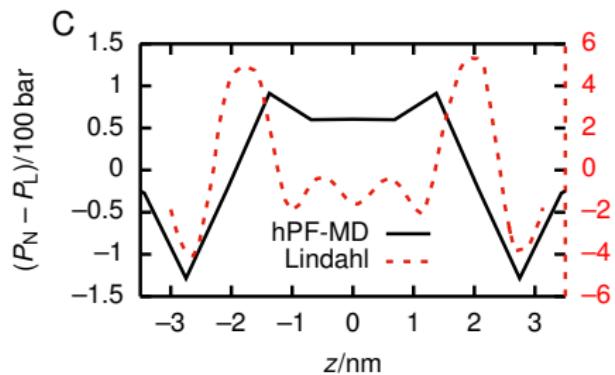
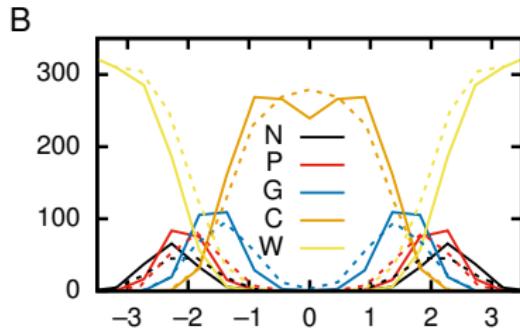
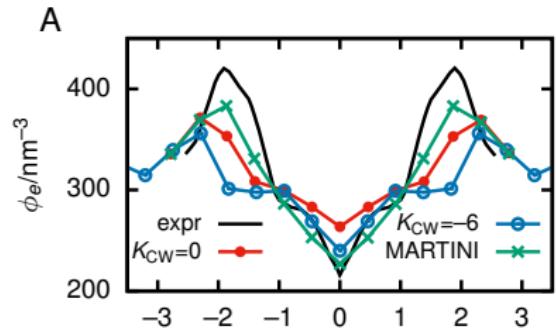
Modeling of surface tension

$$W_1 \simeq \frac{1}{\rho_0} \int d\mathbf{r} K_{CW} \nabla \phi_W(\mathbf{r}) \cdot \nabla \phi_C(\mathbf{r})$$

Lipid bilayer simulation: NVT parametrization



Lipid bilayer simulation: *NPT* simulations



Conclusions and outlook

New methodology for:

- ▶ Electrostatics
- ▶ Constant-pressure simulations

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- ▶ Parameterization of models
- ▶ OpenMP parallelization

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 - ▶ OpenMP parallelization
- ⇒ Realistic representation of large biological systems

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Michele Cascella

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Morten Ledum

Simen Kvaal

Victoria Ariel Bjørnestad

Reidar Lund



OCCAM
Molecular Dynamics

The logo for Hylleraas consists of two overlapping circles, one light blue and one light blue, followed by the word "Hylleraas" in a bold, black, sans-serif font.

Yamagata University, Japan:

Giuseppe Milano

Antonio De Nicola

Tsudo Yamanaka

Sendai University, Japan:

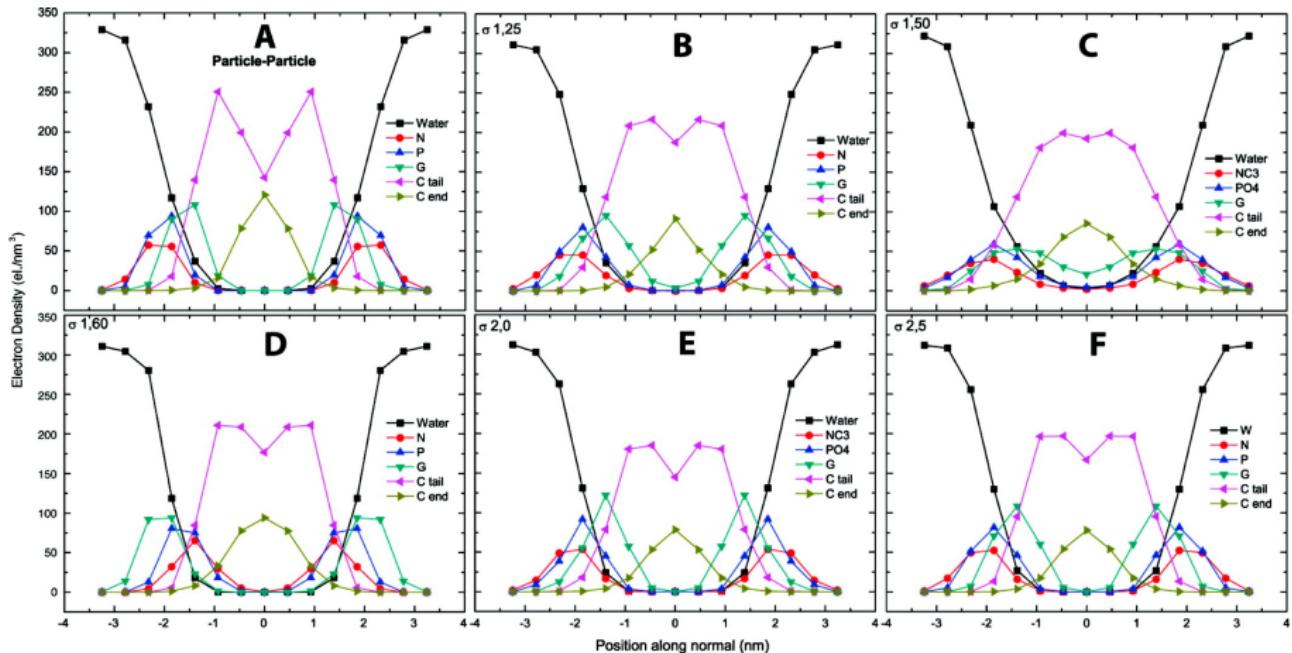
Toshihiro Kawakatsu

The logo for notur features a circular pattern of vertical lines forming a grid-like structure, with the word "notur" in a large, bold, dark blue sans-serif font to its right.



UiO :

Effect of grid size: DPPC electron density profiles



$(\sigma = 0.47 \text{ nm}, \text{Van der Waals radius of particle-particle model})$

Grid size problems and solutions

Problems:

1. Grid sets the range of interactions
2. Forces do not converge when refining the grid

Possible solutions:

1. Define models for specific grid sizes
 - ▶ Adjust grid during constant-pressure simulations
2. Introduce a particle size¹

Additional issues:

- ▶ Smoothness of forces

Coarse-graining and dynamics

The effects of coarse-graining on dynamics:

- ▶ Filtering out of high frequency modes
- ▶ Loss of friction
- ▶ Increased diffusivity

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Can be positive \implies Faster simulations

Coarse-graining and dynamics

The effects of coarse-graining on dynamics:

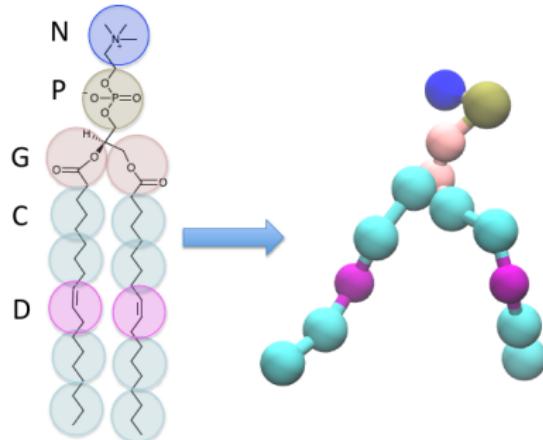
- ▶ Filtering out of high frequency modes
- ▶ Loss of friction
- ▶ Increased diffusivity

Can be positive \implies Faster simulations

Can be negative, but there are remedies:

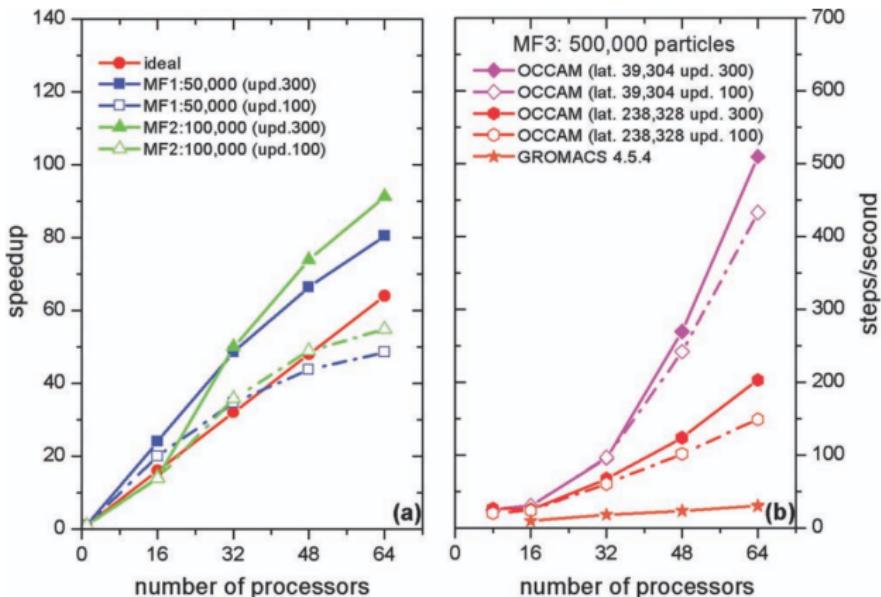
- ▶ Introduce stochastic terms
- ▶ Slip-spring models

Extra slide: Lipids with protein

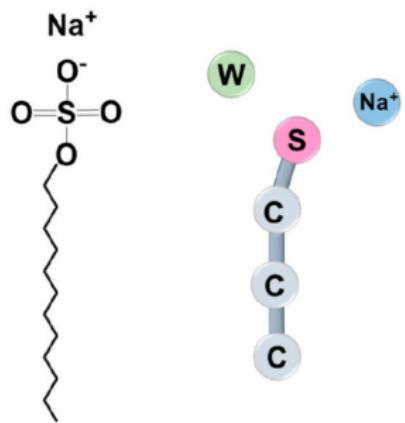


$\tilde{\chi}$	N	P	G	C	D	W	CA	CB _P	CB _H
N	0.00	-1.50	6.30	9.00	7.20	-8.10	0.00	-8.10	9.00
P	-1.50	0.00	4.50	13.50	11.70	-3.60	0.00	-3.60	13.50
G	6.30	4.50	0.00	6.30	6.30	4.50	0.00	4.50	6.30
C	9.00	13.50	6.30	0.00	0.00	33.75	0.00	33.25	0.00
D	7.20	11.70	6.30	0.00	0.00	23.25	0.00	23.25	0.00
W	-8.10	-3.60	4.50	33.75	23.25	0.00	0.00	0.00	33.75
CA	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
CB _P	-8.10	-3.60	4.50	33.75	23.25	0.00	0.00	0.00	33.75
CB _H	9.00	13.50	6.30	0.00	0.00	33.75	0.00	33.25	0.00

Extra slide: Gromacs vs. OCCAM



Extra slide: Sodium dodecyl sulfate (SDS)



Interaction matrix $\tilde{\chi}_{ij} = \chi_{ij} \cdot RT$ (kJ mol⁻¹) for SDS/water system

$\tilde{\chi}_{ij}$	S	C	Na^+	W
S	0.00	13.50	0.00	-3.60
C	13.50	0.00	13.50	33.75
Na^+	0.00	13.50	0.00	0.00
W	-3.60	33.75	0.00	0.00