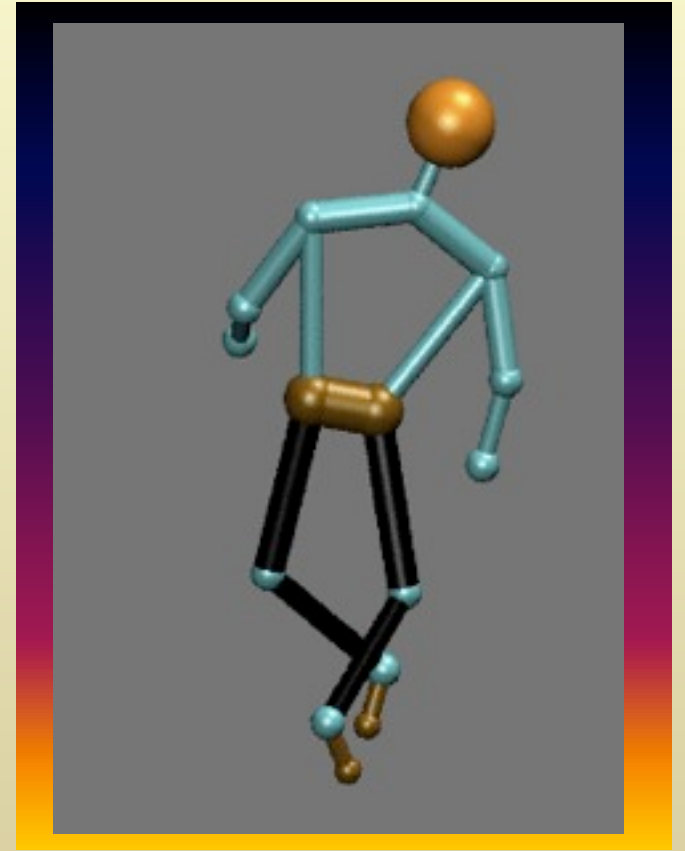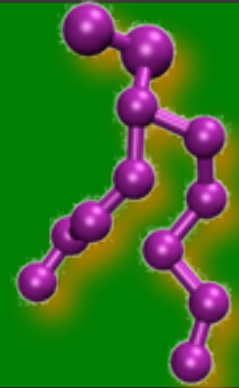# MARTINI
# 2010-2015

# Martini forcefield for biomolecular simulations

# Martini forcefield for biomolecular simulations
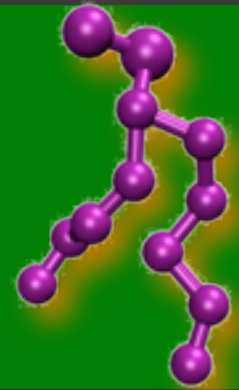
**I**     **Lipids**

- Basic Martini philosophy
- Parameterization
- Applications

# Martini forcefield for biomolecular simulations

**I    Lipids**

- Basic Martini philosophy
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**II    Proteins & Sugars**

- Parameterization
- Elastic networks
- Applications

# Martini forcefield for biomolecular simulations
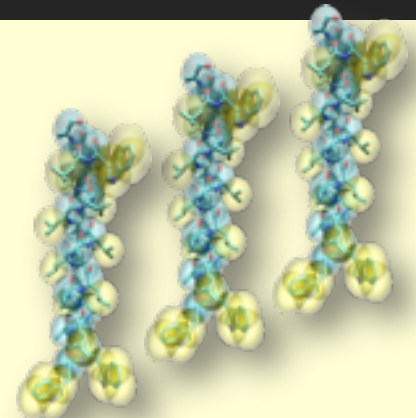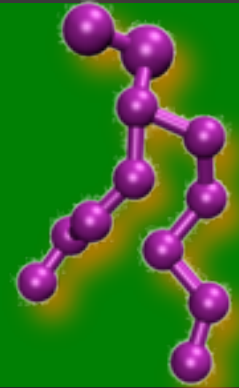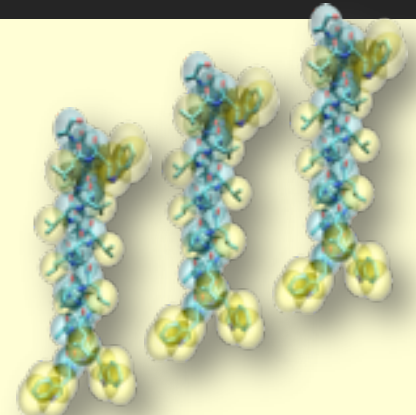
**I**  **Lipids**

- Basic Martini philosophy
- Parameterization
- Applications

**II**  **Proteins & Sugars**

- Parameterization
- Elastic networks
- Applications

**III**  **Future**

- Hybrid models
- Polarizable Martini

# Hybrid models

# Hybrid models

Resolution transformation
- Testing CG configurations
- Testing all-atom forcefields

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Spatially resolved resolution
- High resolution only at area of interest
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- High resolution only at area of interest
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Mixed models
- Still fast, more accurate
- Hamiltonian exchange

# Resolution Transformation

Outline of the method

# Resolution Transformation

## Outline of the method

- START: Random placement of fine-grained particles within sphere centered at CG bead
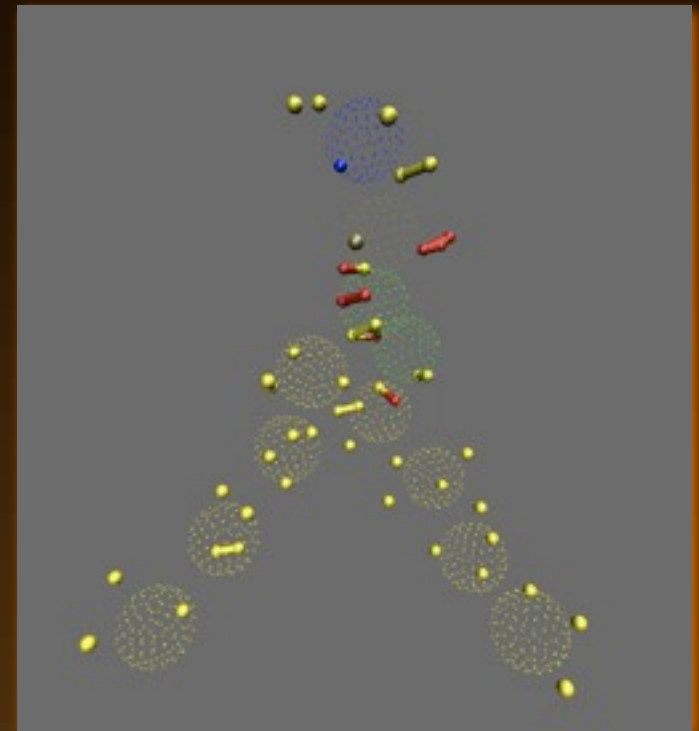
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## Outline of the method

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- SA: Simulated annealing slowly decreasing temperature, using a harmonic restraining potential

$$U^{\text{tot}} = U^{\text{AA}} + U^{\text{restr}},$$

$$U^{\text{restr}} = \sum_{i=1}^{n} \frac{k}{2} \left( \mathbf{r}_i^{\text{CG}} - \mathbf{r}_i^{\text{AA,com}} \right)^2.$$

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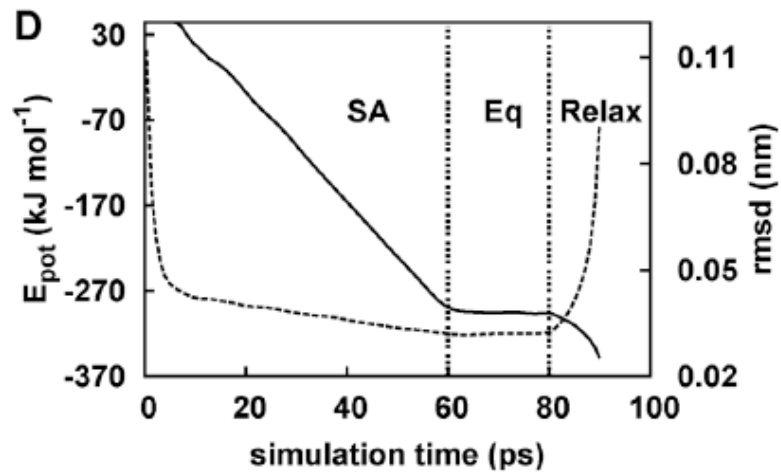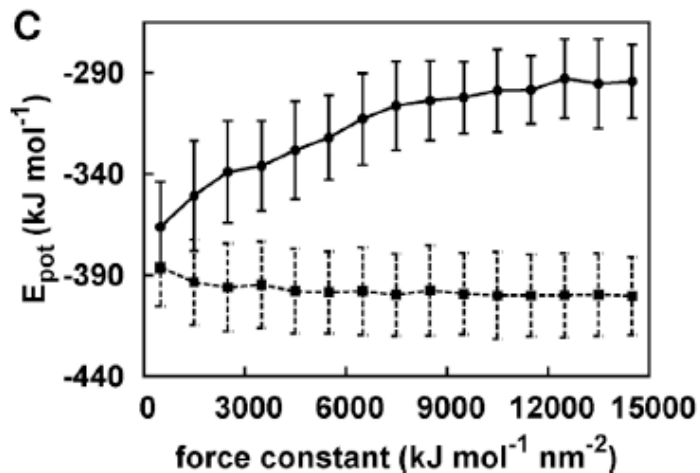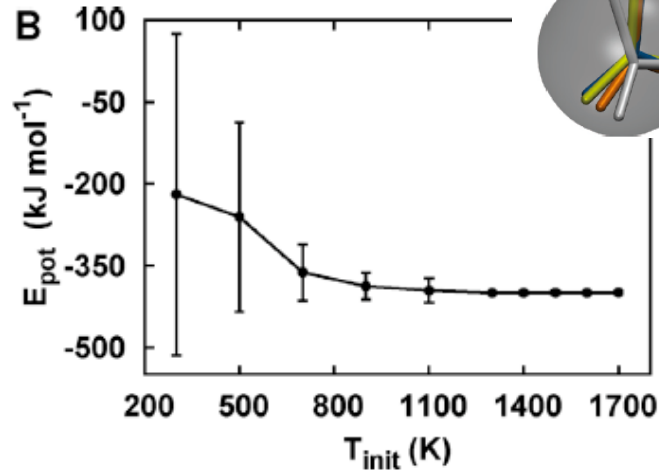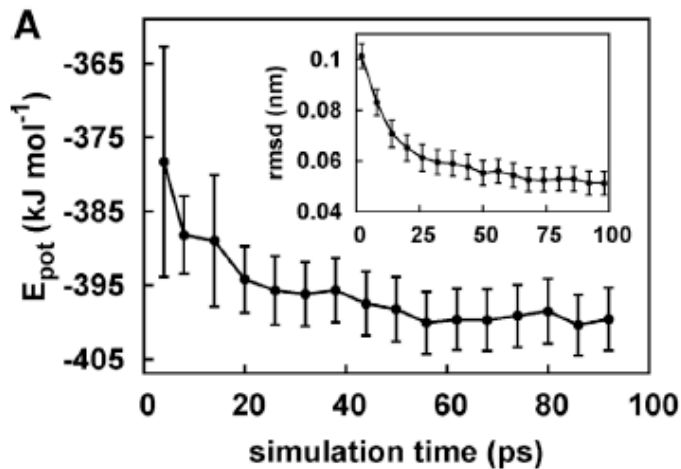$$U^{\text{restr}} = \sum_{i=1}^{n} \frac{k}{2} \left( \mathbf{r}_i^{\text{CG}} - \mathbf{r}_i^{\text{AA,com}} \right)^2$$

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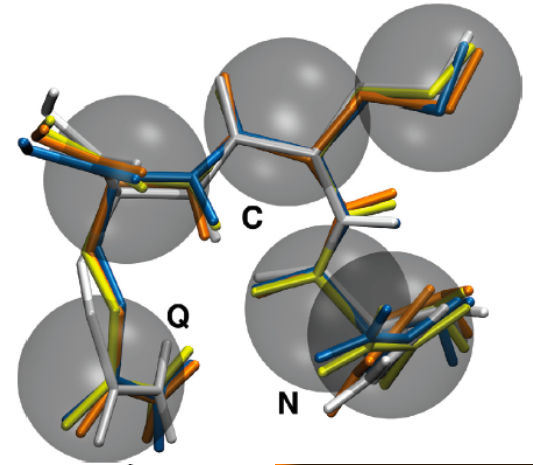$$U^{\text{tot}} = U^{\text{AA}} + U^{\text{restr}}$$

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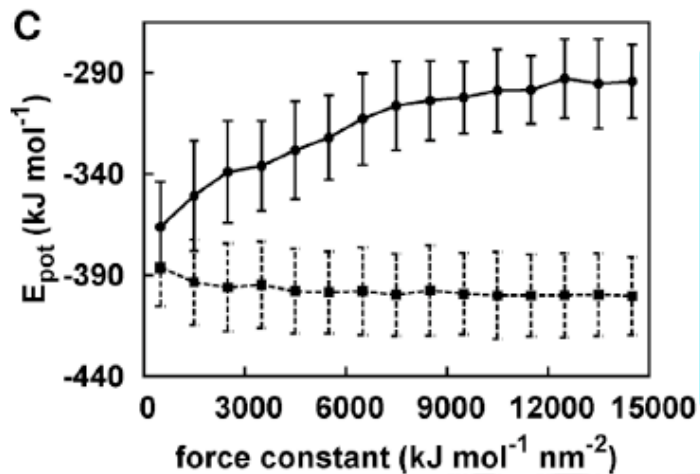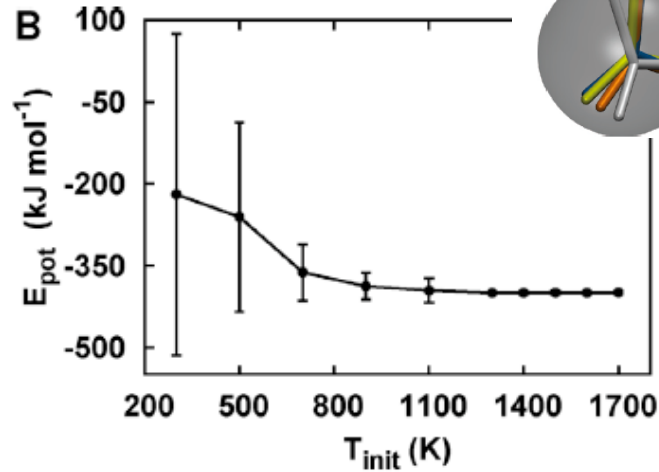
- RELAX: Relaxation with normal fine-grained potentials

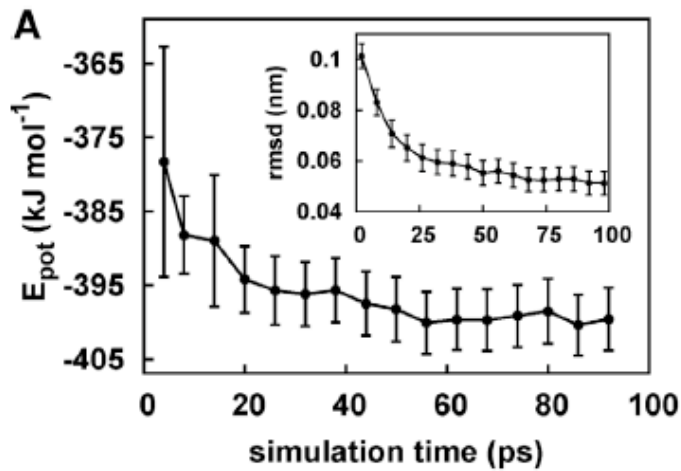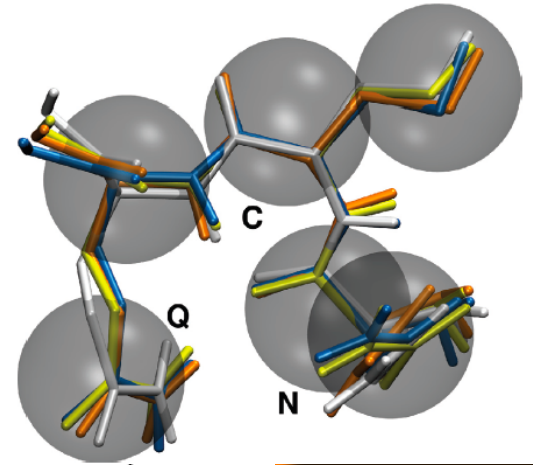# Resolution Transformation
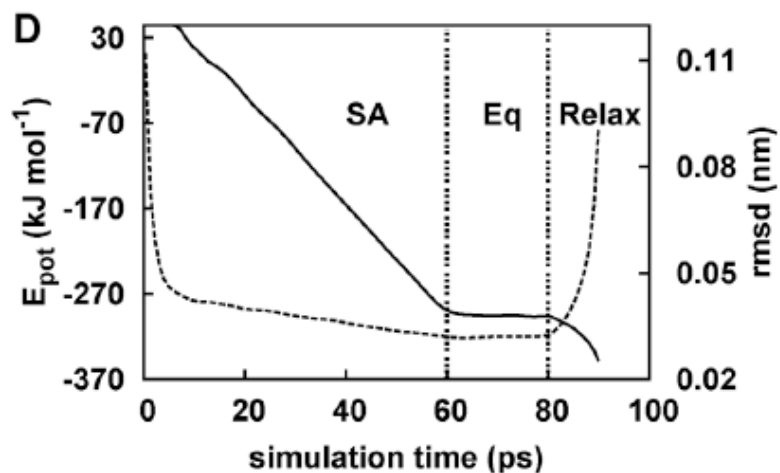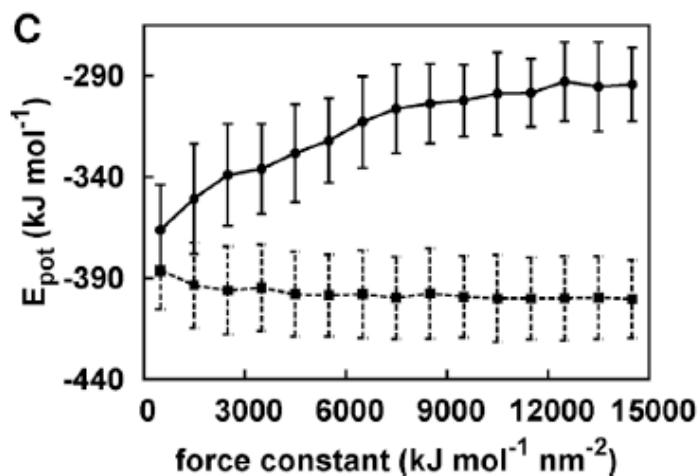
Testing on small peptide: parameter optimization

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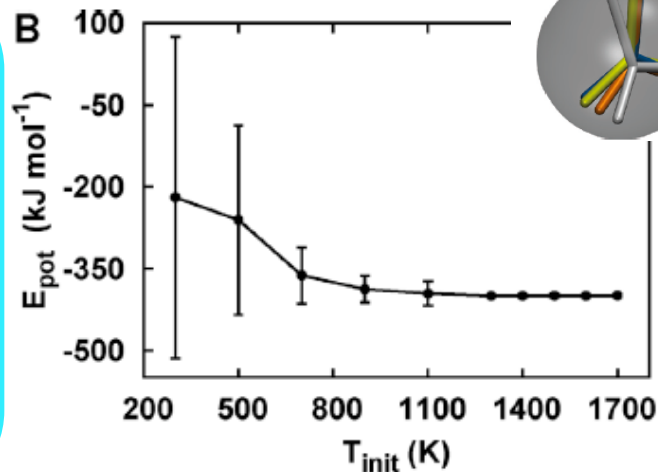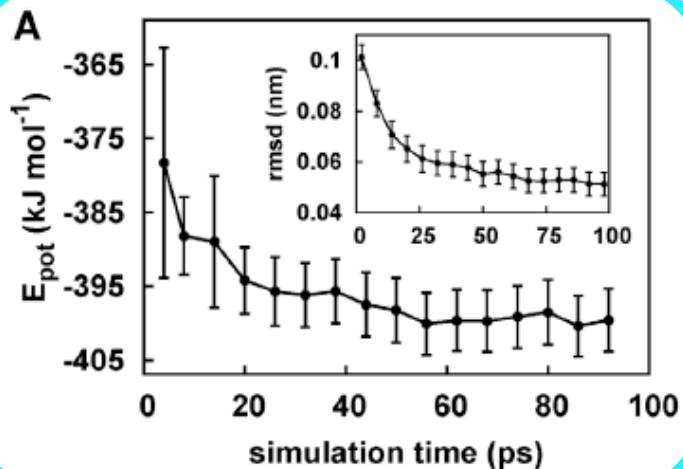
Testing on small peptide: parameter optimization

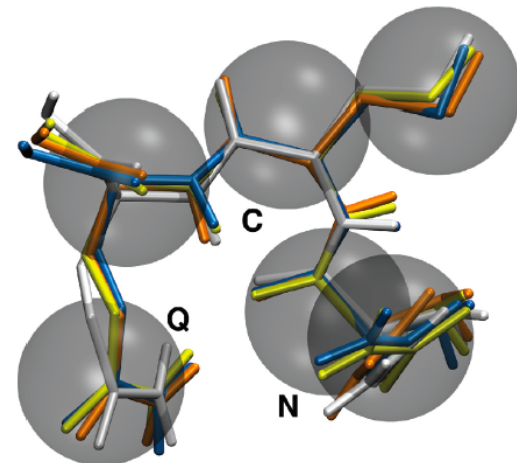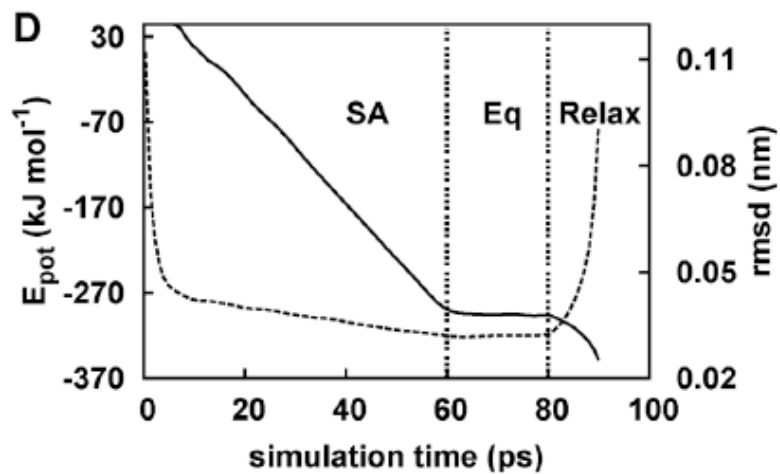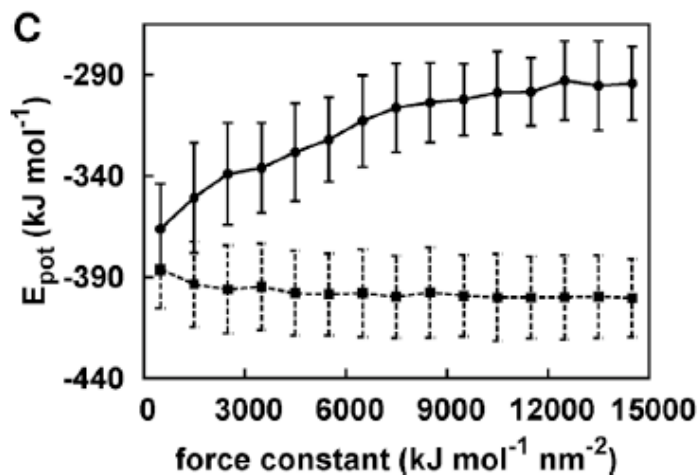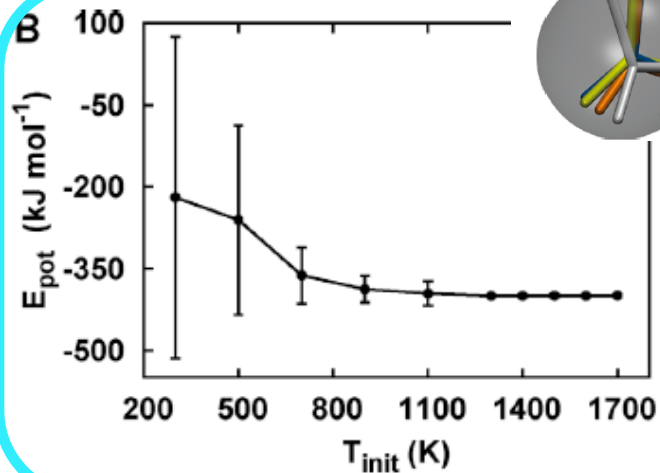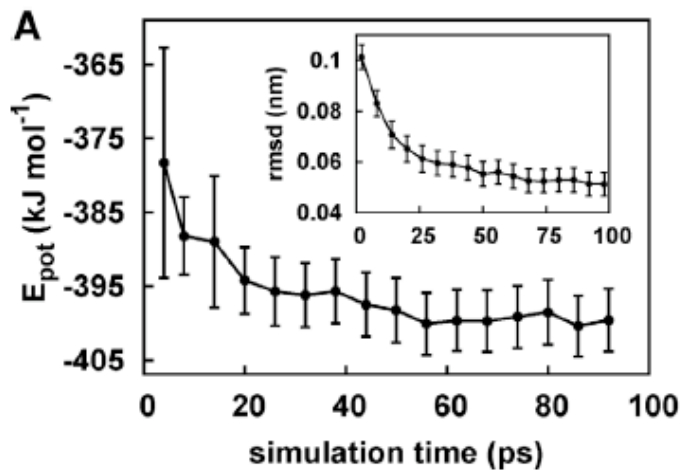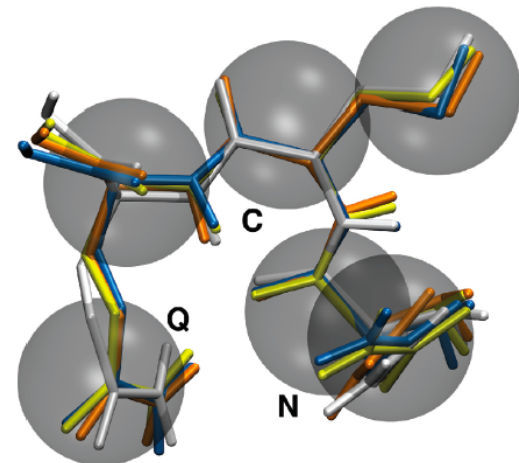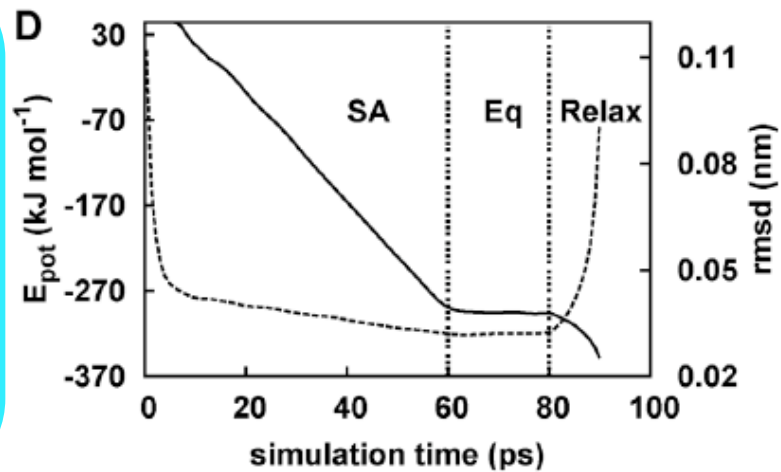# Resolution Transformation

Testing on small peptide: parameter optimization

# Resolution Transformation

Overview of parameters

| Parameter | mdp-option | Recommended value |
|---|---|---|
| Initial capping force $F_{\mathrm{cap},0}$ | cap_force | $15{,}000\ \mathrm{kJ\ mol^{-1}\ nm^{-1}}$ |
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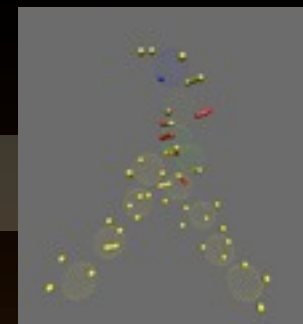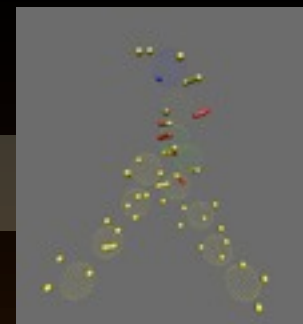| Parameter | mdp-option | Recommended value |
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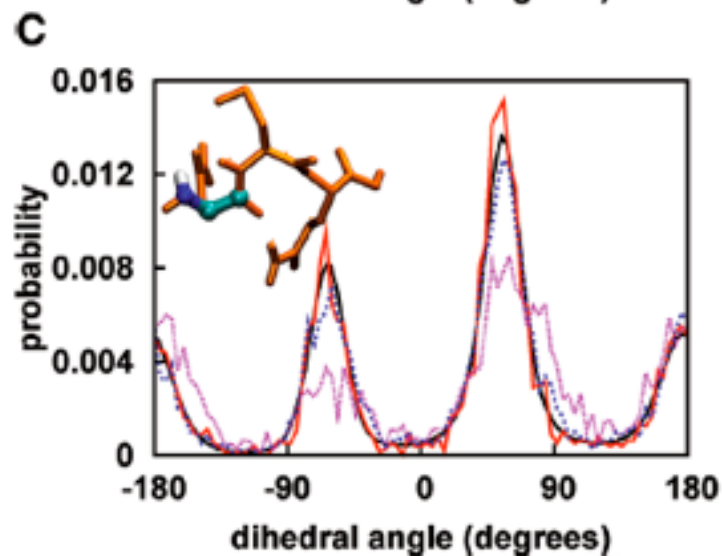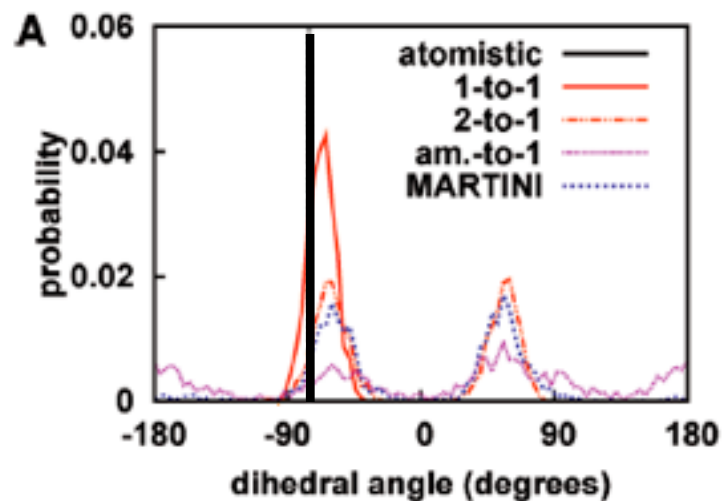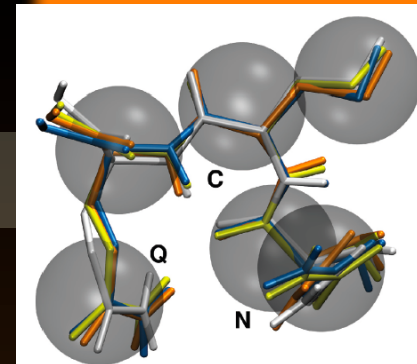| Parameter | mdp-option | Recommended value |
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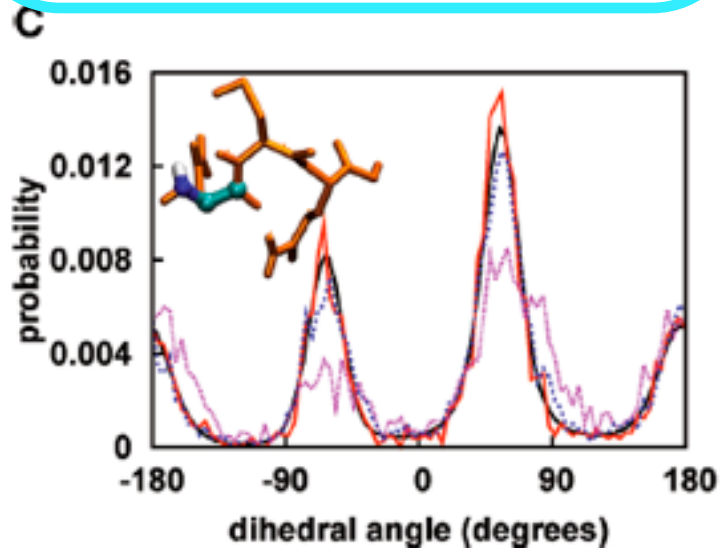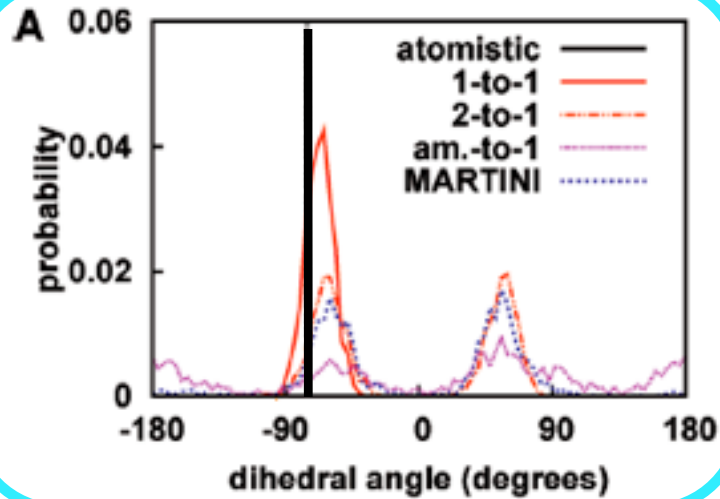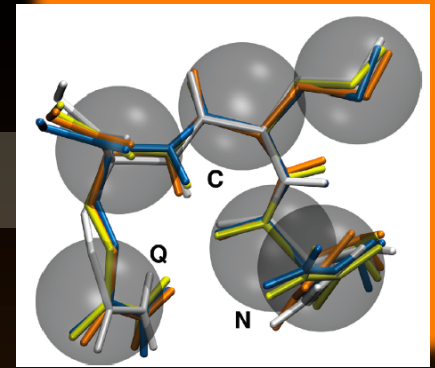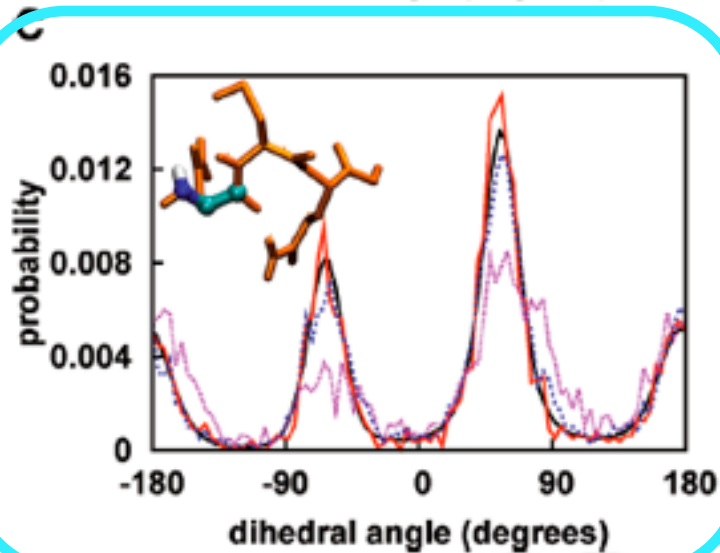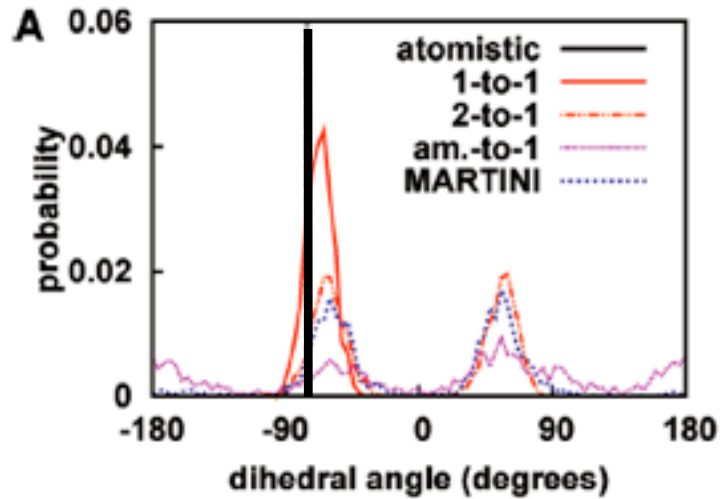| Parameter | mdp-option | Recommended value |
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Testing on small peptide: generation of proper ensemble

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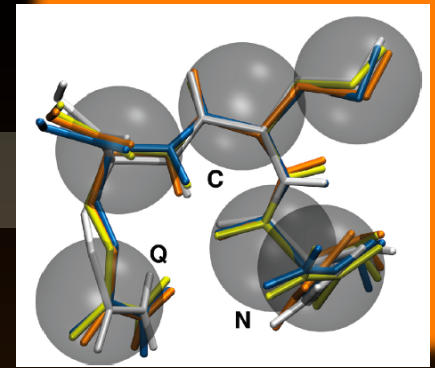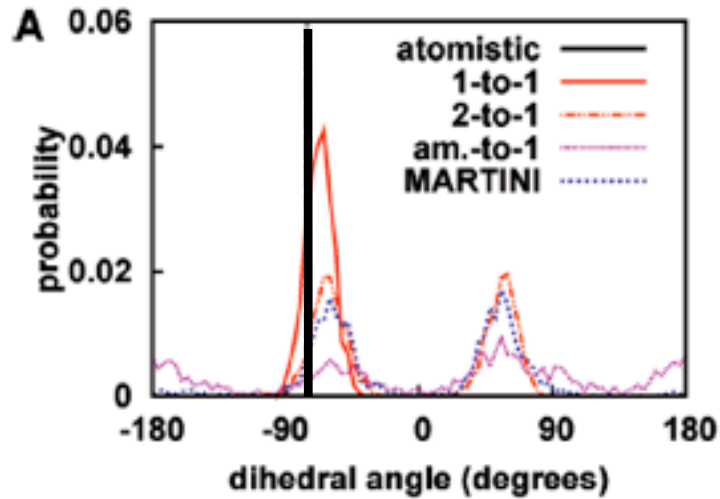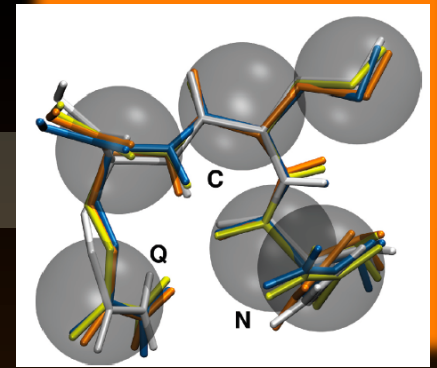
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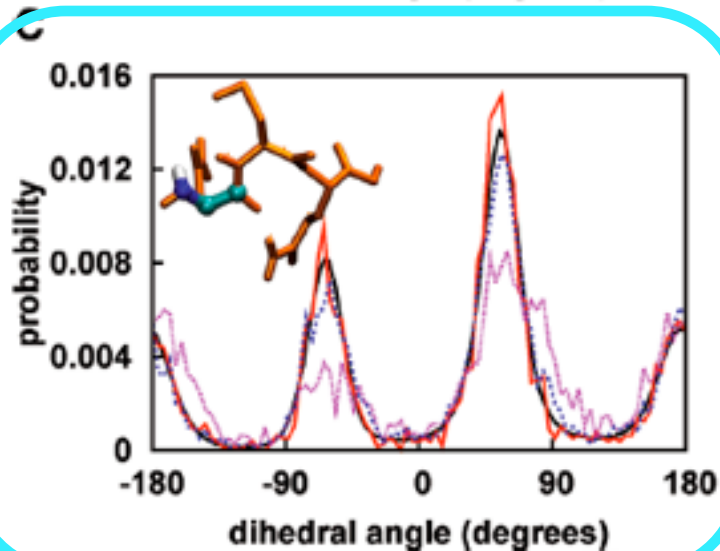Testing on small peptide: generation of proper ensemble

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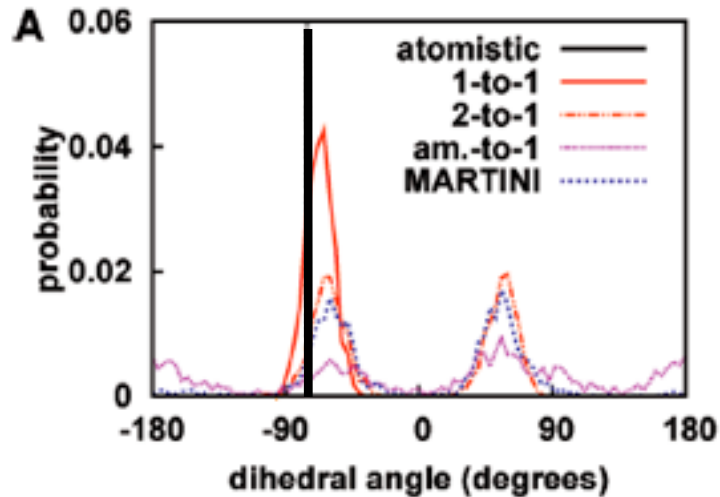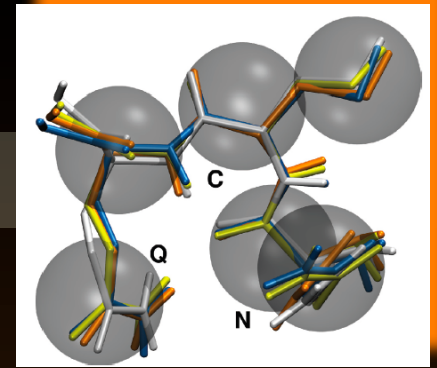




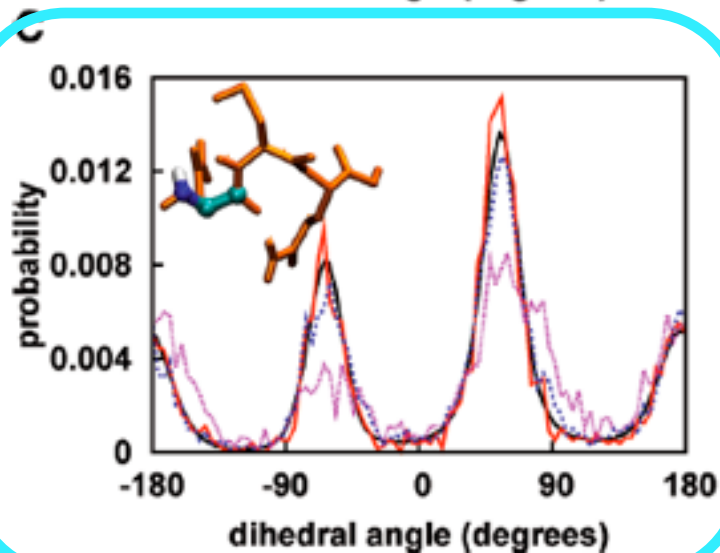Reconstruction algorithm generates proper ensemble !

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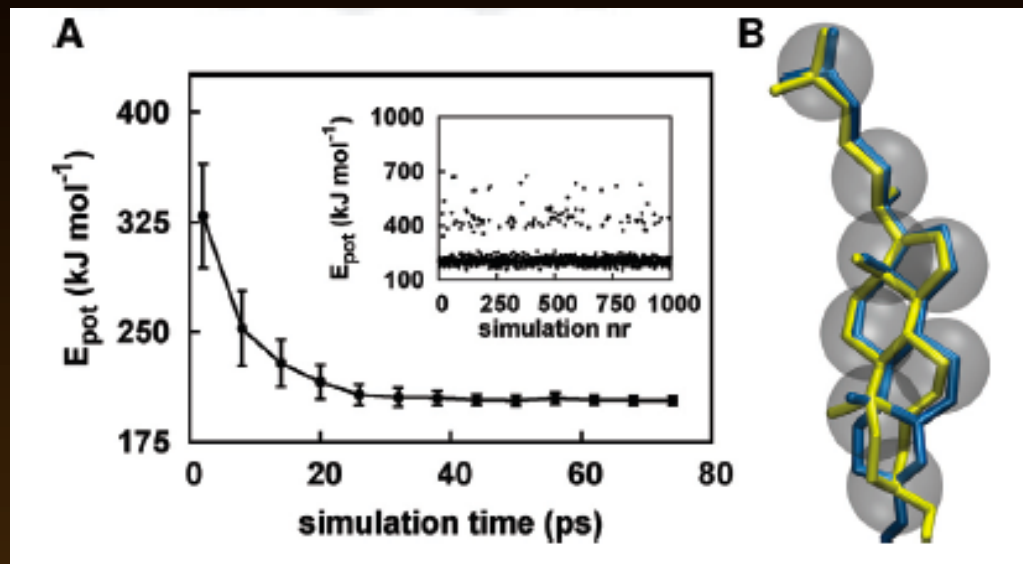


Reconstruction algorithm generates proper ensemble !

Idea: use it to test validity of atomistic forcefield

# Resolution Transformation

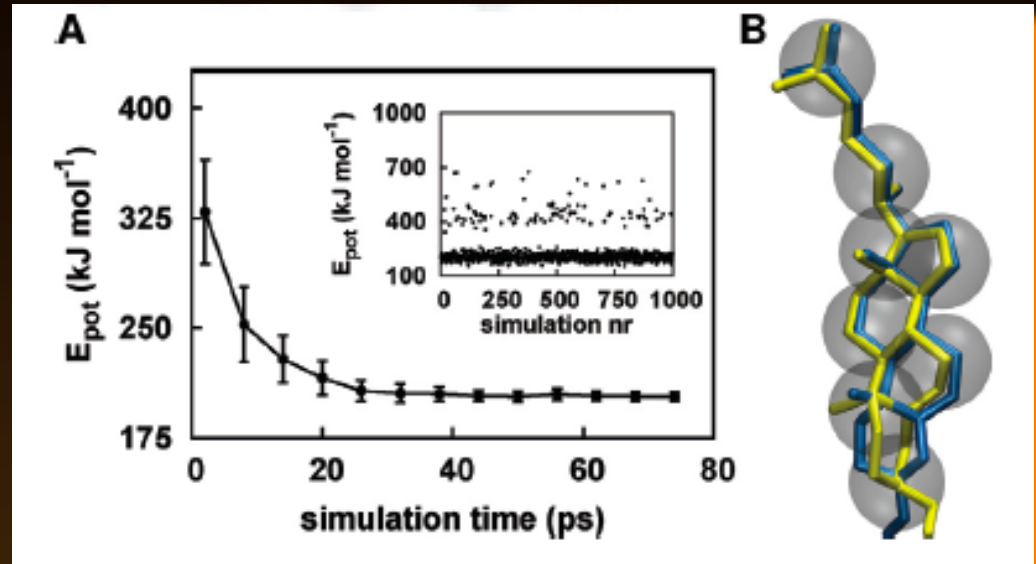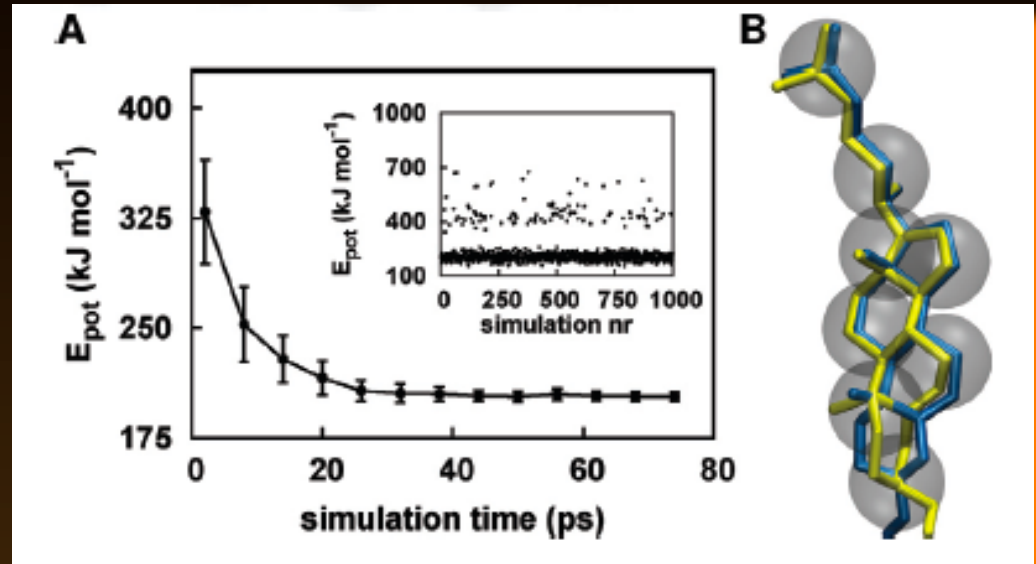Special cases

## Special cases

- Configurations which are high energy but remain trapped
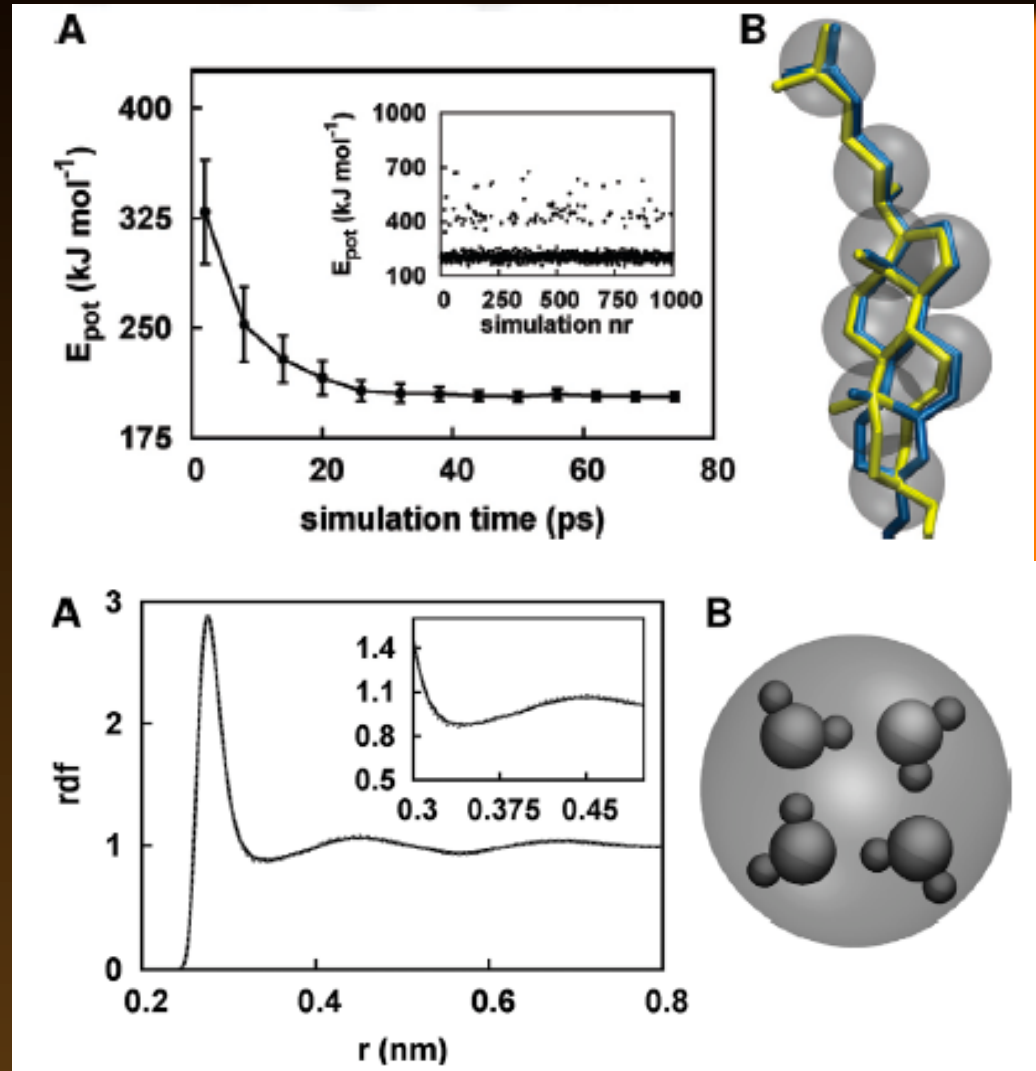
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  >> block certain dihedral angles

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- Multiple molecules mapped to single bead

## Special cases

- Configurations which are high energy but remain trapped

  >> block certain dihedral angles

- Multiple molecules mapped to single bead

  >> add special restraining potential

$$U_j^{\text{restr,W}} = \begin{cases} 0 & \text{for } r_{ij} \leq r_{\text{CGW}} \\ \dfrac{k_{\text{W}}}{2}(r_{ij} - r_{\text{CGW}})^2 & \text{for } r_{ij} > r_{\text{CGW}} \end{cases}$$
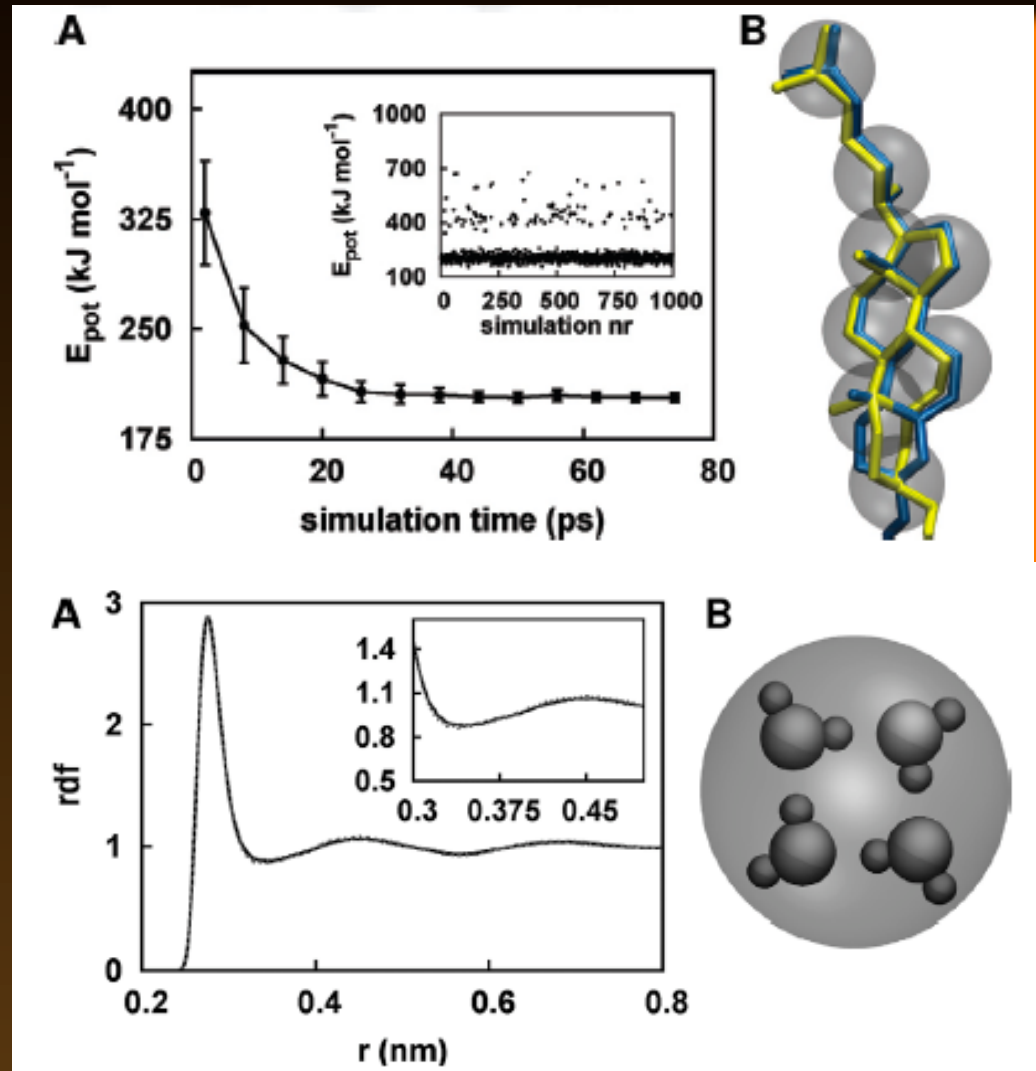
# Resolution Transformation

Application to complex system
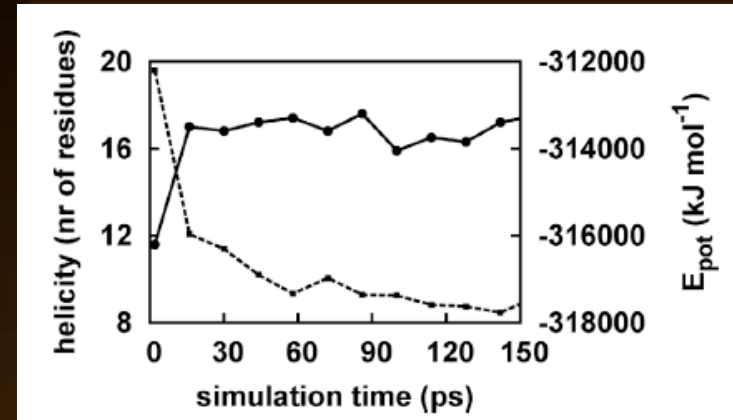
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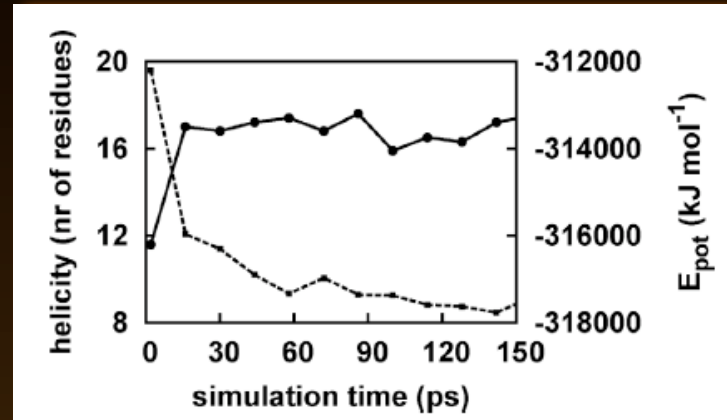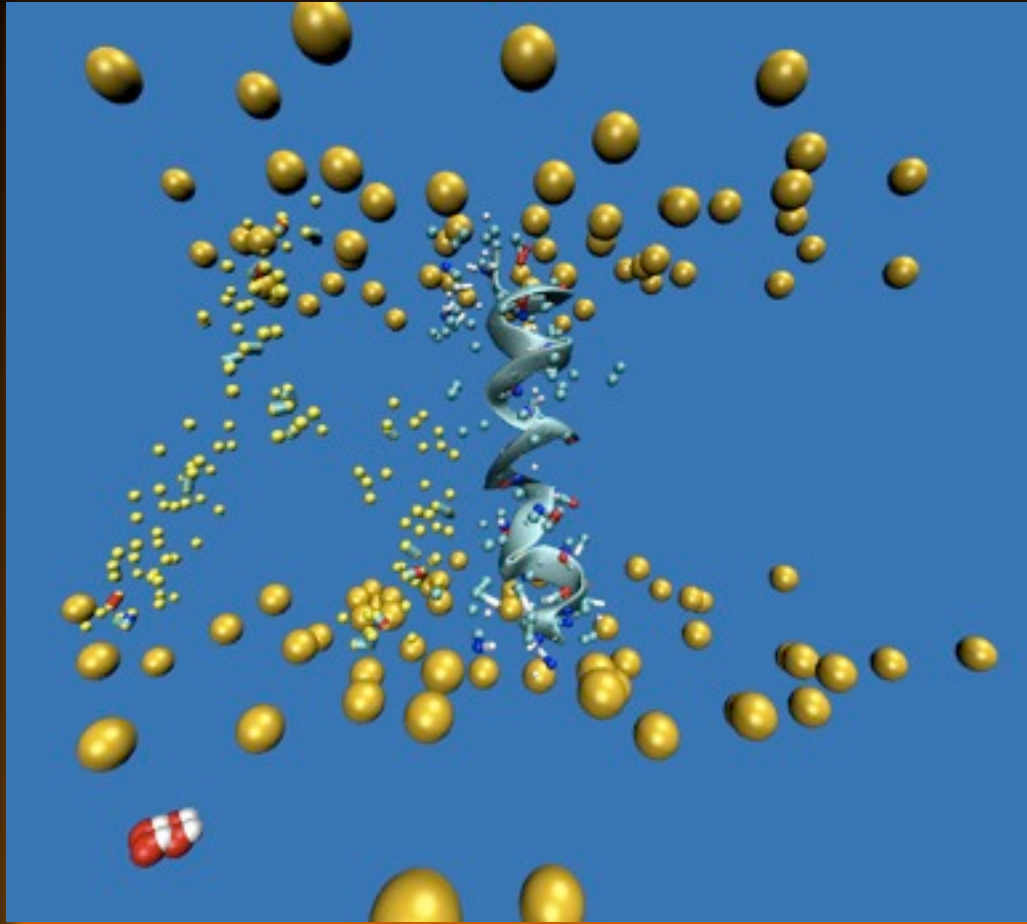
# Spatially Resolved Resolution

Static approach (in progress)

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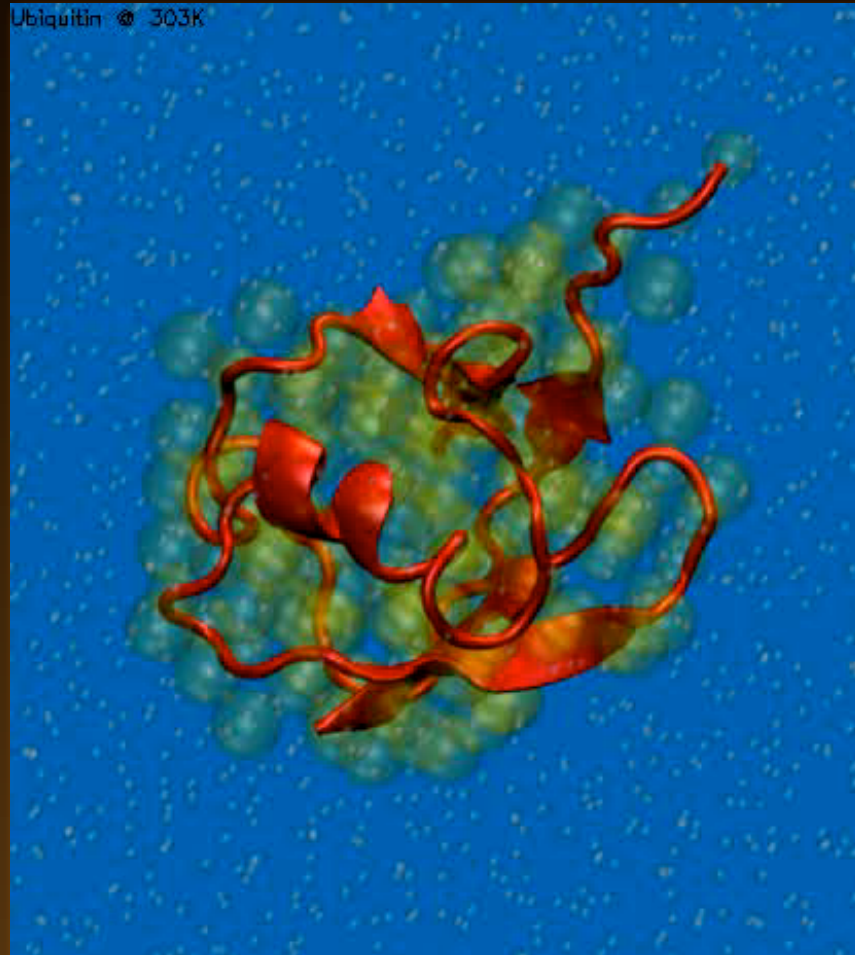


Protein modeled at both
all-atom and coarse-grained level

Solvent coarse-grained only

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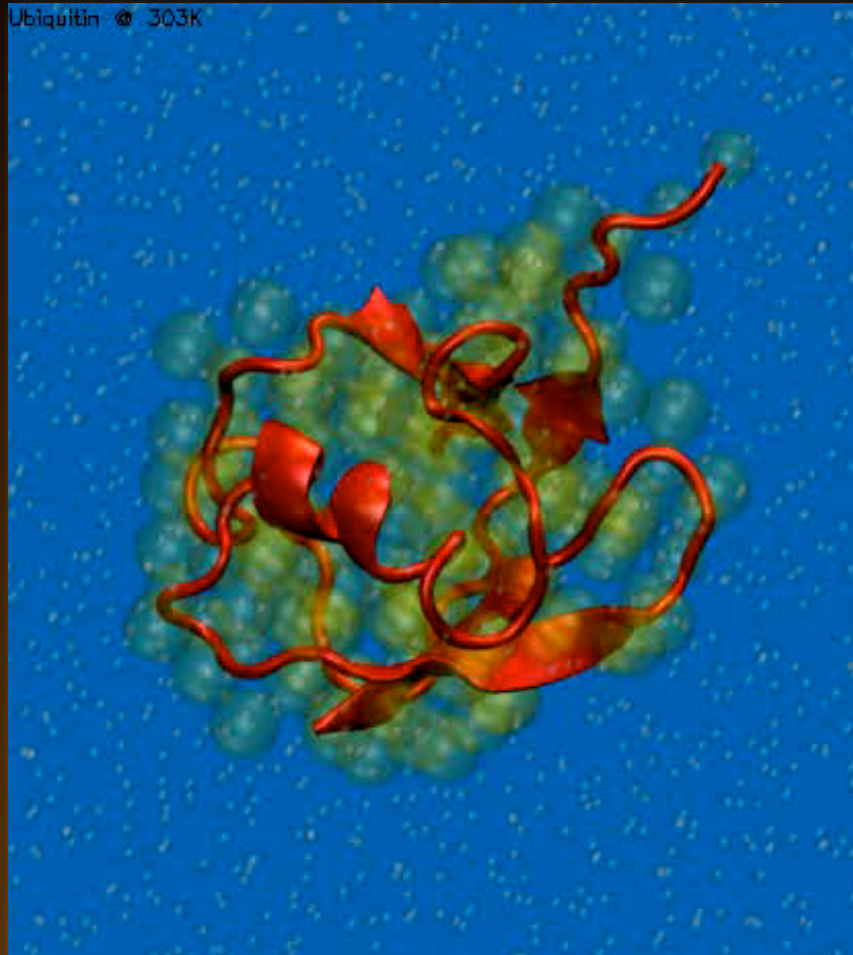
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*Protein-protein: all-atom*

*Solvent-solvent: coarse-grained*

*Protein-solvent: coarse-grained*

# Spatially Resolved Resolution

Static approach (in progress)



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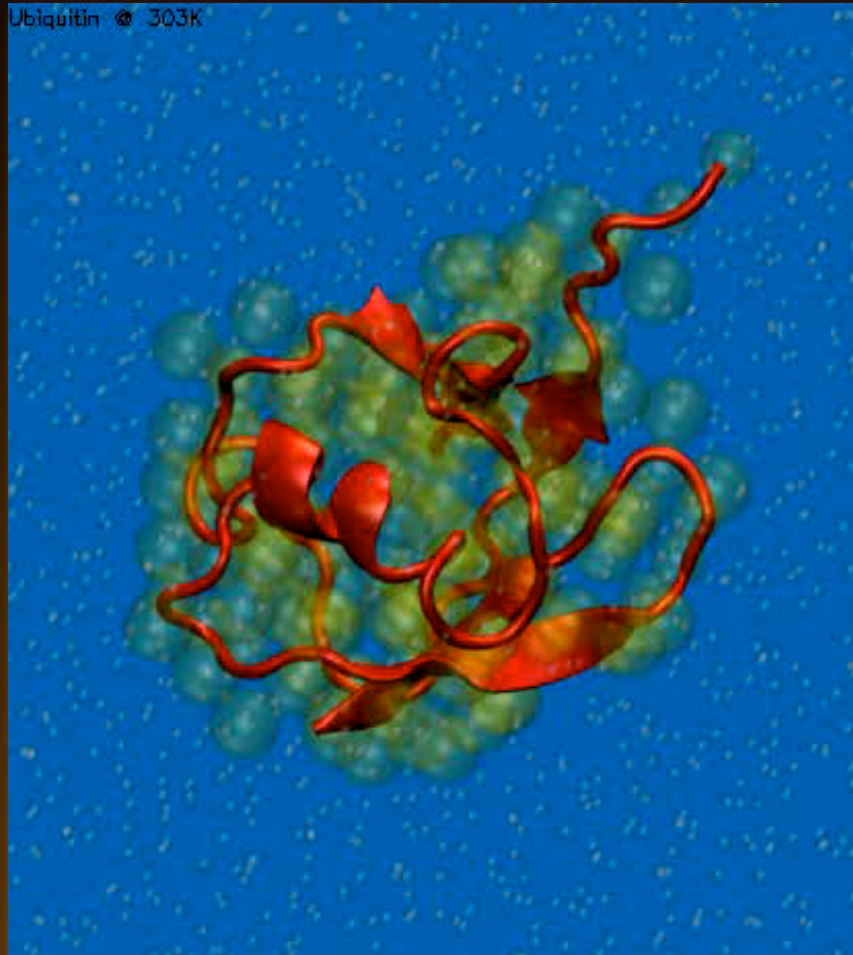*Protein-protein: all-atom*

*Solvent-solvent: coarse-grained*

*Protein-solvent: coarse-grained*

# Polarizable coarse-grained model
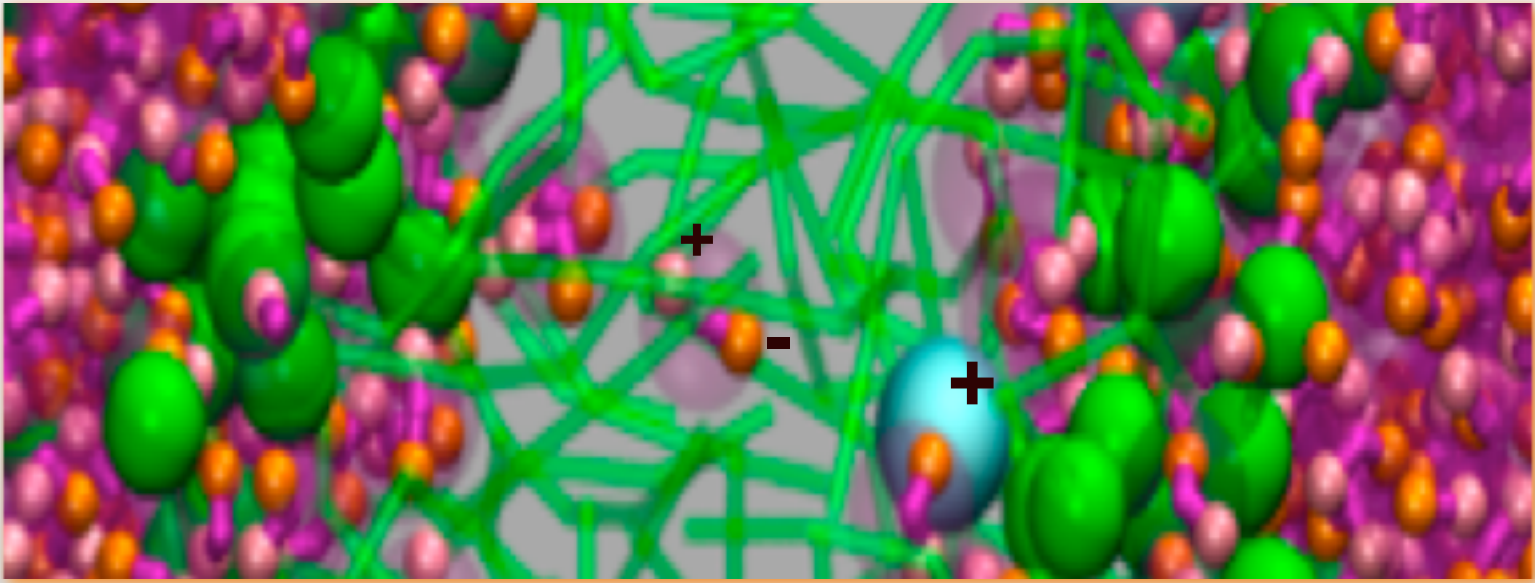
# Polarizable coarse-grained model

Mimicking orientational polarizability for water

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Mimicking orientational polarizability for water

- Water is ubiquitous solvent in biological systems

  → Treatment crucial to properties derived from simulations

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(a)     (b)

WP     $+q$     $\theta$

$K_\theta$     W

$-q$     $l$

WM

**Original MARTINI model**     **new 3-bead MARTINI model**
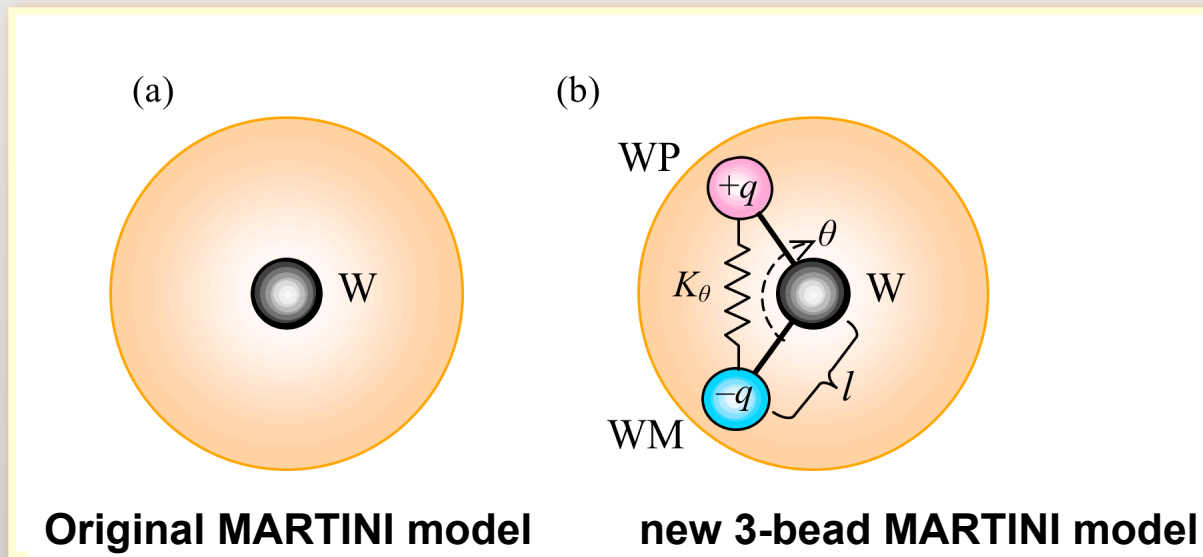
# Polarizable coarse-grained model

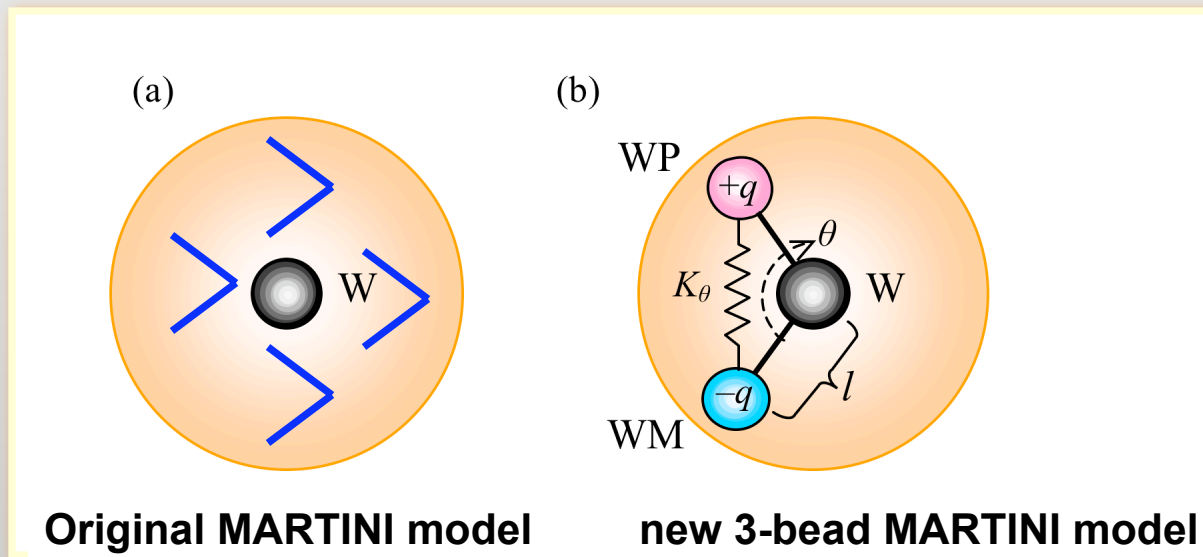Mimicking orientational polarizability for water

- Water is ubiquitous solvent in biological systems

  → Treatment crucial to properties derived from simulations

- Most CG force fields (also MARTINI): water modelled as vdW fluid; no orientational polarizability

  → Potential for improvements



(a)    (b)

WP

$+q$

$\theta$

$K_\theta$    W

$-q$

$l$

WM

**Original MARTINI model**    **new 3-bead MARTINI model**

# Polarizable coarse-grained model

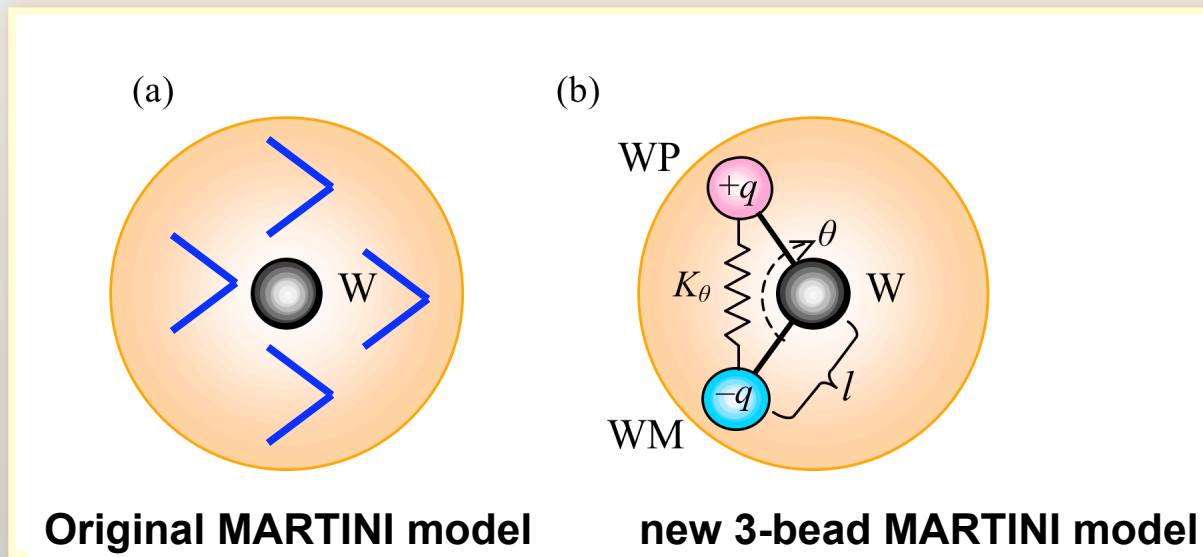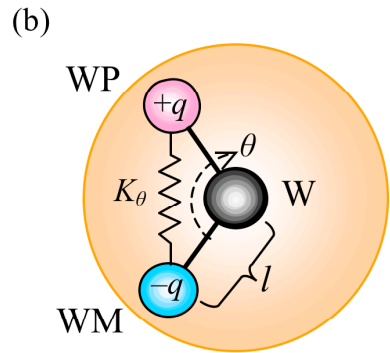Mimicking orientational polarizability for water

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# Polarizable coarse-grained model

Parameterization



(b)

WP

$+q$

$\theta$

$K_\theta$

W

$-q$

$l$

WM

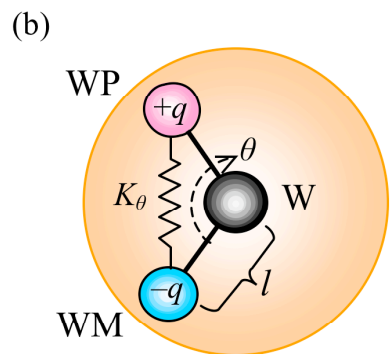Criteria for parametrization:

- Density close to that of  real water
- Dielectric constant $e$ close to 78 at 300 K
- Same partitioning $\Delta G$'s as standard MARTINI

# Polarizable coarse-grained model

Parameterization



(b)

WP

$+q$

$K_\theta$    $\theta$

W

$-q$    $l$

WM



(a)

dielectric constant $\varepsilon$

(b)

volume $F$

virtual charge $q$

Criteria for parametrization:

- Density close to that of real water
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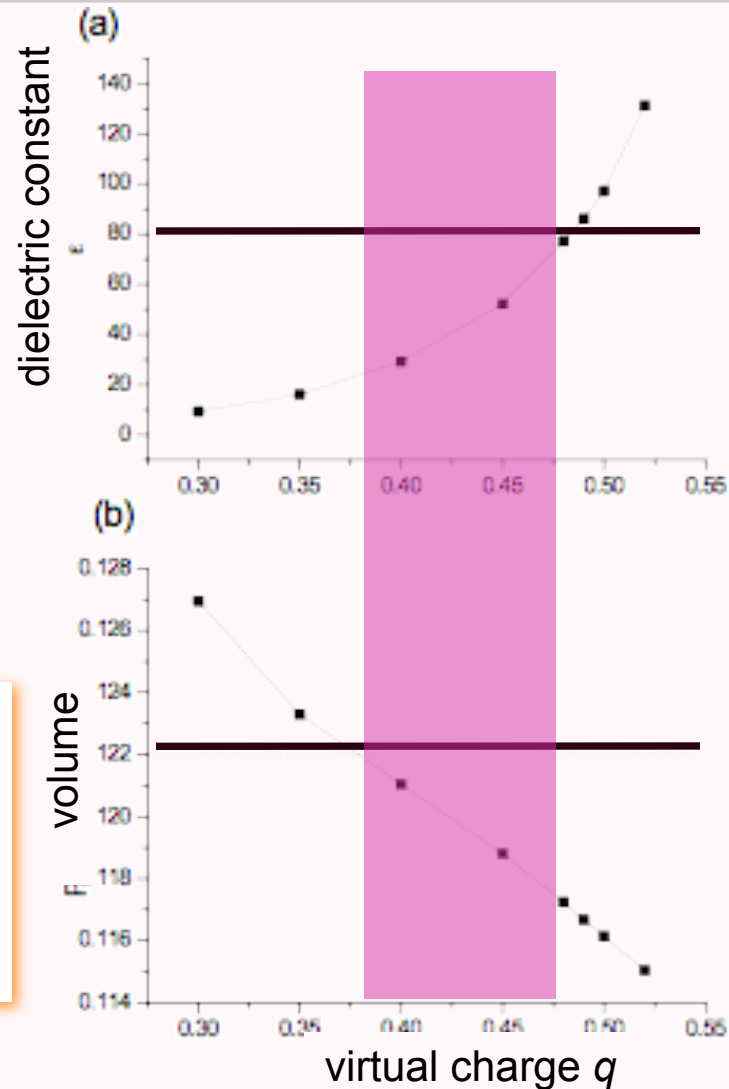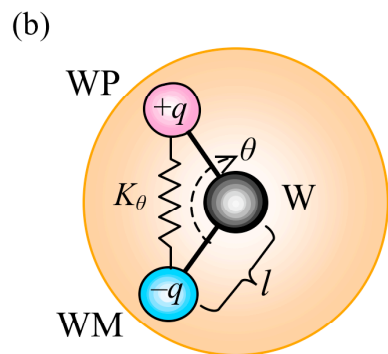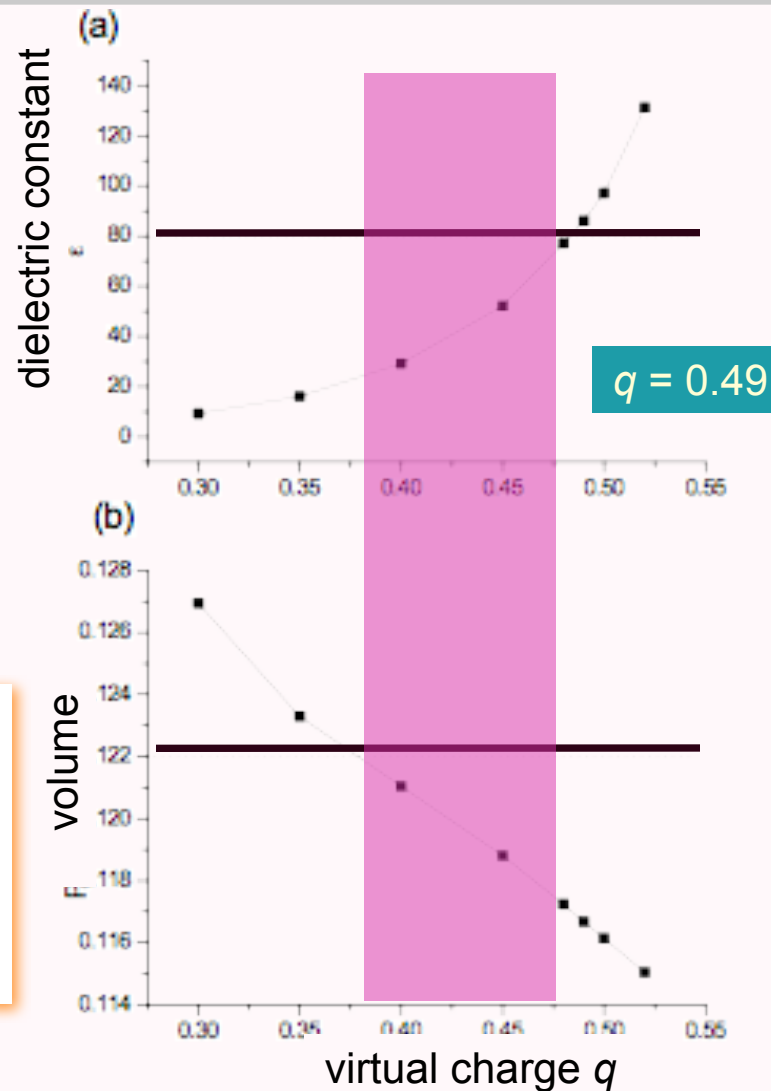- Same partitioning $\Delta G$'s as standard MARTINI

# Polarizable coarse-grained model

## Parameterization



Criteria for parametrization:
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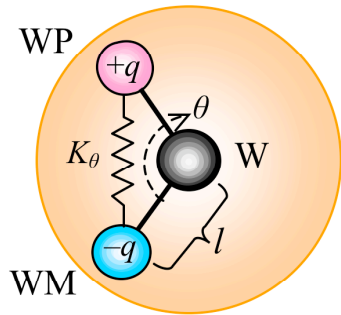- Same partitioning $\Delta G$'s as standard MARTINI
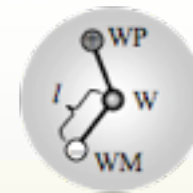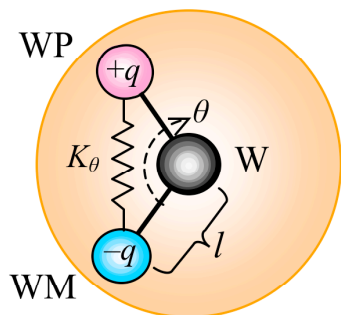
# Polarizable coarse-grained model

## Parameters & Properties

(b)

WP

$+q$

$\theta$

$K_\theta$

W

$-q$

$l$

WM

- Computational cost: ca. factor 3
- Shifted cut-off & PME

S Yesylevskyy, LV Schäfer, D Sengupta, SJ Marrink, in preparation

# Polarizable coarse-grained model

## Parameters & Properties



(b)

- Computational cost: ca. factor 3

- Shifted cut-off & PME

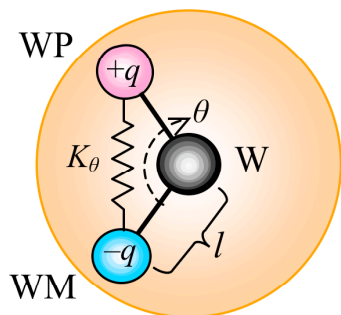| Parameters | | Properties[a] | |
|---|---|---|---|
| charge WP,WM | $q = \pm 0.46$ | density | 1043 kg m$^{-3}$ |
| bond W-WP, W-WM | $l = 0.14$ nm | dielectric constant | 75.6 |
| angle WP-W-WM | $\theta = 0$ rad | dipole moment | 4.9 D |
| | $K_\theta = 4.2$ kJ mol$^{-1}$ rad$^{-2}$ | self diffusion | 2.45 10$^{-5}$ cm$^2$ s$^{-1}$ |
| LJ$_{W-W}$ | $\varepsilon = 4.0$ kJ mol$^{-1}$ | hydration free energy | -18.7 kJ mol$^{-1}$ |
| | $\sigma = 0.47$ nm | freezing temperature | $282 \pm 3$ K |
| relative screening | $\varepsilon_{rel} = 2.5$ | | |

S Yesylevskyy, LV Schäfer, D Sengupta, SJ Marrink, in preparation

# Polarizable coarse-grained model

## Parameters & Properties



- Computational cost: ca. factor 3
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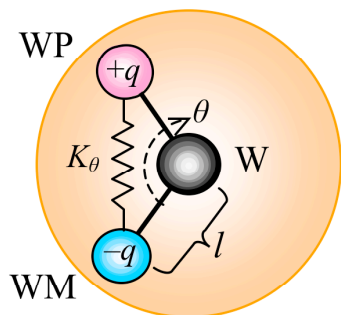| Parameters | | Properties[a] | |
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# Polarizable coarse-grained model

## Parameters & Properties

(b)

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S Yesylevskyy, LV Schäfer, D Sengupta, SJ Marrink, in preparation
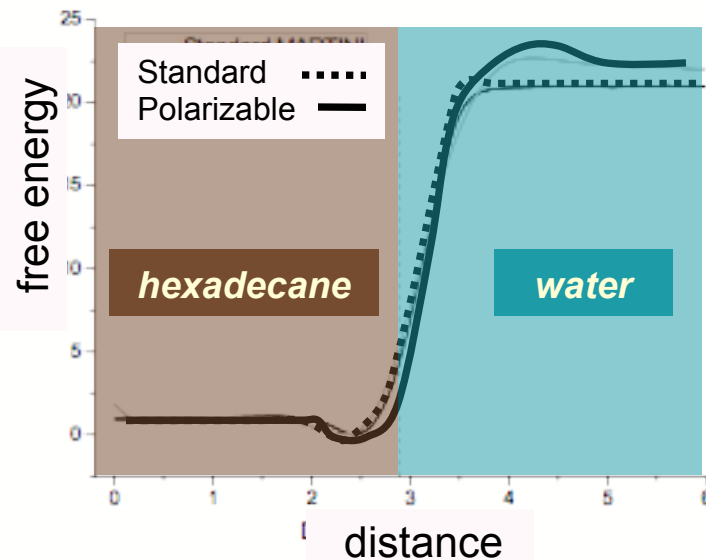
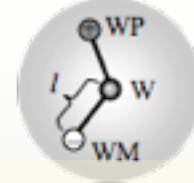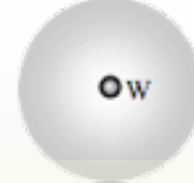# Polarizable coarse-grained model

Testing
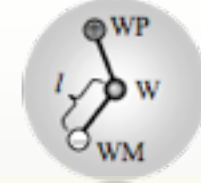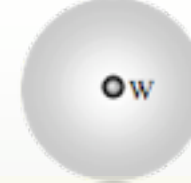


Density profile DPPC membrane
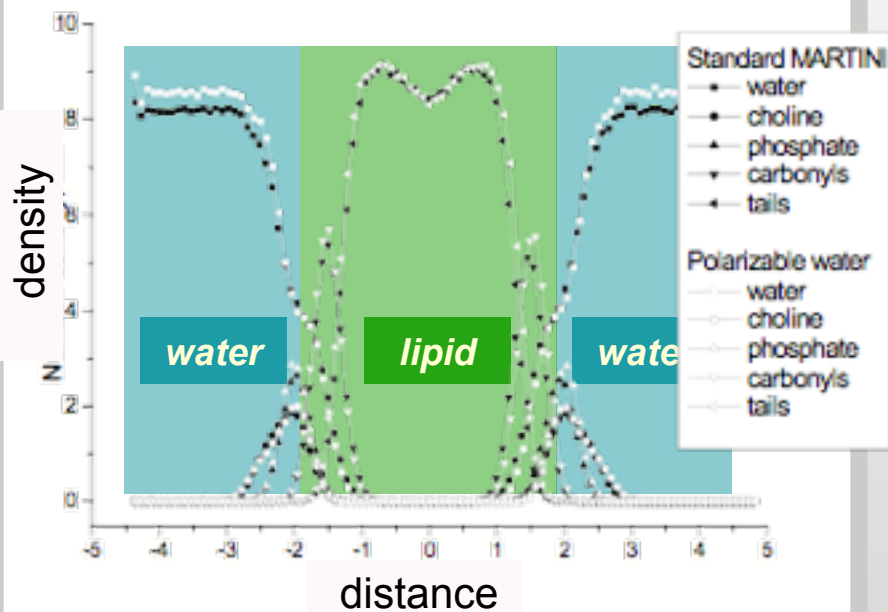
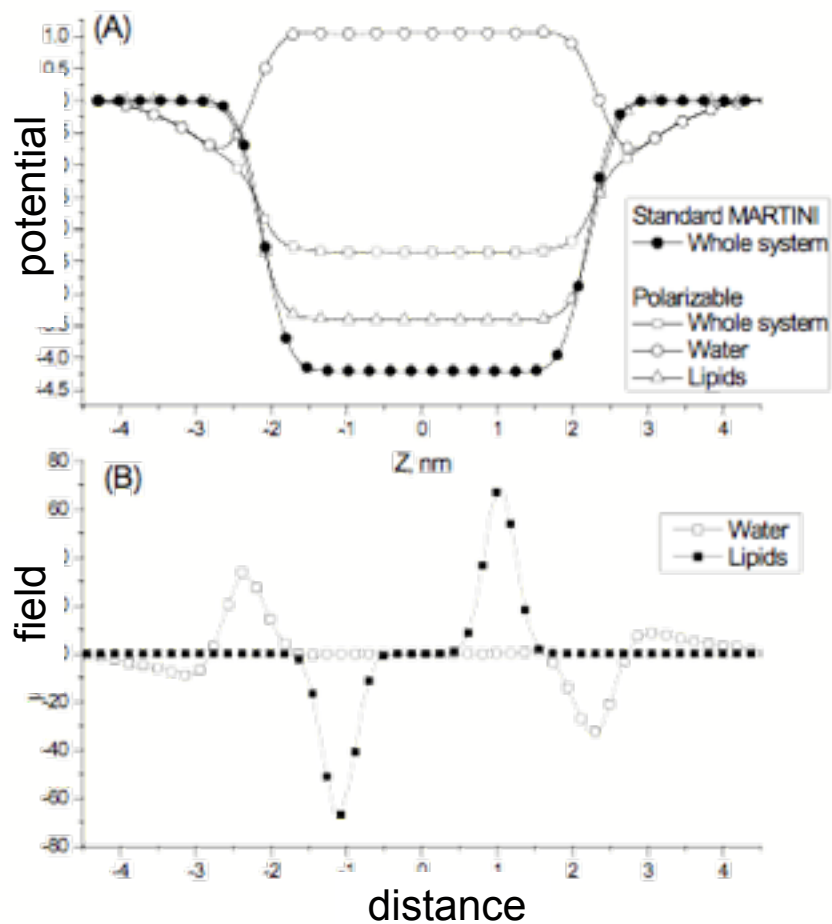Partitioning free energy of butane

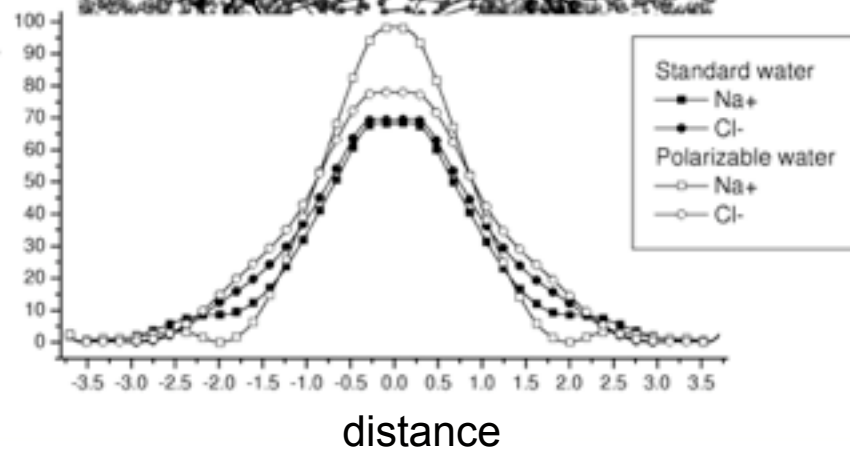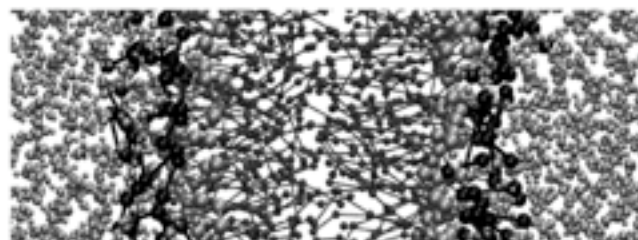# Polarizable coarse-grained model

Improved electrostatic response



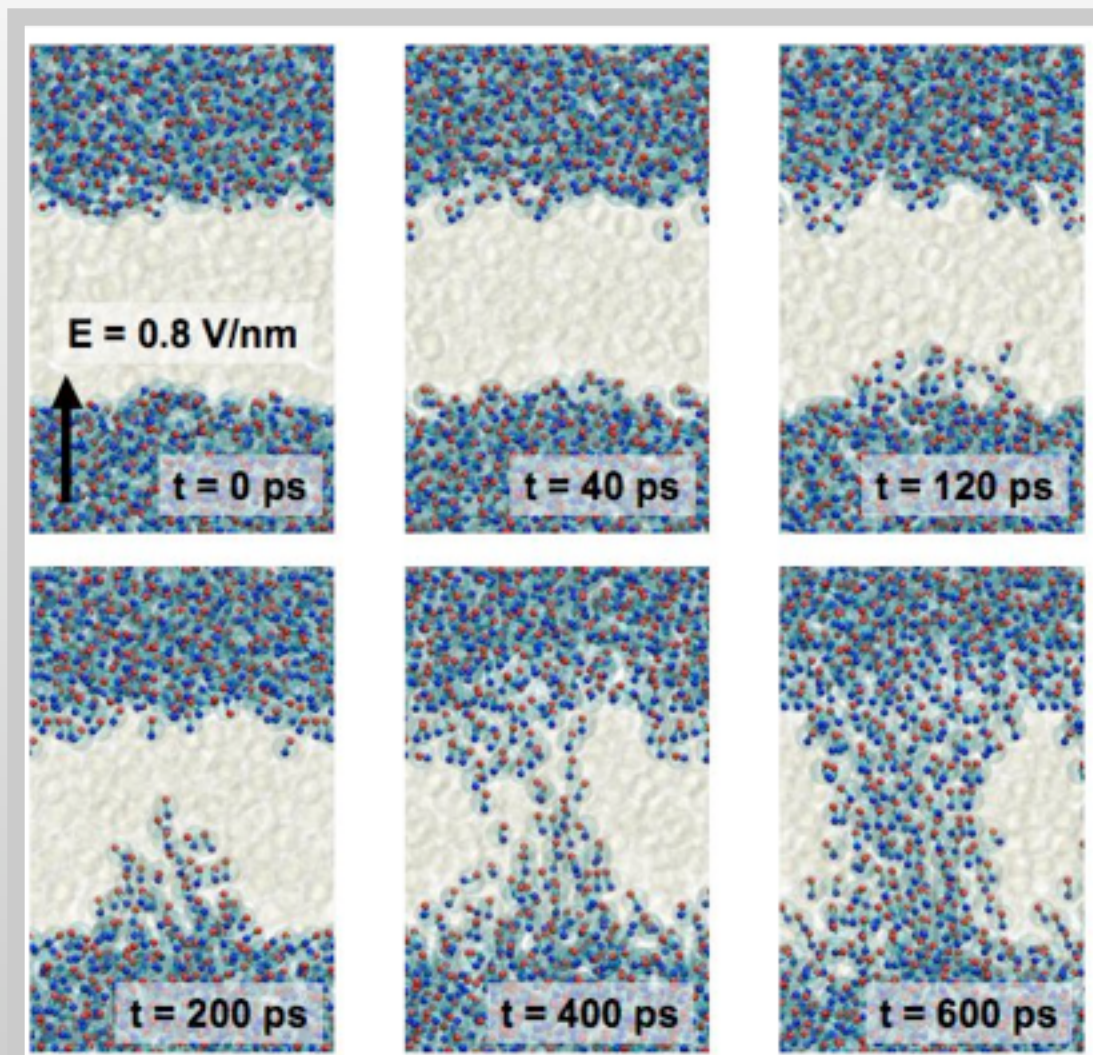**Electrostatic potential & field across DPPC membrane**

**Ion PMF across DPPC membrane**

# Polarizable coarse-grained model

Electroporation of an octane slab



E = 0.8 V/nm

t = 0 ps

t = 40 ps

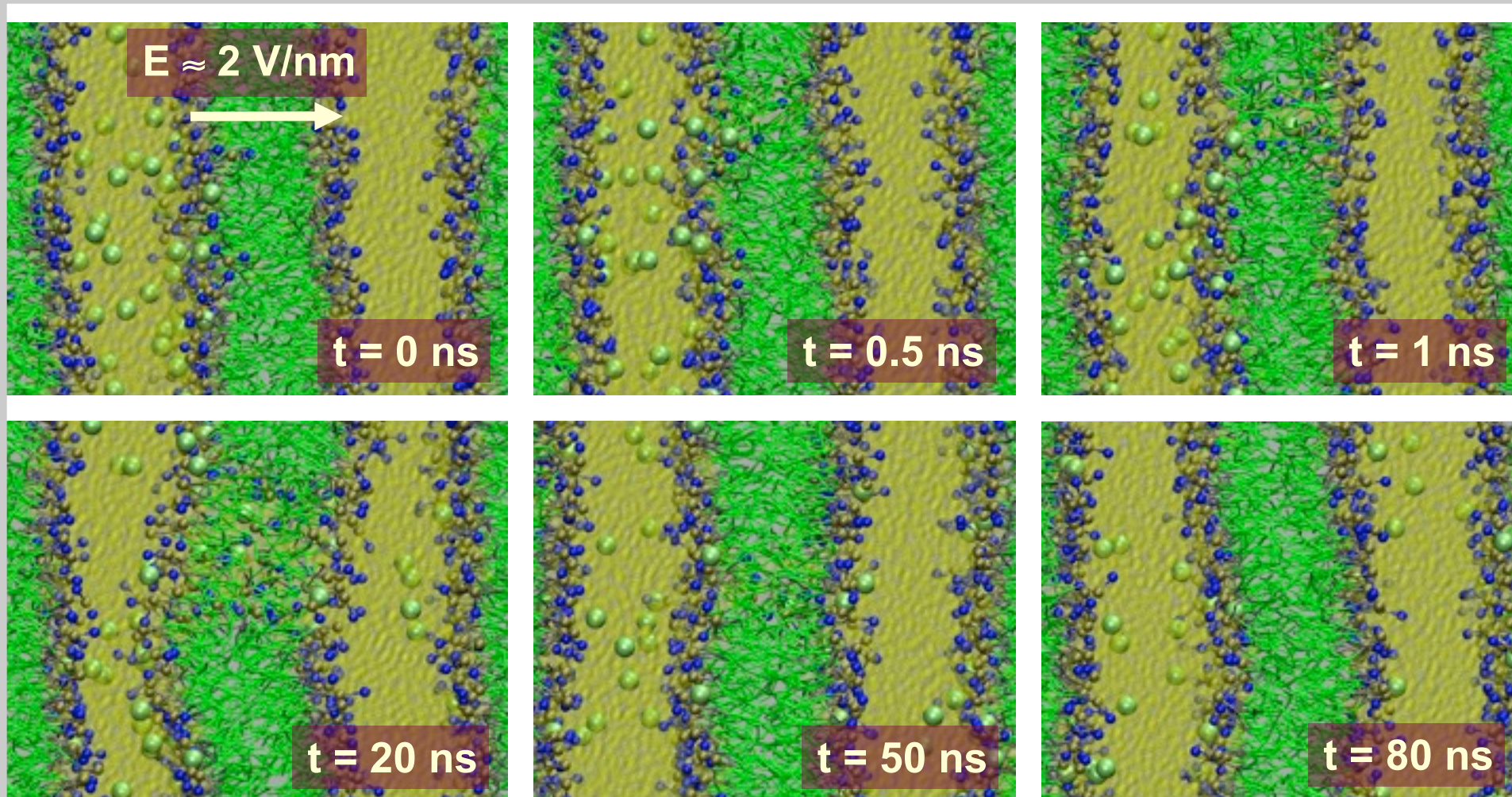t = 120 ps

t = 200 ps

t = 400 ps

t = 600 ps
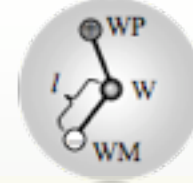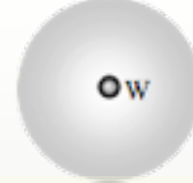
**(similar to atomistic simulations by Tieleman)**

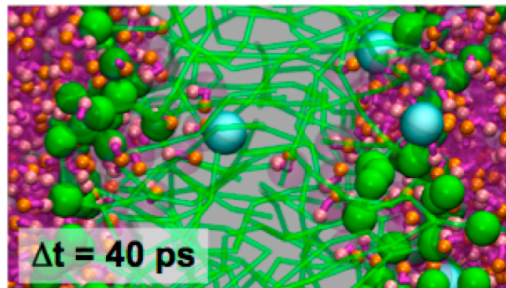# Polarizable coarse-grained model

Electroporation of a lipid membrane by charge imbalance
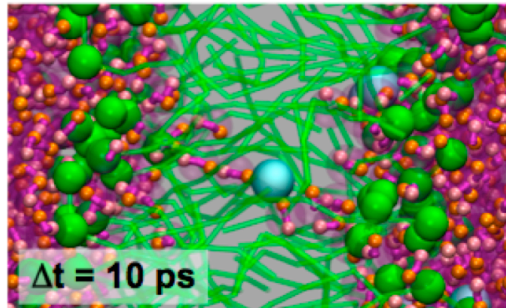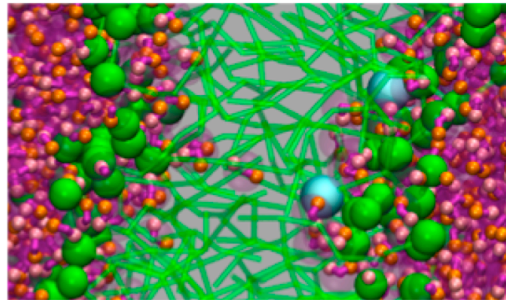
(very similar to atomistic work by the group of Vattulainen)

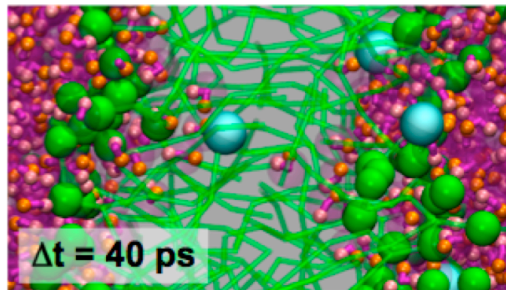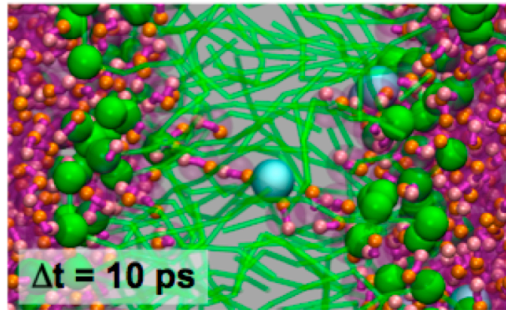# Polarizable coarse-grained model

Electroporation of a lipid membrane by charge imbalance

# Polarizable coarse-grained model

Electroporation of a lipid membrane by charge imbalance



Δt = 10 ps

Δt = 40 ps
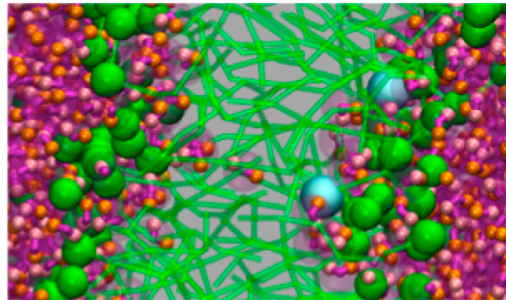
At lower field strengths: ion leakage through 'water finger'

# Polarizable coarse-grained model
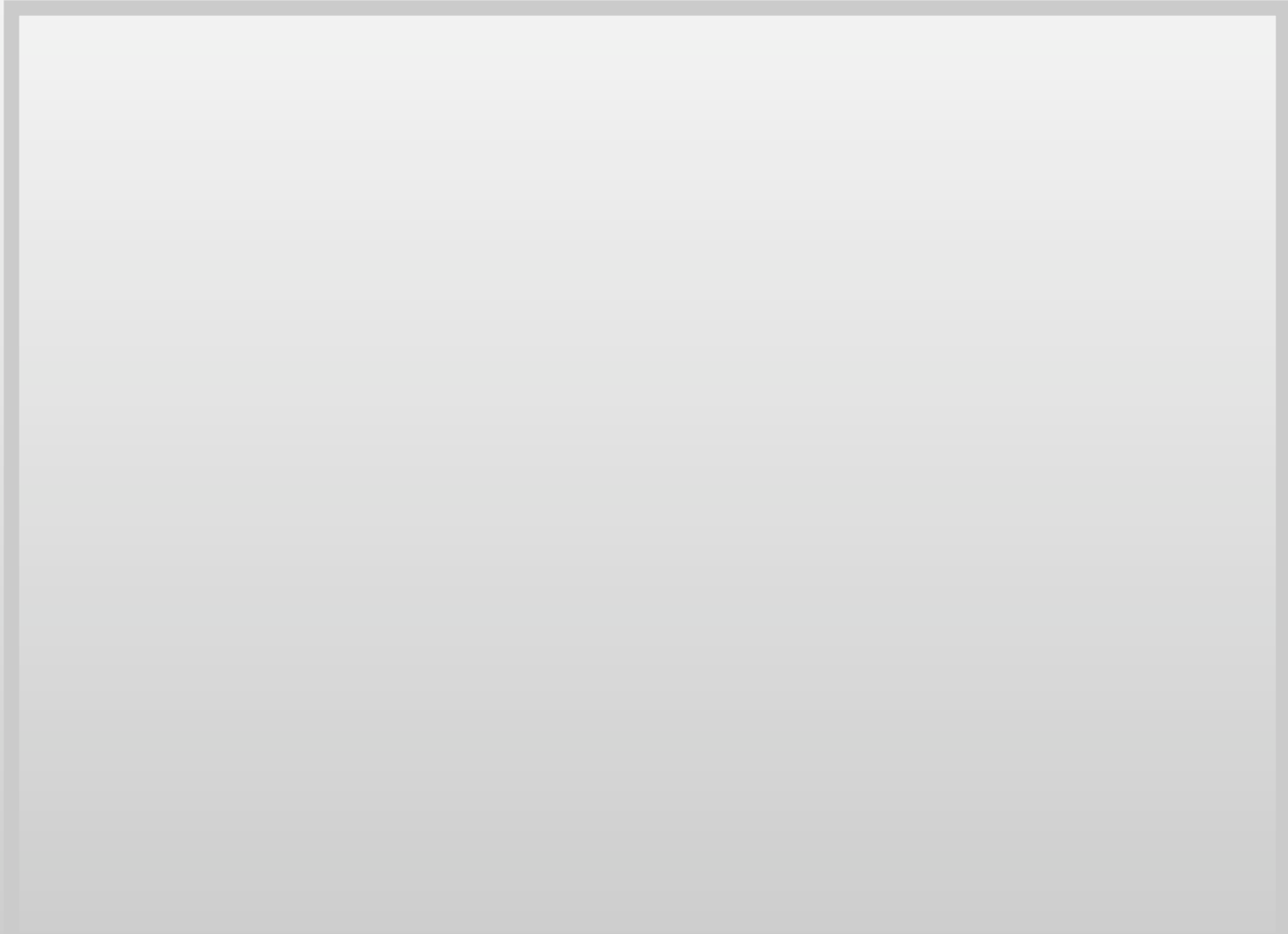
Advantages & Drawbacks

**Electroporation - Electrofusion ....**

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**Voltage gated channels - Antimicrobial peptides**

# Polarizable coarse-grained model

Advantages & Drawbacks

**More realistic screening in inhomogeneous systems**

**Electroporation - Electrofusion ....**

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**Factor 3 slower**

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**Water/vapor surface tension only marginally improved**

# Polarizable coarse-grained model

Advantages & Drawbacks

**More realistic screening in inhomogeneous systems**

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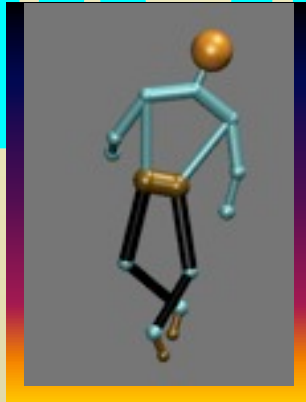
**Voltage gated channels - Antimicrobial peptides**

**Factor 3 slower**

**Water/vapor surface tension only marginally improved**

**Not well tested (yet)**

# MARTINI
## 2010-2014



**Complete lipid database**
*(SM, PS, PG, glycolipids ...)*

**Softer potentials** *(LJ 9-6)*

**Multiscaling**
*(Hamiltonian exchange,
hybrid simulations*)

**Nucleotides** *(DNA, RNA)*

**Polarizable Martini**

**Secondary structure changes**