

Advances in the Hybrid Particle-Field Approach Towards Biological Systems

Sigbjørn Løland Bore

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PhD lecture, Oslo, 23 April 2020

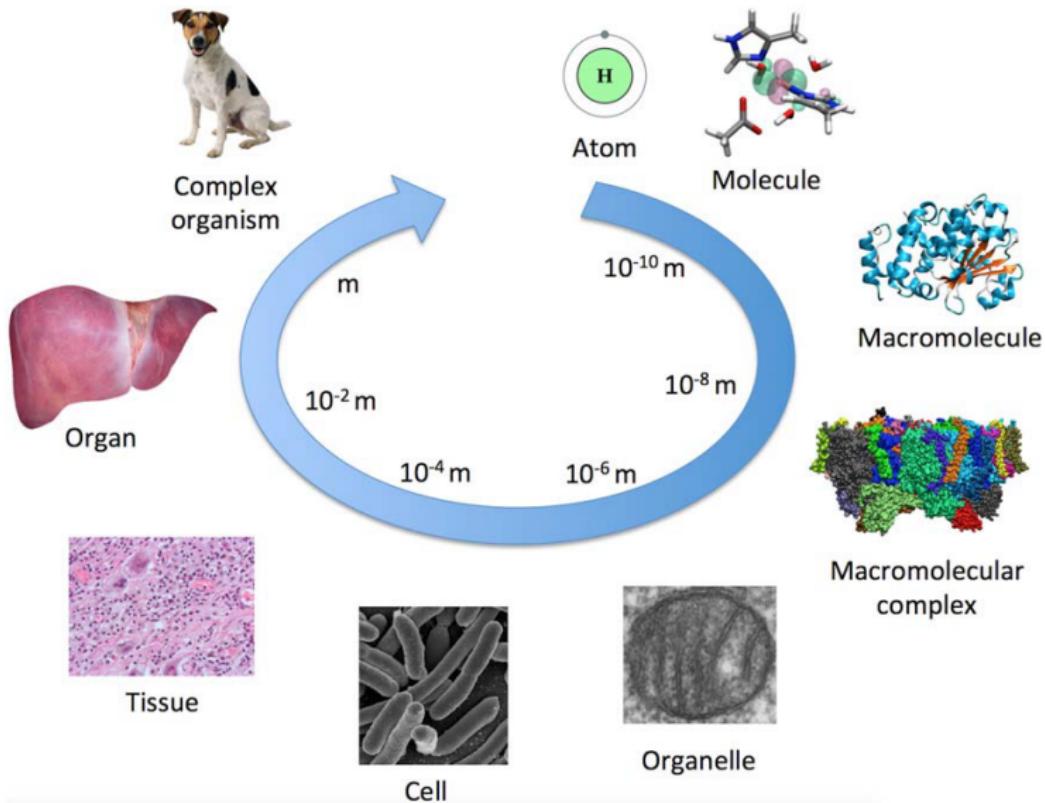


UiO • **University of Oslo**

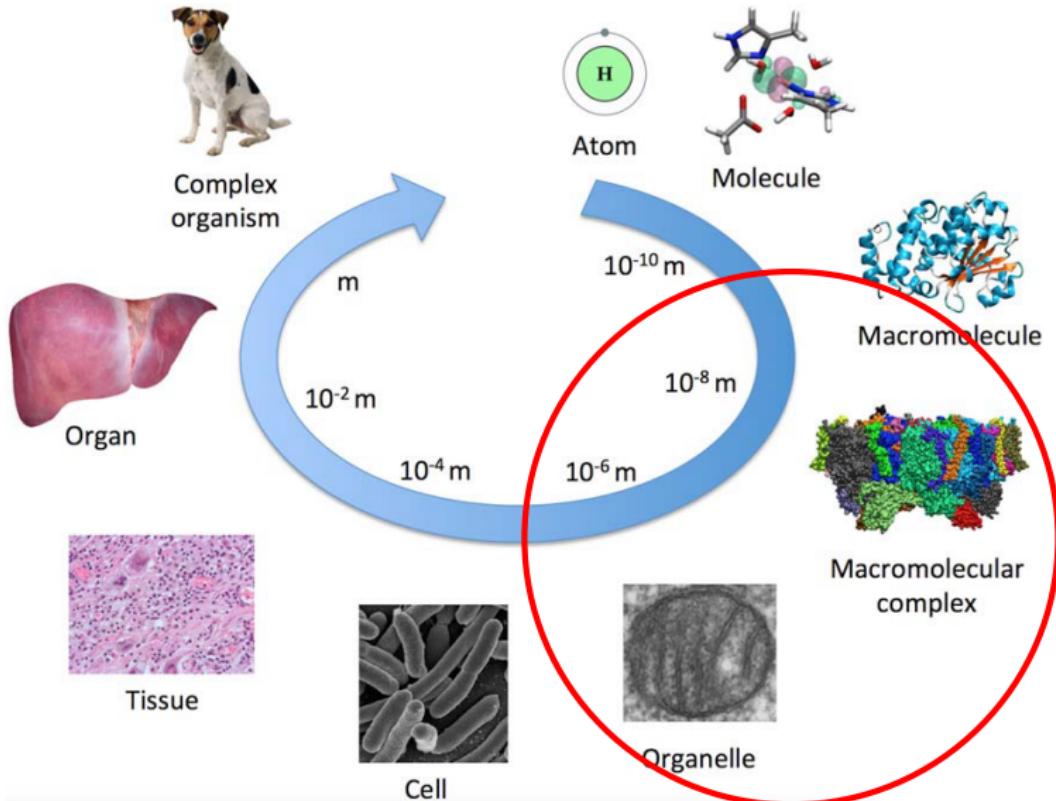


Hylleraas

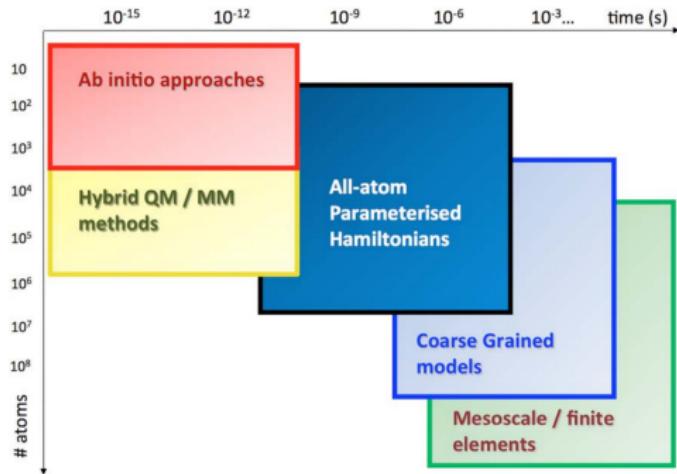
Scope of the work



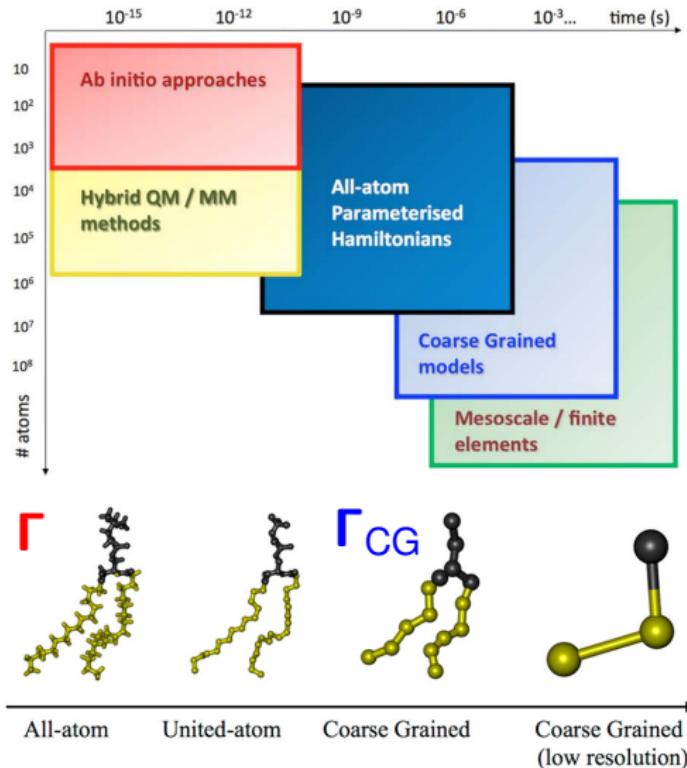
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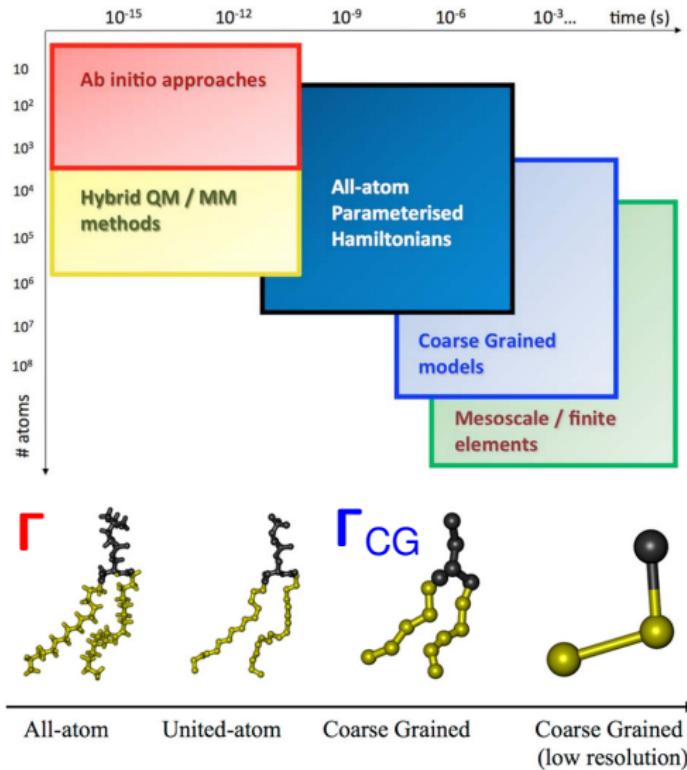
Coarse-grained methods



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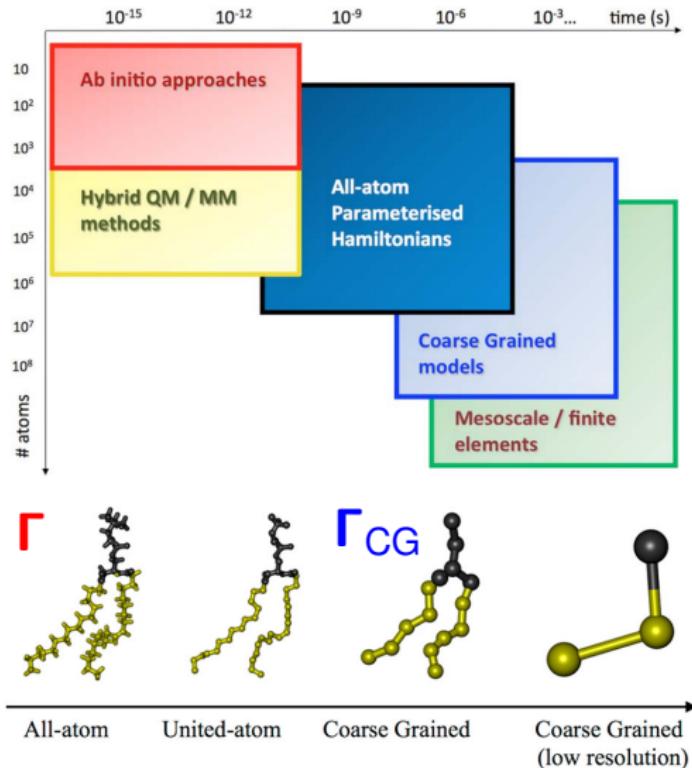


$$Z = \int d\Gamma e^{-\beta H(\Gamma)}$$

↓

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

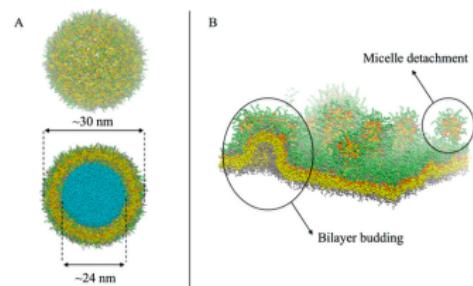
Coarse-grained methods



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

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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*)

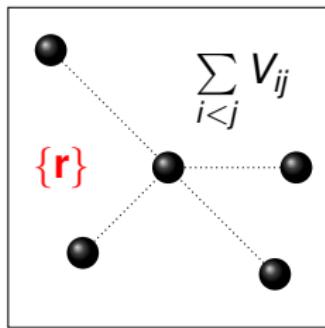
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Intermolecular interactions

Particle-particle



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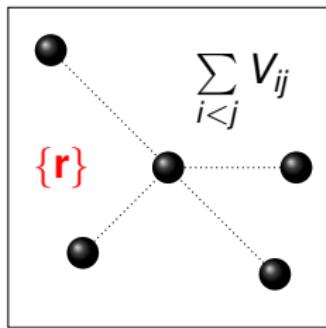
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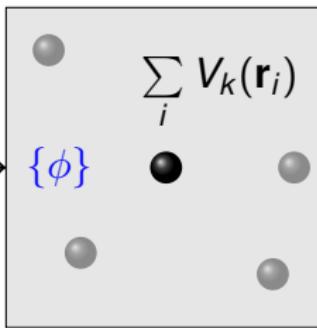
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Intermolecular interactions

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Particle-field



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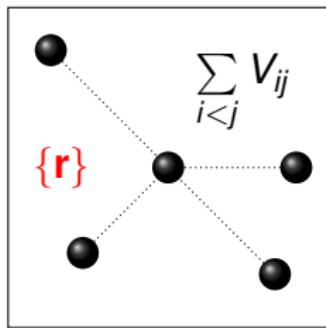
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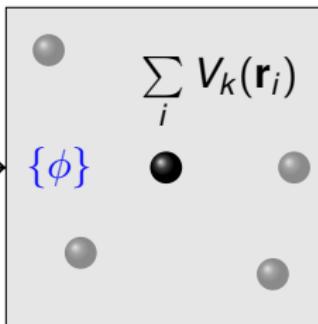
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Intermolecular interactions

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)

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

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

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$\kappa \sim 0 \rightarrow$ incompressible

$\kappa \gg 0 \rightarrow$ very compressible

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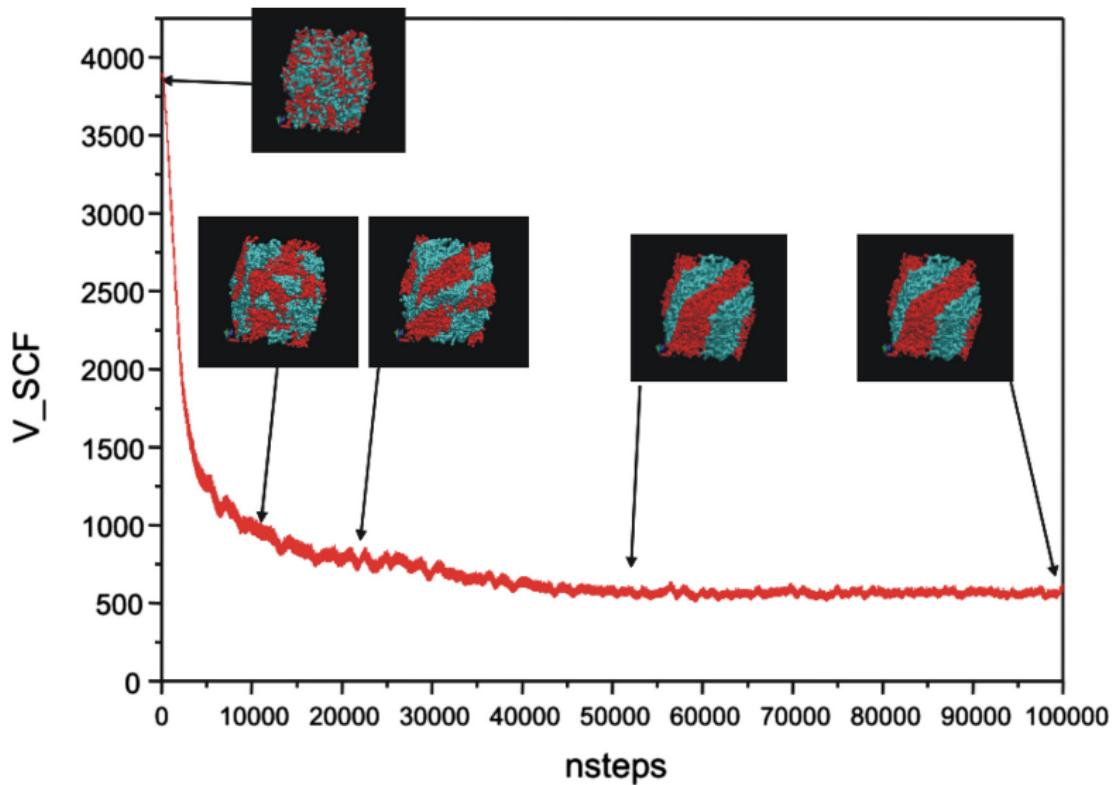
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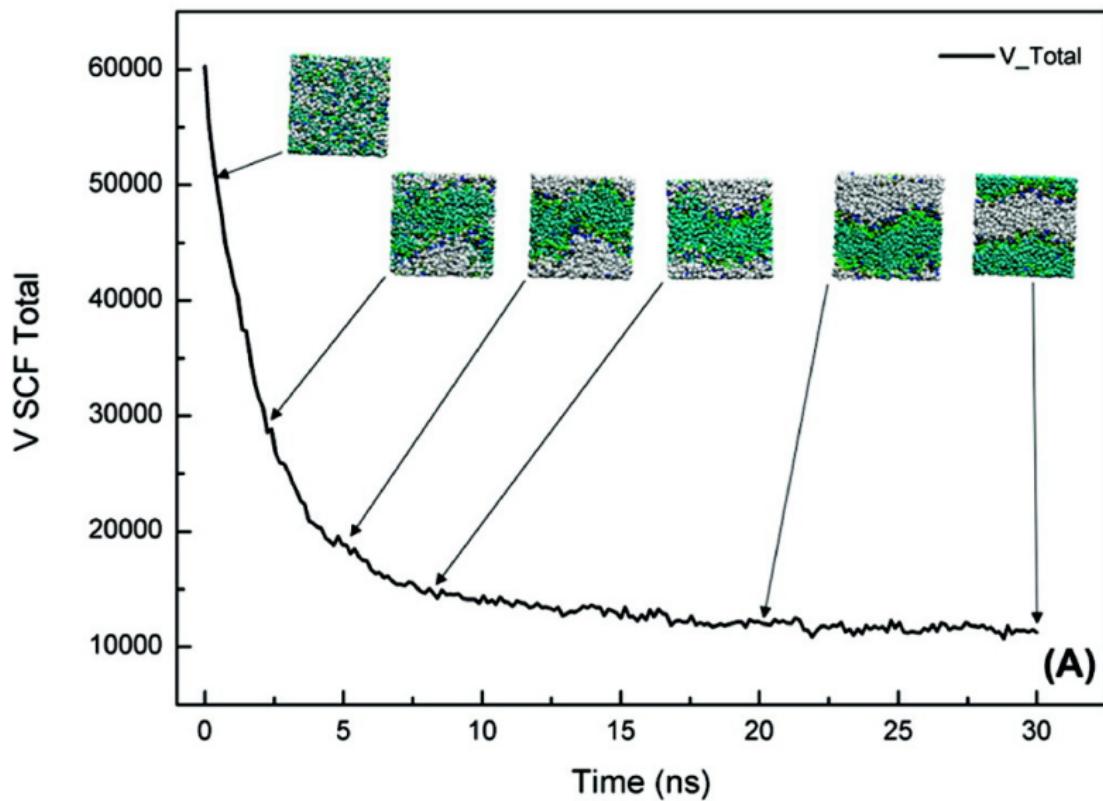
Net effect $\Rightarrow V_k(\mathbf{r}) = \frac{1}{\rho_0} \left(\sum_\ell \tilde{\chi}_{k\ell} \phi_\ell(\mathbf{r}) + \frac{1}{\kappa} \left(\sum_\ell \phi_\ell(\mathbf{r}) - \rho_0 \right) \right)$

(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

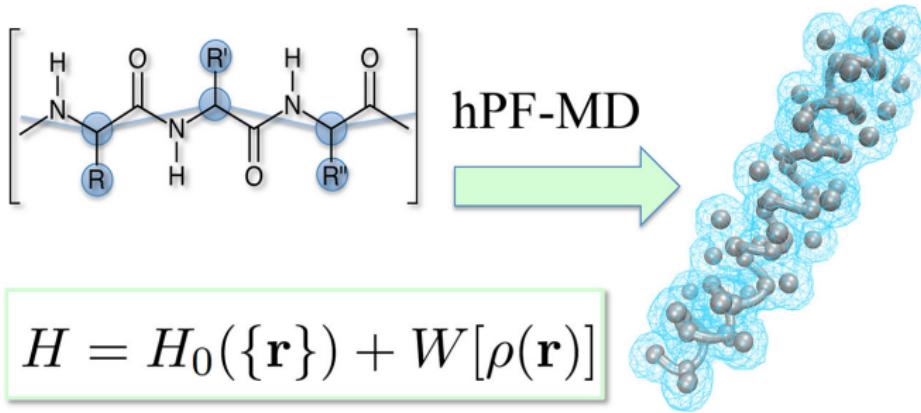
- I: *Hybrid Particle-Field Model for Conformational Dynamics of Peptide Chains* **Sigbjørn Løland Bore** et al. JCTC **14**, 1120–1130 (2018)
- II: *Hybrid Particle-Field Molecular Dynamics Simulations of Charged Amphiphiles in Aqueous Environment* Hima Bindu Kolli et al. JCTC **14**, 4928–4937 (2018)
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- 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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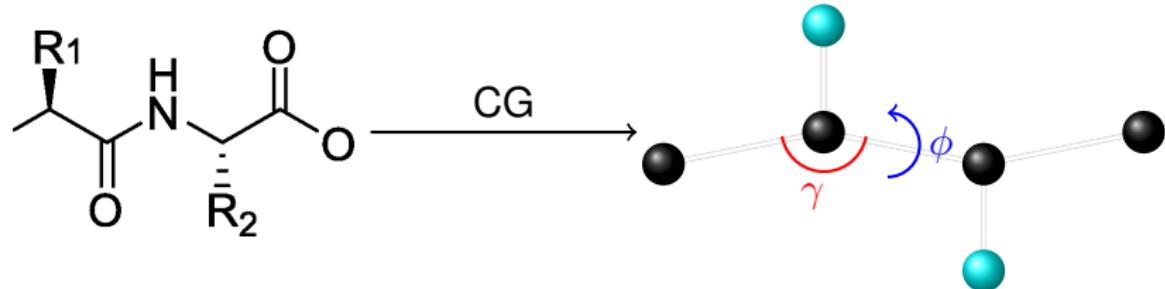
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Proteins, Electrostatics, Multiphase electrolytes, Constant-pressure

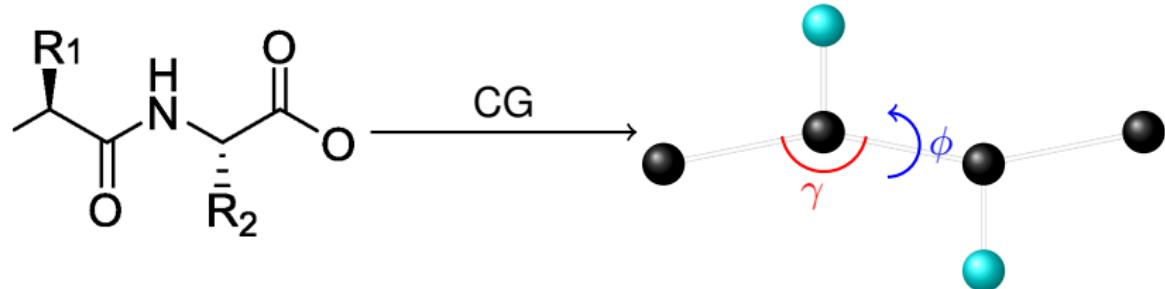
Hybrid Particle-Field Model for Proteins



Intramolecular model: H_0

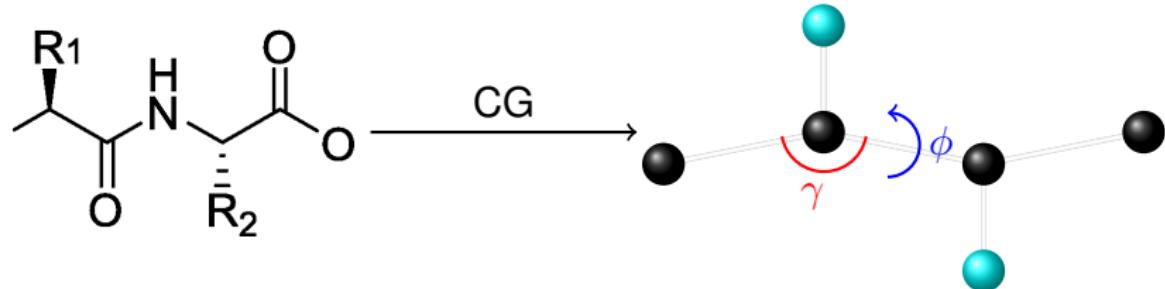


Intramolecular model: H_0



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

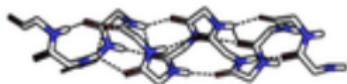
Intramolecular model: H_0



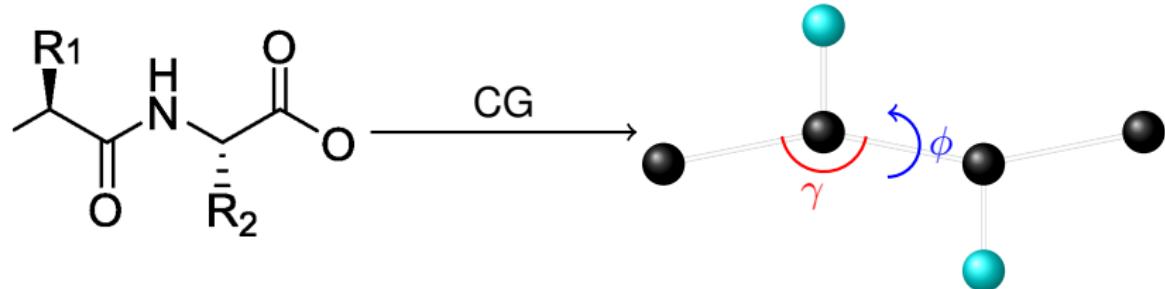
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$$\lambda = -1$$

Helical



Intramolecular model: H_0



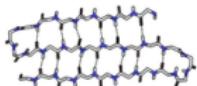
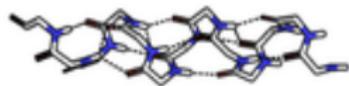
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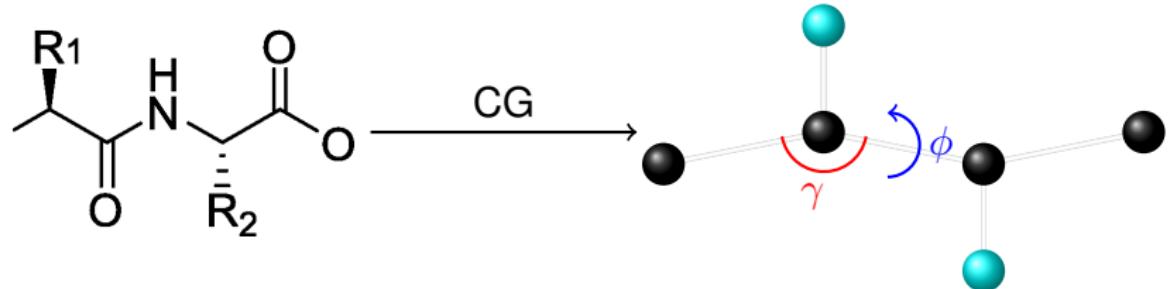
Helical

$$\lambda = 1$$

Extended



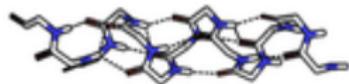
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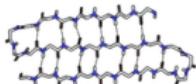
$$\lambda = -1$$

Helical



$$\lambda = 1$$

Extended



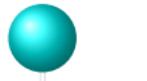
$$\lambda = 0$$

Random



Intermolecular model: W

Hydrophobic



Polar

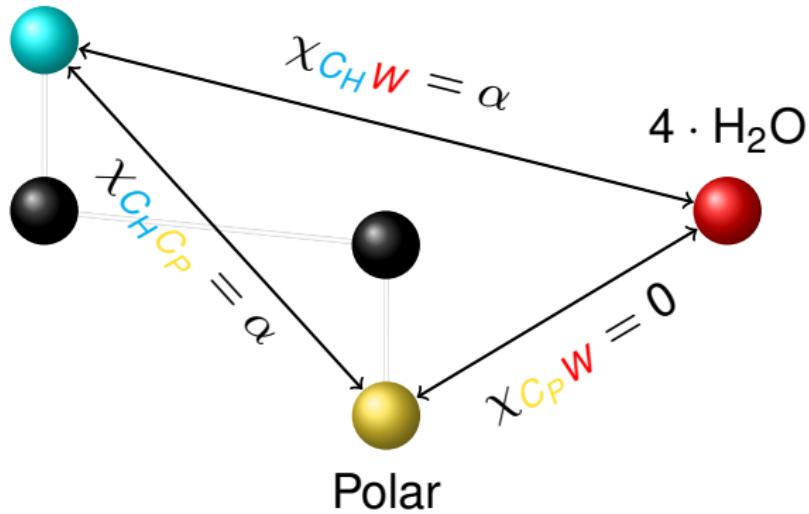
$4 \cdot \text{H}_2\text{O}$



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

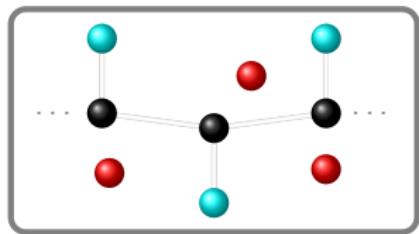
Intermolecular model: W

Hydrophobic



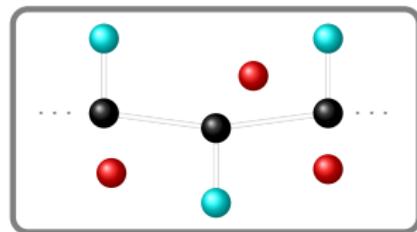
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Phase-diagram: Solvated homo-poly-peptide



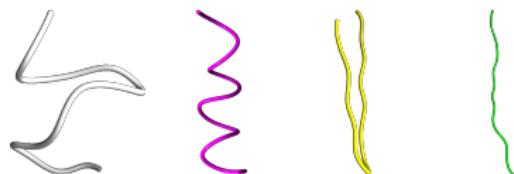
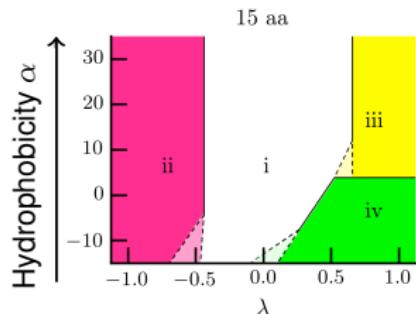
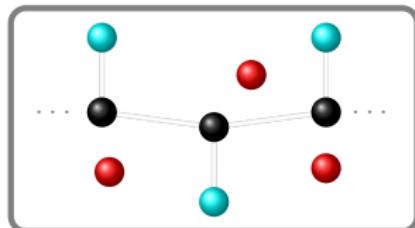
Phase-diagram: Solvated homo-poly-peptide

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



Phase-diagram: Solvated homo-poly-peptide

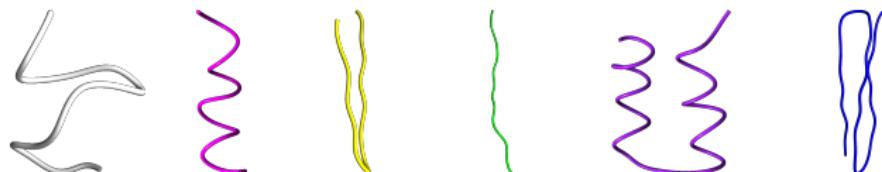
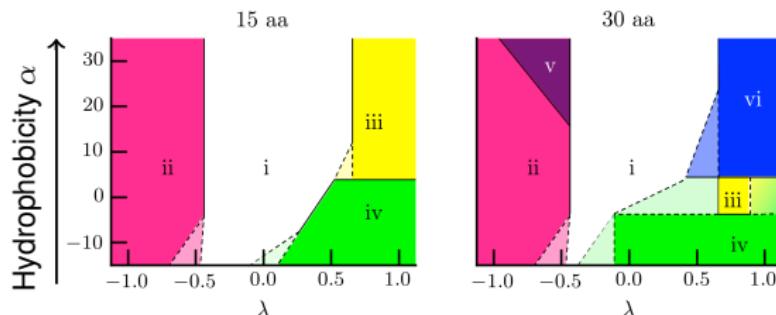
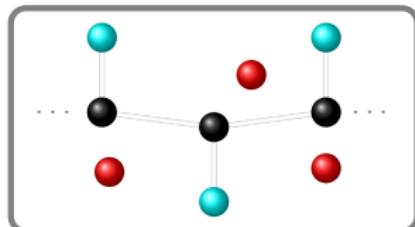
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i: Random coil ii: α -helix iii: β -hairpin iv: Extended

Phase-diagram: Solvated homo-poly-peptide

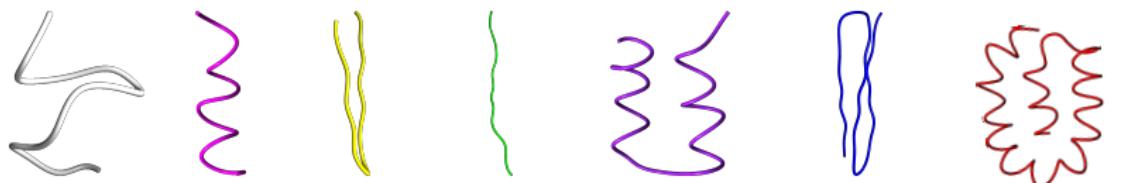
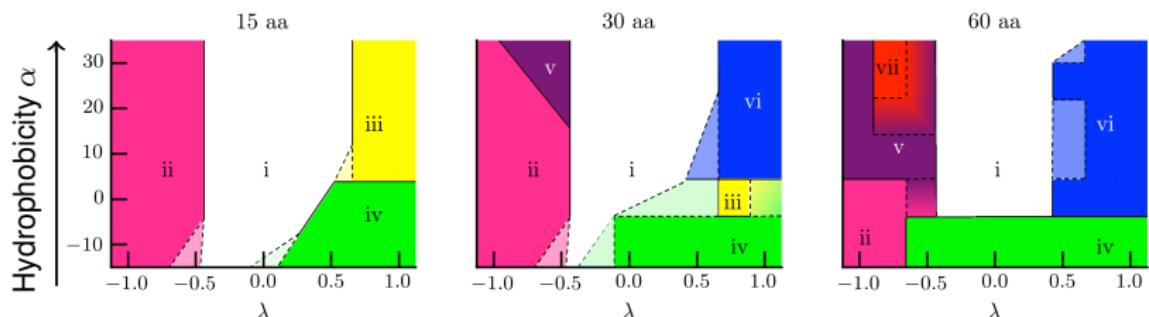
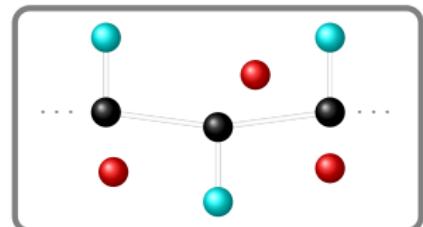
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Phase-diagram: Solvated homo-poly-peptide

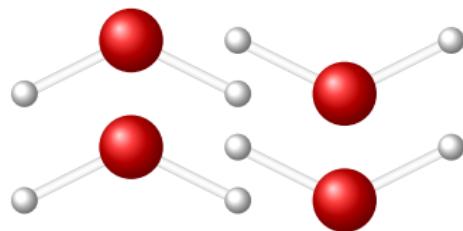
| $\tilde{\chi}_{k\ell}$ | CB | $4 \cdot H_2O$ |
|------------------------|----------|----------------|
| CB | 0 | α |
| $4 \cdot H_2O$ | α | 0 |



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

Electrostatics Coarse-Grained Simulations

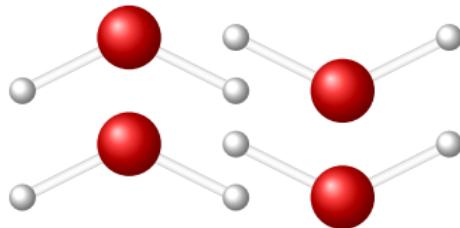
All-atom molecular dynamics:



Electrostatics Coarse-Grained Simulations

All-atom molecular dynamics:

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



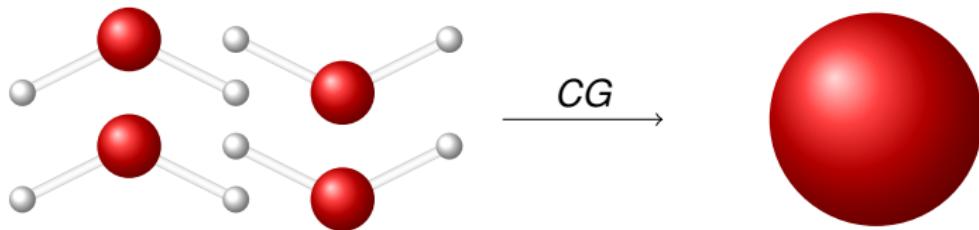
Electrostatics Coarse-Grained Simulations

All-atom molecular dynamics:

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- ▶ *Screening is modeled directly*

Coarse-grained molecular dynamics:

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



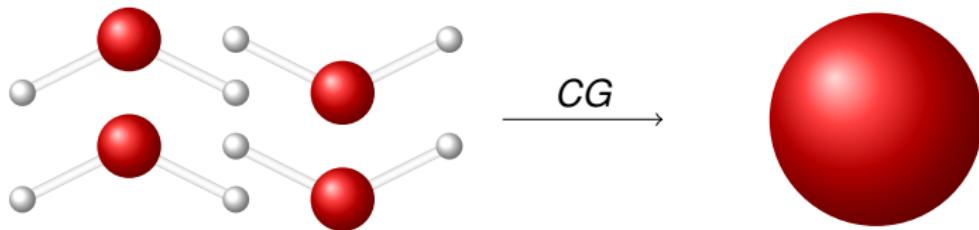
Electrostatics Coarse-Grained Simulations

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:

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

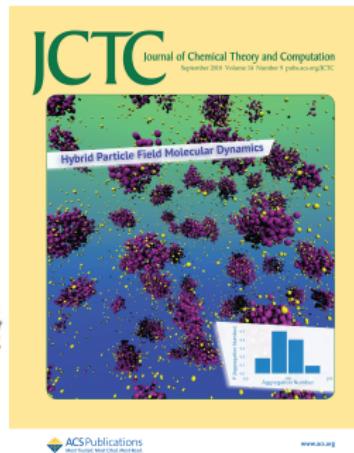
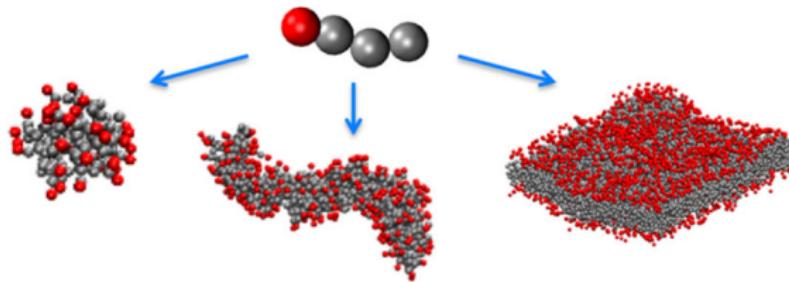
External potential:

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

Solution for ψ :

Particle-Mesh-Ewald by FFT

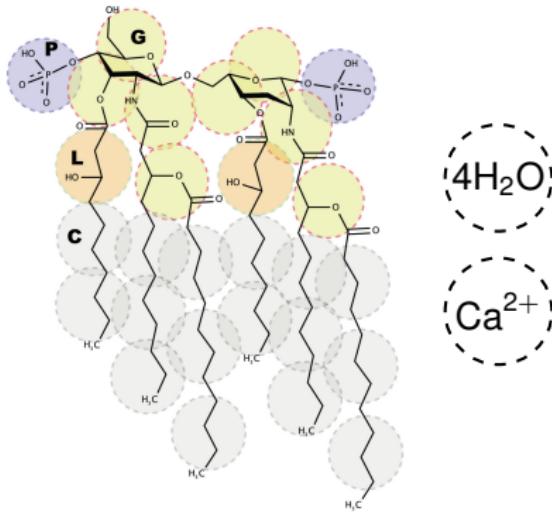
hPF-MD + electrostatics



Y.L. Zhu et al., *Phys. Chem. Chem. Phys.* **18**, 9799–9808 (2016)
H.B. Kolli et al., *J. Chem. Theory Comput.* **14**, 4928–4937 (2018)

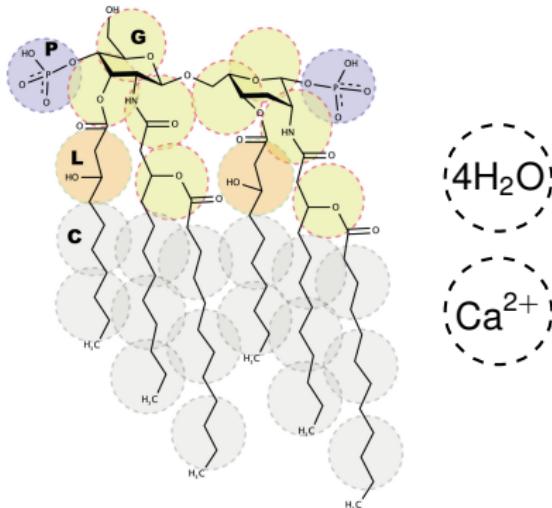
Application: Hybrid particle-field model for lipid A

CG-Representation



Application: Hybrid particle-field model for lipid A

CG-Representation



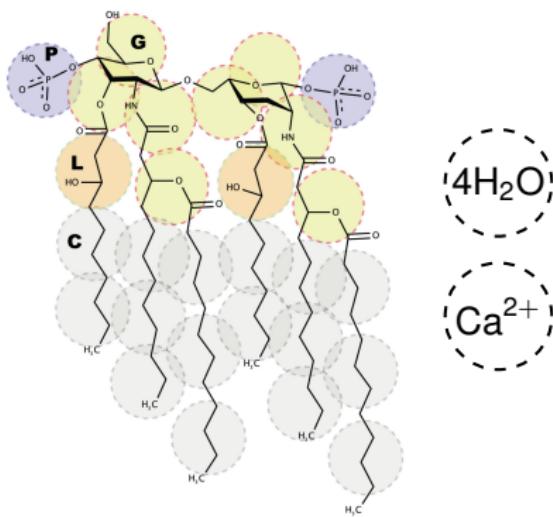
Free parameters:

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

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

Application: Hybrid particle-field model for lipid A

CG-Representation



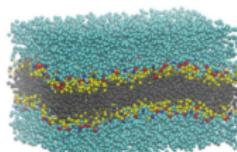
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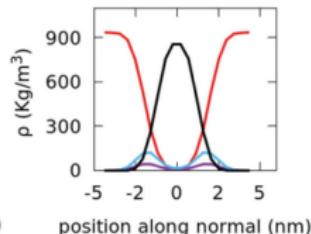
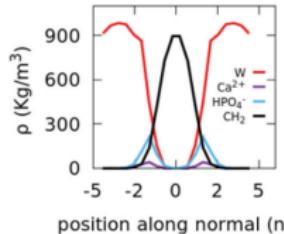
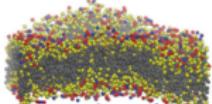
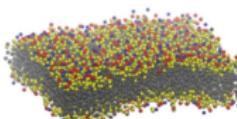
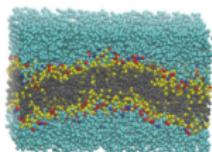
$$V_k(\mathbf{r}) = \frac{1}{\rho_0} \sum_{\ell} \left(\tilde{\chi}_{k\ell} + \frac{1}{\kappa} \right) \phi_{\ell}(\mathbf{r})$$

Parameterization

all-atom



$$\epsilon_r = 15$$



Tuning of ϵ_r and χ

Lipid A aggregation

Variable dielectrics approach

Model of paper III:

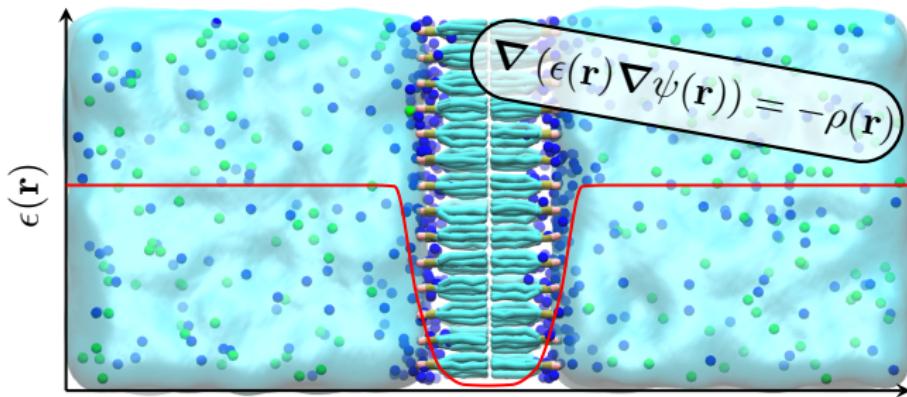
$$\nabla \cdot (\epsilon(\mathbf{r}) \nabla \psi(\mathbf{r})) = -\rho(\mathbf{r})$$

Solution for ψ :

Successive Over-Relaxation

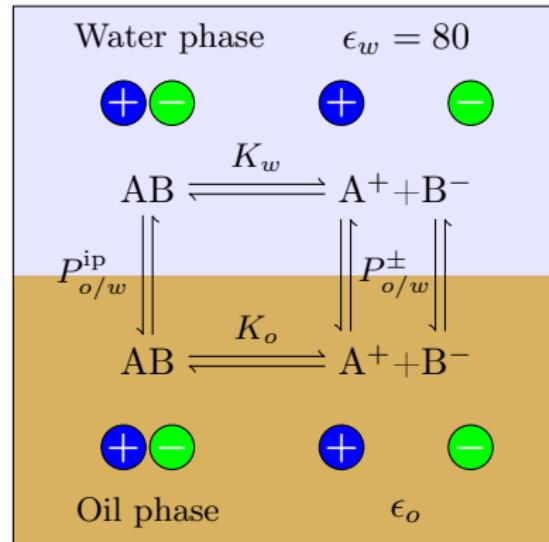
External potential:

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



Application in paper III: Partitioning of ions (1)

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



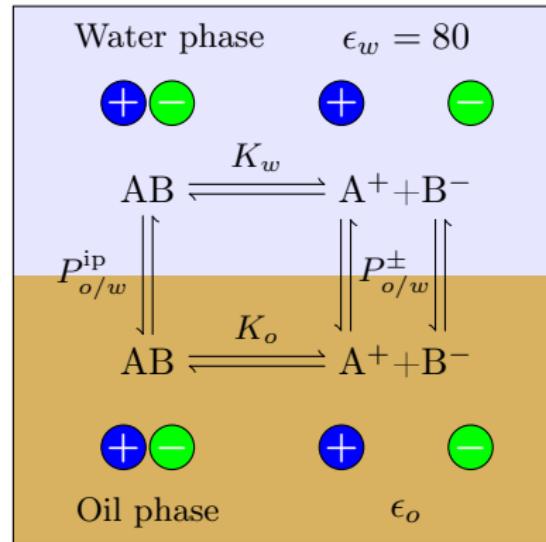
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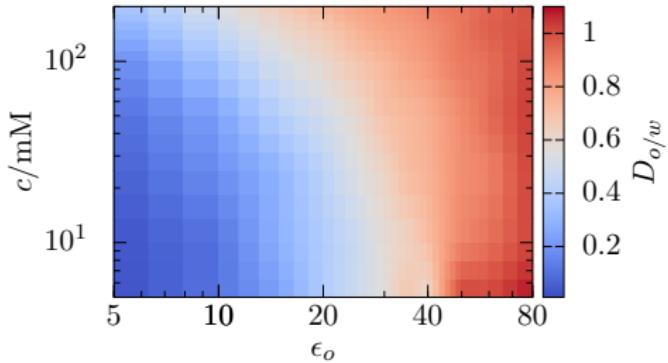
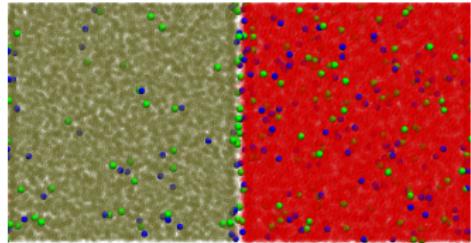
Distribution coefficient:

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

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



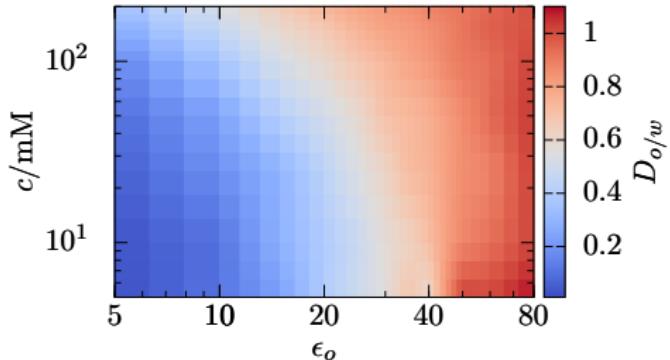
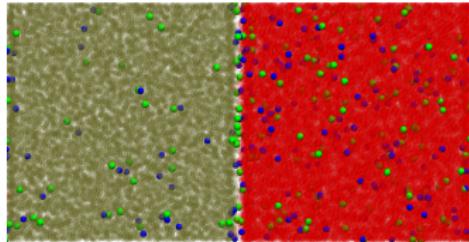
Application in paper III: Partitioning of ions (2)



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

c: concentration of ions.

Application in paper III: Partitioning of ions (2)

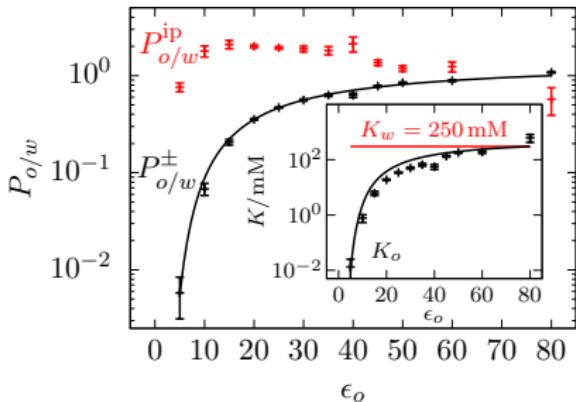


$$D_{o/w} = f(c, P_{o,w}^\pm, P_{o,w}^{\text{ip}}, K_w)$$

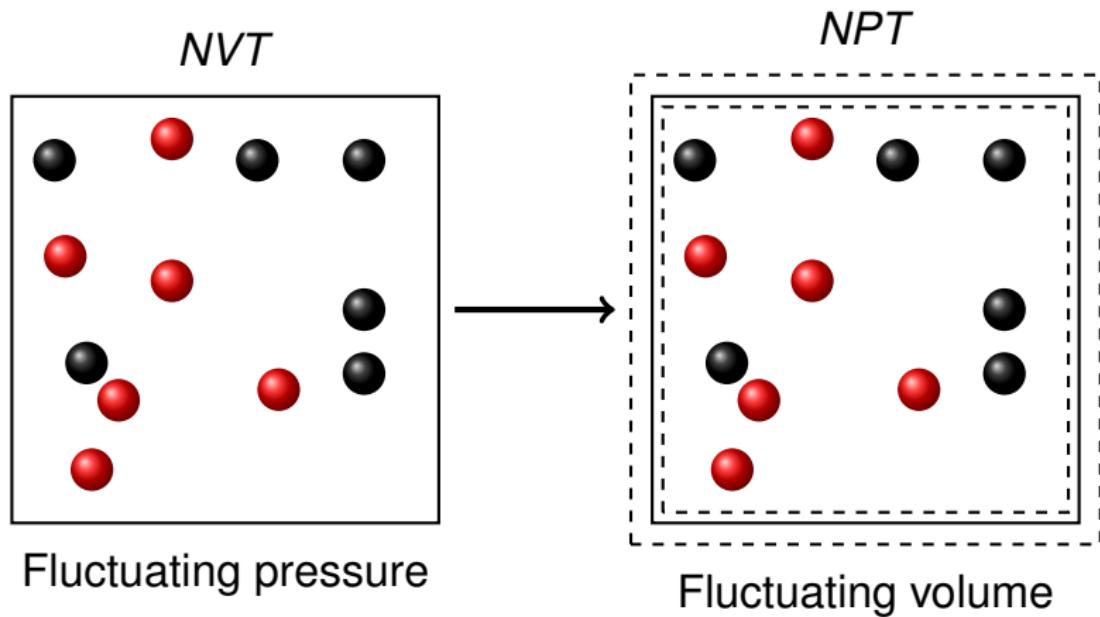
c: concentration of ions.

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.)

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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:

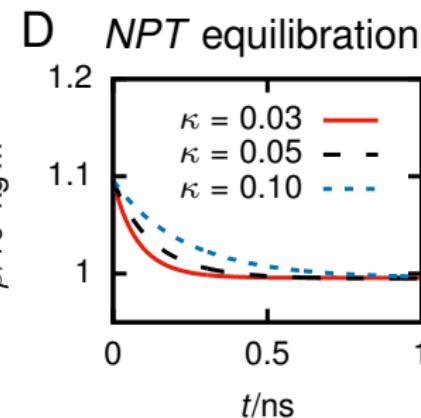
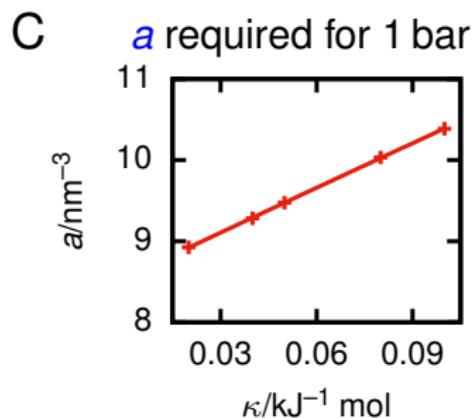
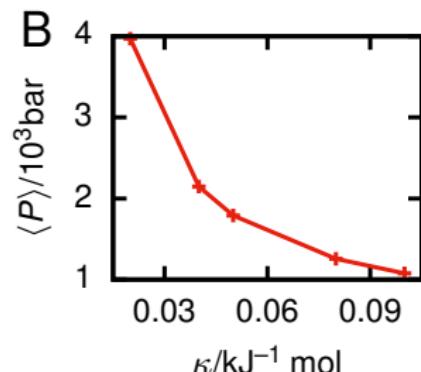
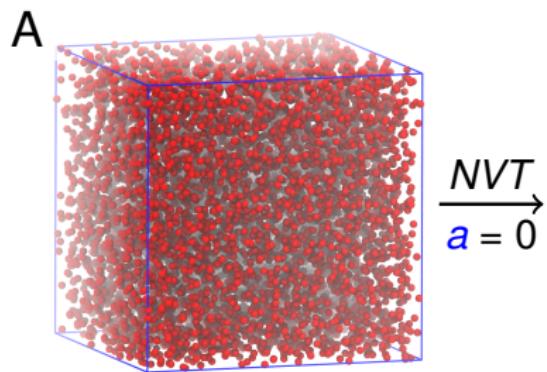
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$$P_{0,\mu} = \frac{1}{V} \int d\mathbf{r} \frac{1}{\rho_0} \left(\sum_{k\ell} \frac{\tilde{\chi}_{k\ell}}{2} \phi_k(\mathbf{r}) \phi_\ell(\mathbf{r}) + \frac{1}{2\kappa} \left(\phi(\mathbf{r})^2 - a^2 \right) \right),$$

(a : equation of state parameter.)

Parameterization of water model



Conclusions and outlook

New methodology for:

- ▶ Electrostatics
- ▶ Constant-pressure simulations

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- ⇒ Realistic representation of large biological systems

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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 graphic composed of vertical lines forming a grid-like pattern, next to the word "notur" in a large, bold, dark blue sans-serif font.



The logo for the University of Oslo (UiO) consists of the letters "UiO" in a large, bold, black sans-serif font, with a red dot positioned to the right of the letter "O".