Advances in the Hybrid Particle-Field Approach

Towards Biological Systems

Sigbjørn Løland Bore

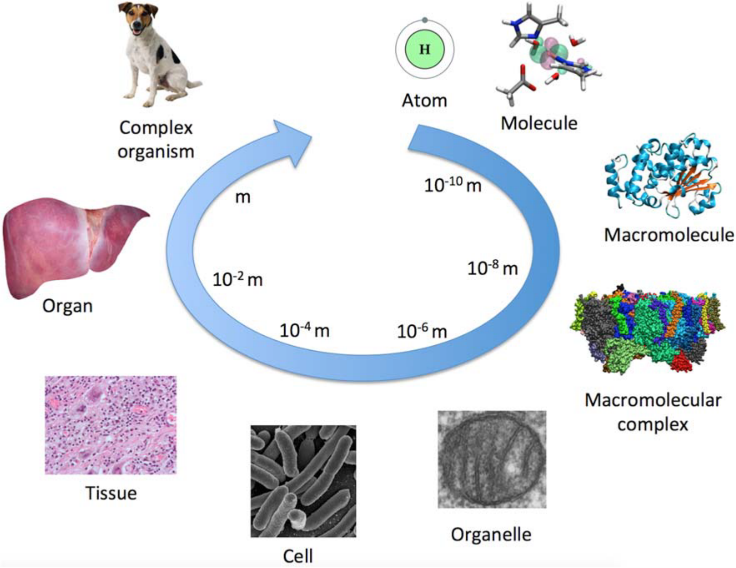
Hylleraas Centre for Quantum Molecular Sciences,
Department of Chemistry, University of Oslo, Norway

PhD lecture, Oslo, 23 April 2020

UiO : University of Oslo

Hylleraas

Scope of the work



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

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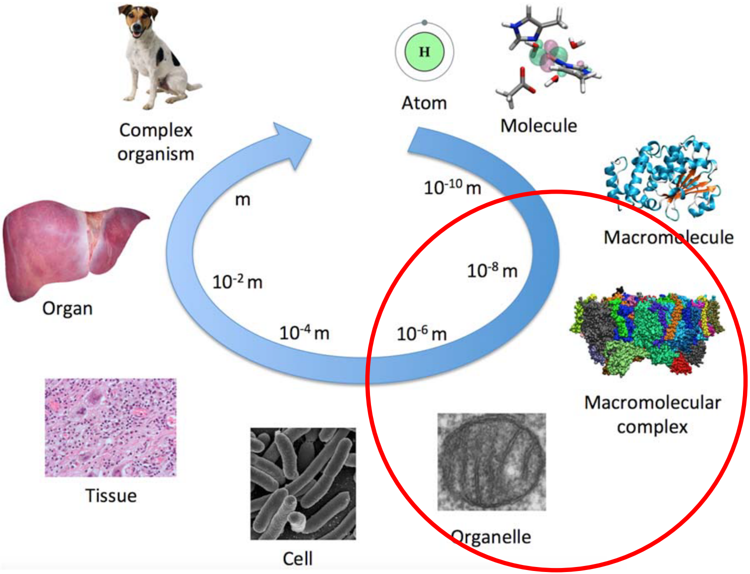

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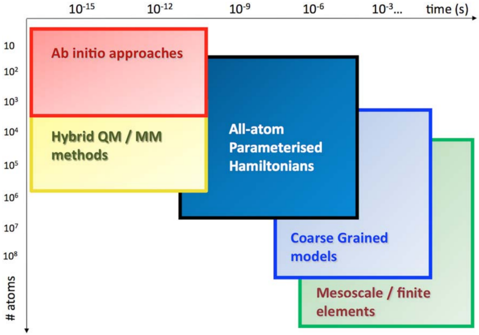
Coarse-grained methods



*M. Cascella and S. Vanni, Chem. Modell. **12**, 1–52 (2016)*
*T.A. Soares et al., J. Phys. Chem. Lett. **8**, 3586–3594 (2017)*

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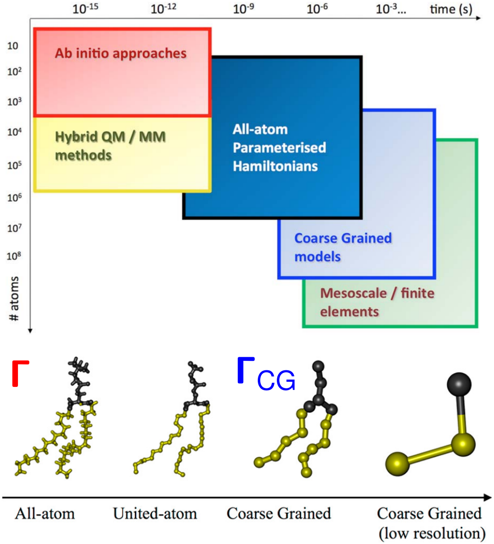

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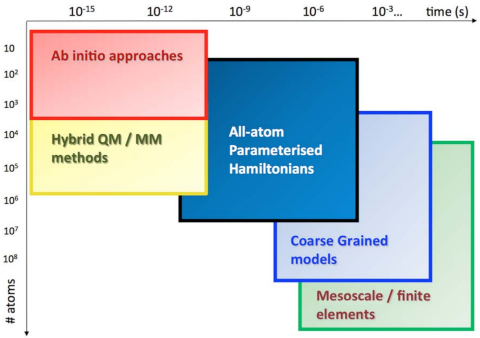
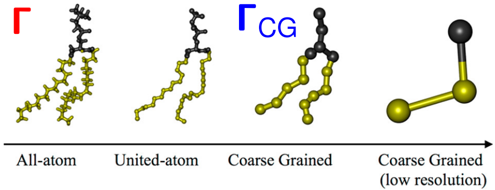


$$Z = \int \mathrm{d}\boldsymbol{\Gamma}\; e^{-\beta H(\boldsymbol{\Gamma})}$$

$$\downarrow$$

$$Z \simeq \int \mathrm{d}\boldsymbol{\Gamma}_{\mathrm{CG}}\; e^{-\beta H(\boldsymbol{\Gamma}_{\mathrm{CG}})}$$



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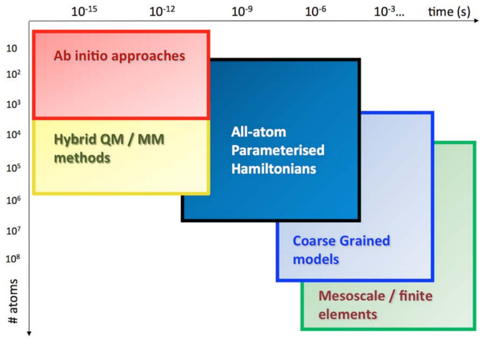

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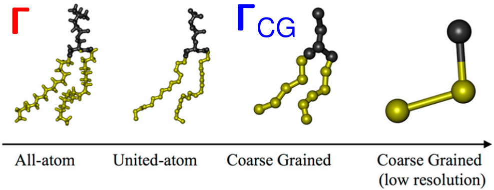

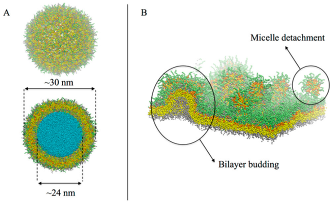

Large systems and long time scales!

M. Cascella and S. Vanni, Chem. Modell. ***12****, 1–52 (2016)*
T.A. Soares et al., J. Phys. Chem. Lett. ***8****, 3586–3594 (2017)*

The hybrid particle-field method

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

($\{\mathbf{r}\} \equiv \{\mathbf{r}_1, \ldots, \mathbf{r}_N\}$, *particle positions*)
($\{\phi\} \equiv \{\phi_1, \ldots, \phi_M\}$, *particle-type number densities*)

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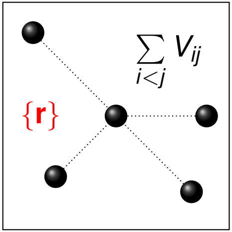
Intermolecular interactions

Particle-particle



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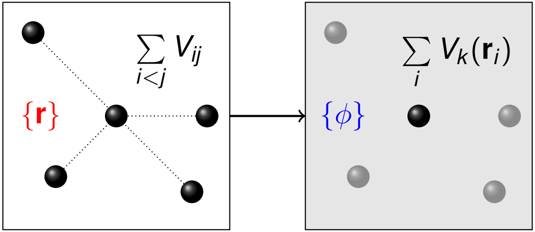
Particle-field



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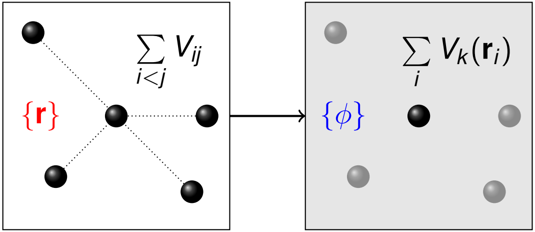

$$V_k(\mathbf{r}) = \frac{\delta W[\{\phi\}]}{\delta \phi_k(\mathbf{r})}$$

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

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($\{\phi\} \equiv \{\phi_1, \ldots, \phi_M\}$, *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*)

G. Milano and T. Kawakatsu, J. Chem. Phys. ***130****, 214106 (2009)*

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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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$\tilde{\chi}_{k\ell} > 0 \rightarrow$ *Likes not* to mix — $\kappa \sim 0 \rightarrow$ incompressible

$\tilde{\chi}_{k\ell} \leq 0 \rightarrow$ *Likes* to mix — $\kappa \gg 0 \rightarrow$ very compressible

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

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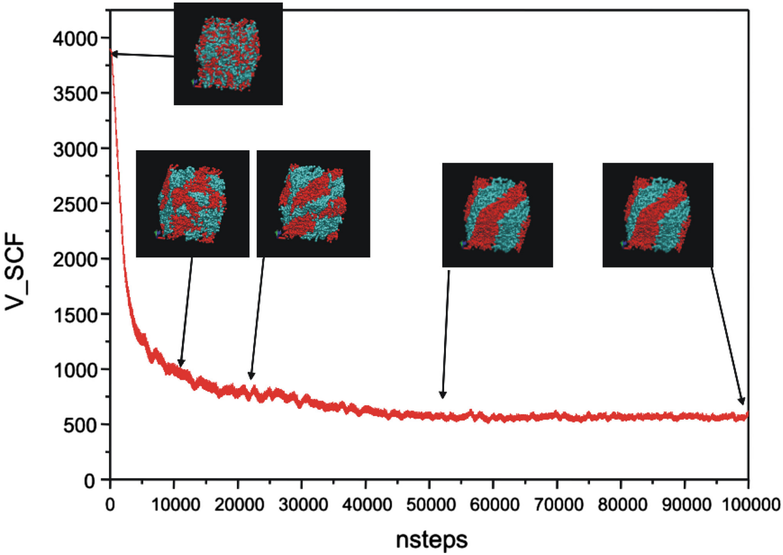
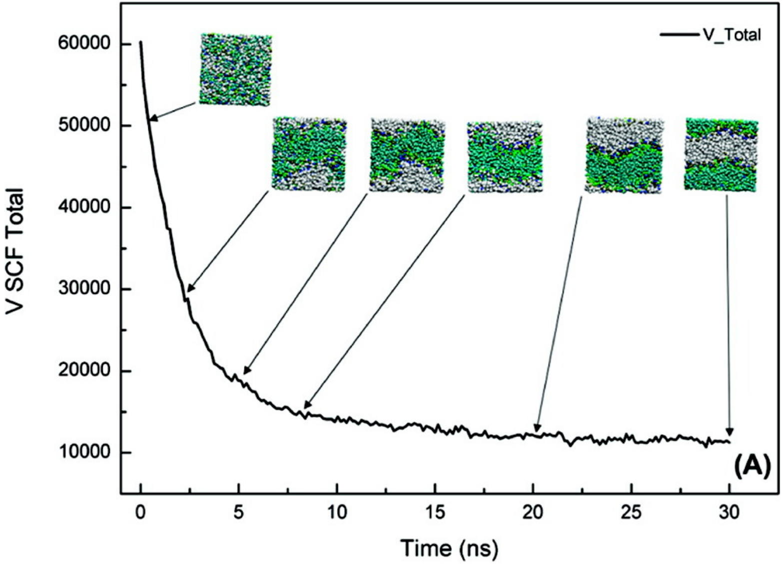
Prototypic applications: Relaxation of polymer melts



G. Milano and T. Kawakatsu J. Chem. Phys. ***130****, 214106 (2009)*

Prototypic applications: Phospholipid aggregation



A. De Nicola et al., Theor. Chem. Acc. ***131****, 1167 (2012)*

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)
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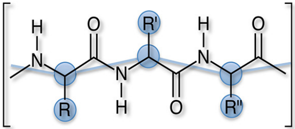
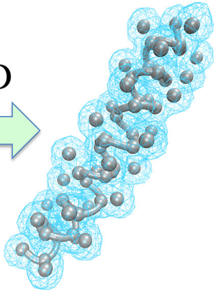
Proteins, Electrostatics, Multiphase electrolytes, Constant-pressure

Hybrid Particle-Field Model for Proteins

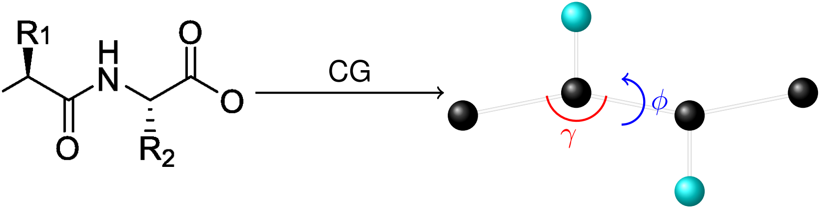


hPF-MD



$$H = H_0(\{\mathbf{r}\}) + W[\rho(\mathbf{r})]$$

Intramolecular model: H_0



S.L. Bore et al., J. Chem. Theory Comput. ***14****, 1120-1130 (2018)*

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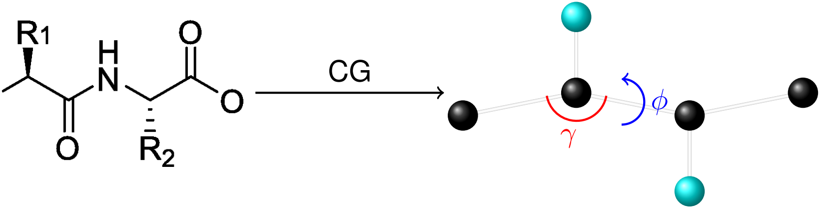

$$V(\gamma,\phi) = \frac{1}{2}k\,(\gamma - \gamma_0(\phi))^2 + V_{\text{propensity}}(\phi,\lambda)$$

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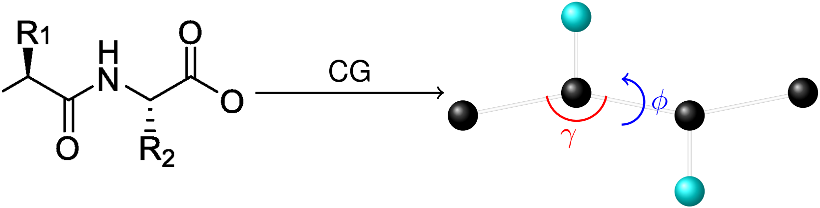

$$V(\gamma,\phi) = \frac{1}{2}k\left(\gamma - \gamma_0(\phi)\right)^2 + V_{\text{propensity}}(\phi,\lambda)$$

$\lambda = -1$

Helical

S.L. Bore et al., J. Chem. Theory Comput. ***14****, 1120-1130 (2018)*

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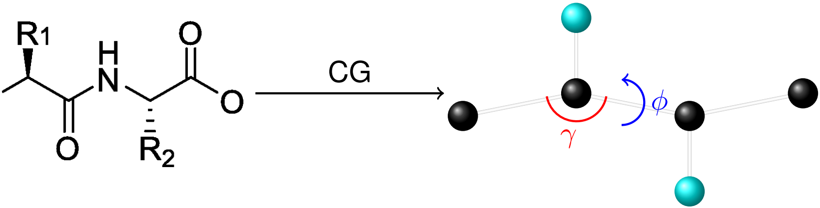
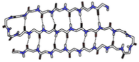


$$V(\gamma,\phi) = \frac{1}{2}k\left(\gamma - \gamma_0(\phi)\right)^2 + V_{\text{propensity}}(\phi,\lambda)$$

$\lambda = -1$	$\lambda = 1$
Helical	Extended
	

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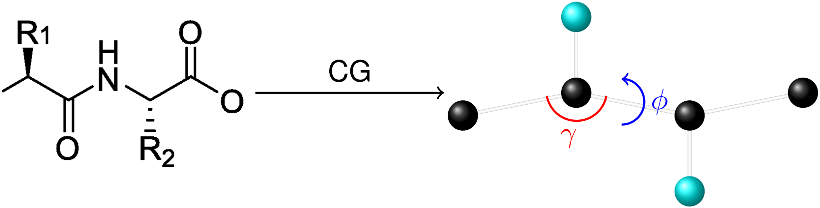

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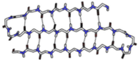
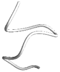
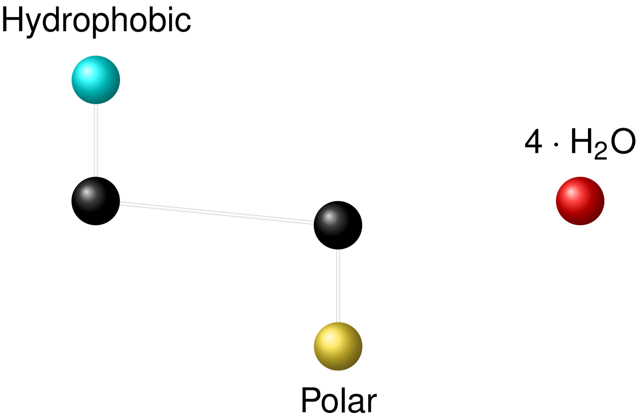
Helical	Extended	Random





S.L. Bore et al., J. Chem. Theory Comput. ***14****, 1120-1130 (2018)*

Intermolecular model: *W*



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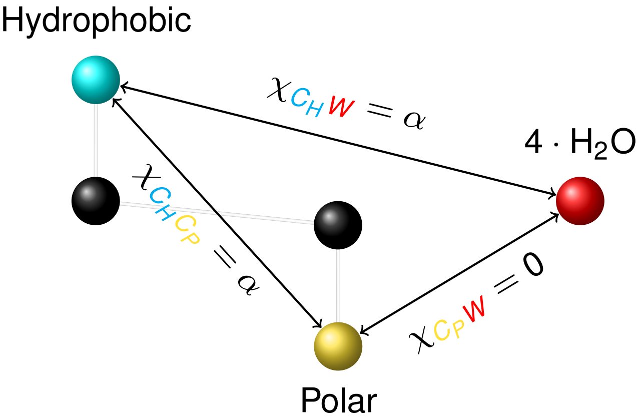

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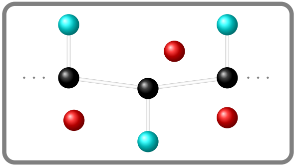
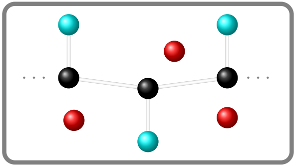
Phase-diagram: Solvated homo-poly-peptide



Phase-diagram: Solvated homo-poly-peptide

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



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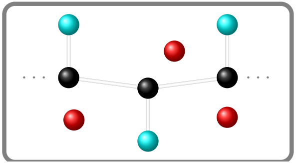

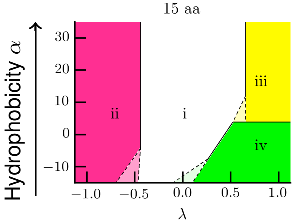

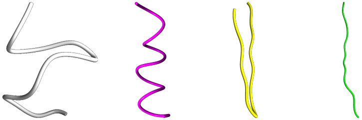

i: Random coil   ii: α-helix   iii: β-hairpin   iv: Extended

Phase-diagram: Solvated homo-poly-peptide

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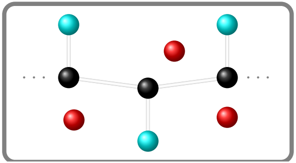

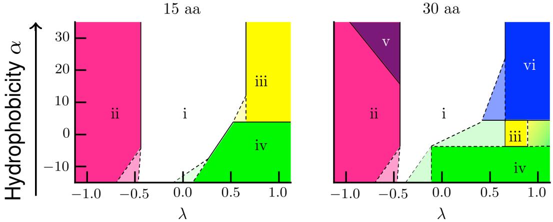

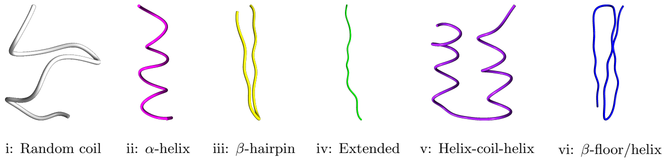

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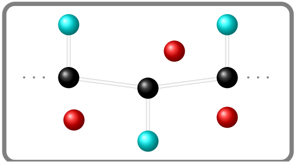
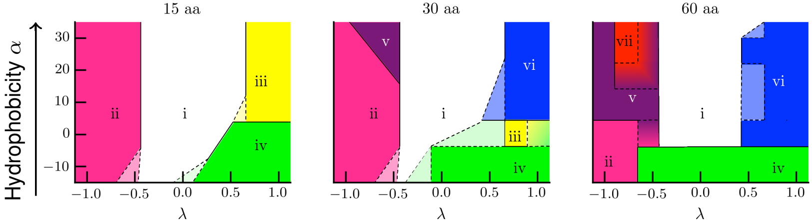
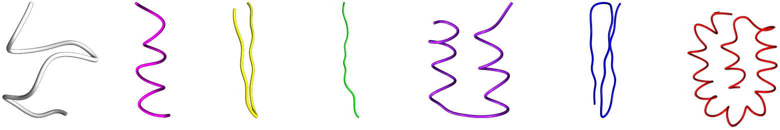


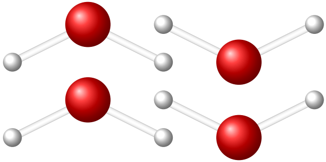




i: Random coil ii: α-helix iii: β-hairpin iv: Extended v: Helix-coil-helix vi: β-floor/helix vii: Helical bundle

Electrostatics Coarse-Grained Simulations

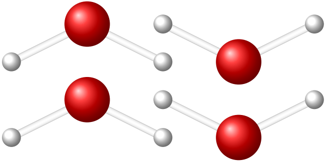
All-atom molecular dynamics:



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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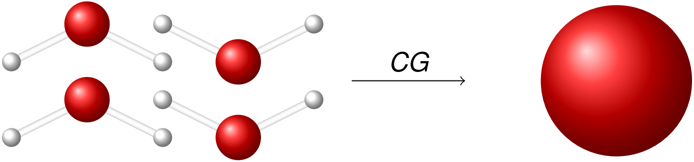
Coarse-grained molecular dynamics:

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



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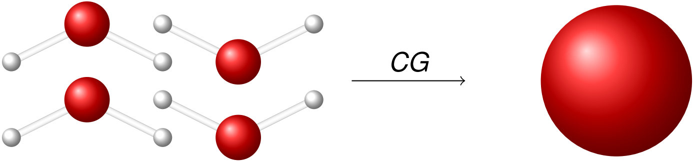
- *Charges are resolved*
- *Screening is modeled directly*

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:

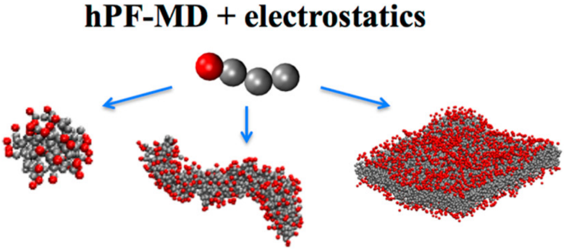
$$\epsilon \nabla^2 \psi = -\rho(\mathbf{r})$$

Solution for ψ:

Particle-Mesh-Ewald by FFT

External potential:

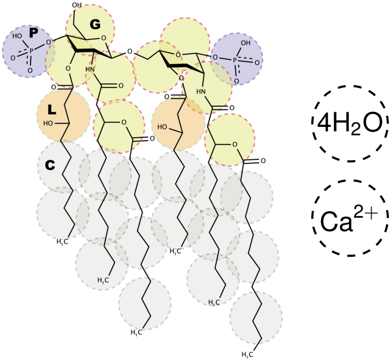
$$V_K(\mathbf{r}) = q_K(\psi_S(\mathbf{r}) + \psi_L(\mathbf{r}))$$



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



A. De Nicola et al., Biochim. Biophys. Acta, in press (2020)

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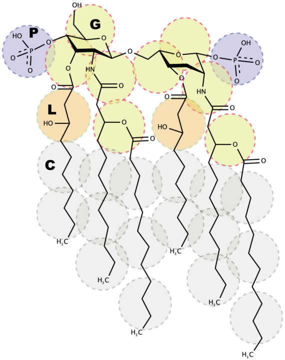

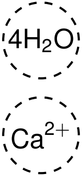

Free parameters:

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

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

A. De Nicola et al., Biochim. Biophys. Acta, in press (2020)

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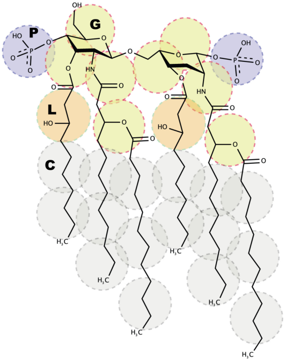
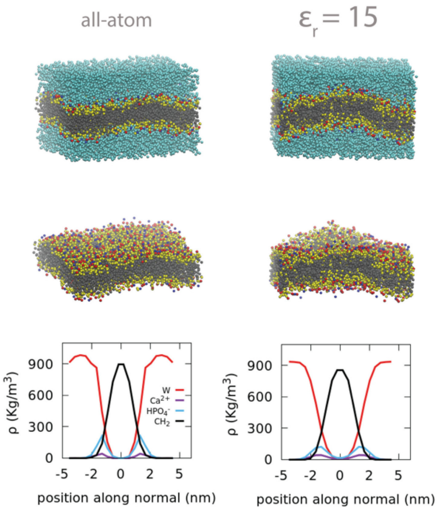


$4H_2O$

Ca^{2+}

Parameterization



Free parameters:

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

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

Tuning of ϵ_r and χ

A. De Nicola et al., Biochim. Biophys. Acta, in press (2020)

Lipid A aggregation

Variable dielectrics approach

Model of paper III:

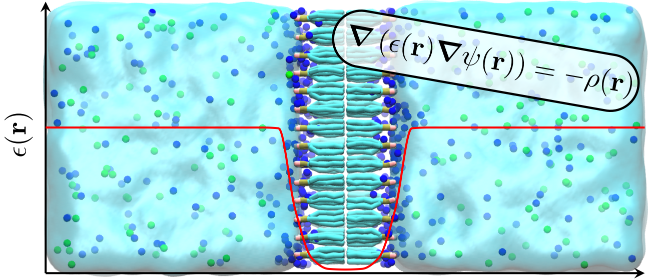
$$\nabla \cdot (\epsilon(\mathbf{r}) \nabla \psi(\mathbf{r})) = -\rho(\mathbf{r})$$

Solution for ψ:

Successive Over-Relaxation

External potential:

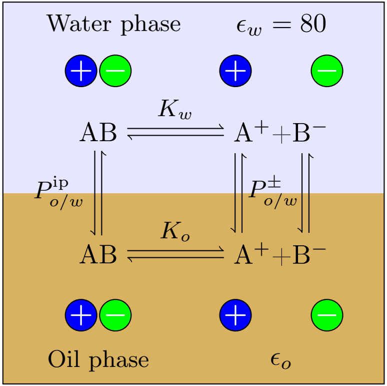
$$V_K(\mathbf{r}) = q_K \psi(\mathbf{r}) - \frac{1}{2} \frac{\partial \epsilon(r)}{\partial \phi_k} \left| \nabla \psi(\mathbf{r}) \right|^2$$



S.L. Bore et al., J. Chem. Theory Comput. ***15****, 2033 (2018)*

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 kJ mol^{-1})



S.L. Bore et al., J. Chem. Theory Comput. ***15****, 2033 (2018)*

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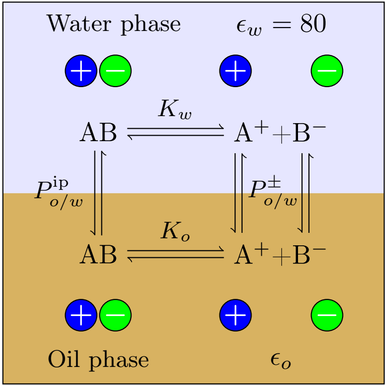
Distribution coefficient:

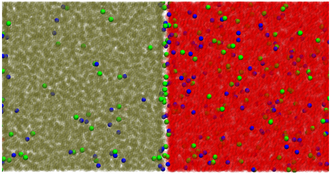
$$D_{o/w} = \frac{c_o}{c_w}$$

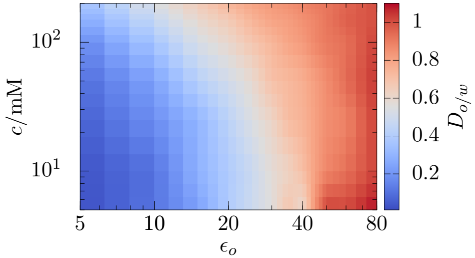
(*c_0 and c_w: concentration of ions within each phase*)



S.L. Bore et al., J. Chem. Theory Comput. **15**, 2033 (2018)

Application in paper III: Partitioning of ions (2)

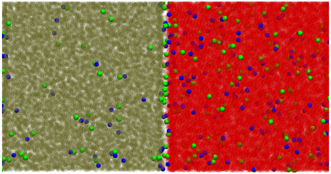


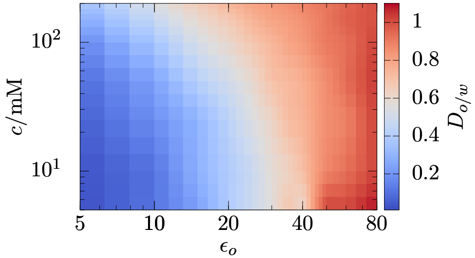


$$D_{o/w} = f(c, P^{\pm}_{o,w}, P^{\mathrm{ip}}_{o,w}, K_w)$$

c: concentration of ions.

Application in paper III: Partitioning of ions (2)



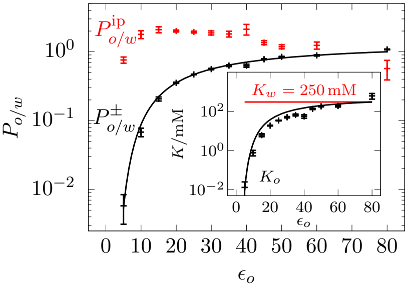


$$D_{o/w} = f(c, P^{\pm}_{o,w}, P^{\mathrm{ip}}_{o,w}, K_w)$$

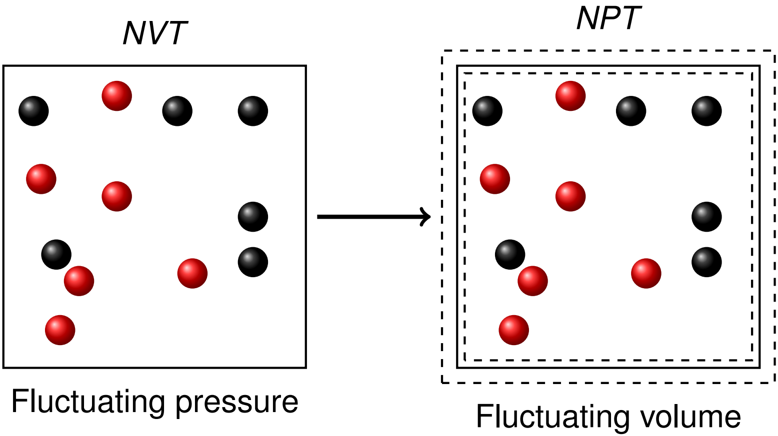
c: concentration of ions.

Born theory of ions:

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



Constant-Pressue Simulations



Pressure for particle-field

Hybrid particle field interaction-energy:

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

(*a: equation of state parameter.*)

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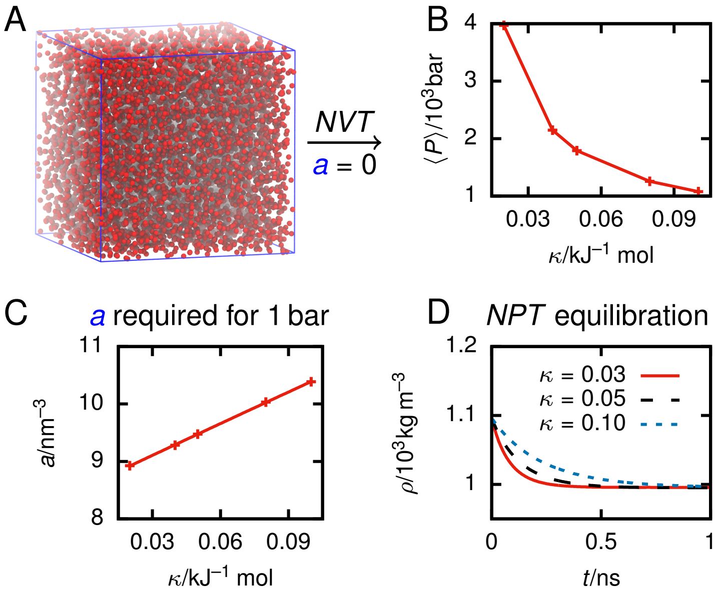
(*a: equation of state parameter.*)

Parameterization of water model



Conclusions and outlook

New methodology for:

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- Constant-pressure simulations

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$\Longrightarrow$ Realistic representation of large biological systems

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