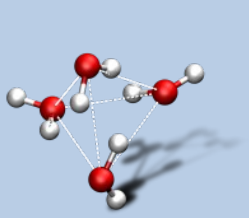
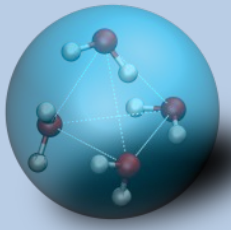
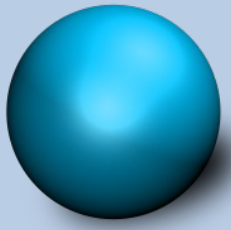




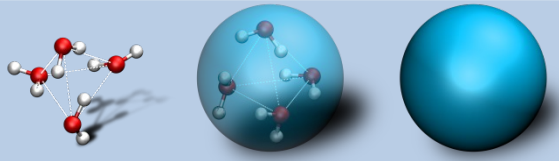
Open Boundary Molecular Dynamics of a DNA molecule in a hybrid explicit/implicit salt solution

Matej Praprotnik

CIRM, Marseille, France

September 17 - 21, 2018

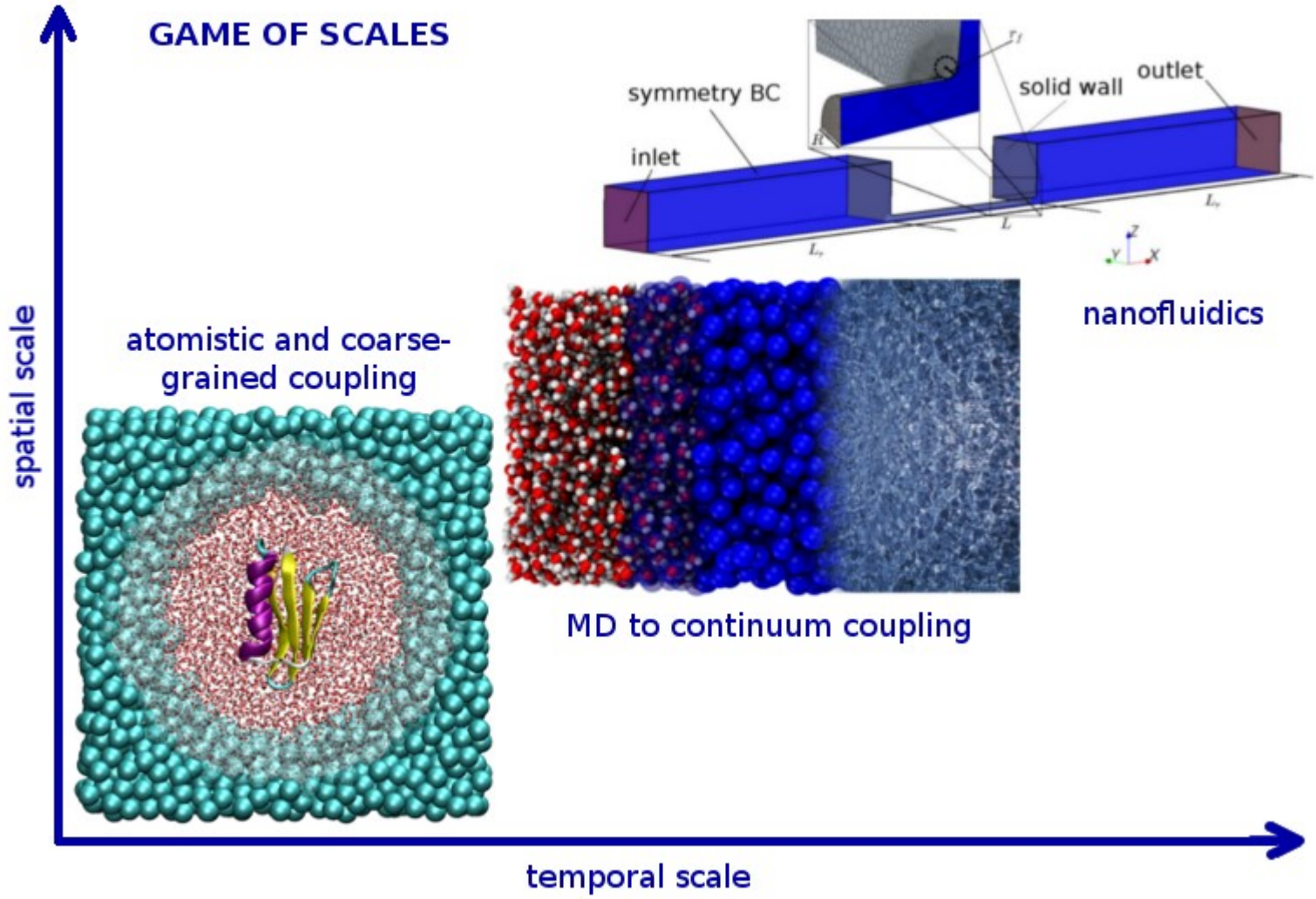
NATIONAL INSTITUTE OF CHEMISTRY



Outline

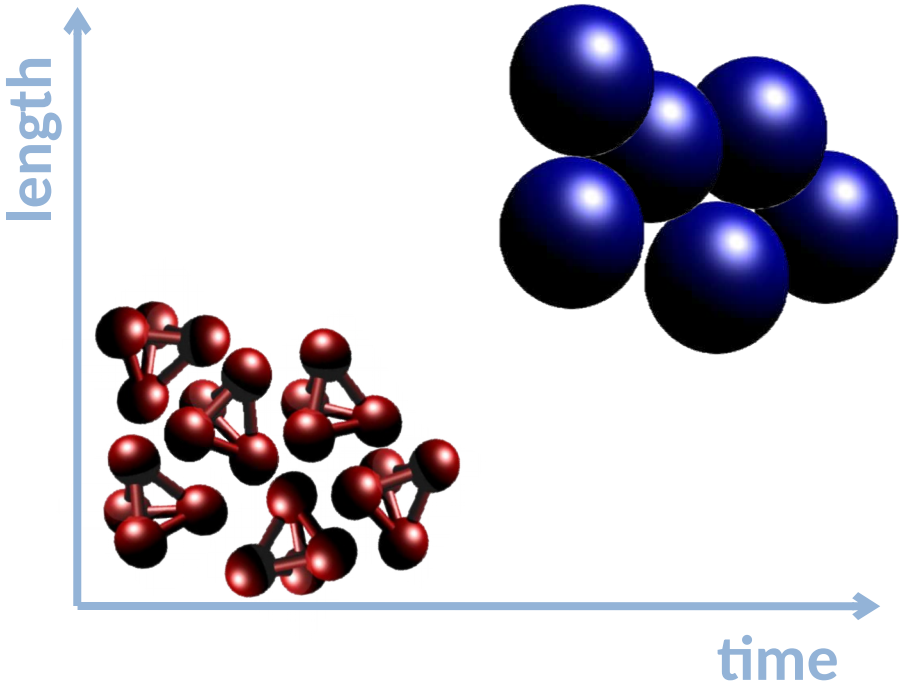
- multiscale simulations:
  1. Adaptive Resolution Scheme (AdResS)
  2. coupling to supramolecular coarse-grained models
  3. Open Boundary Molecular Dynamics (OBMD)
- biomolecular applications:
  1. DNA molecule in salt solution
  2. columnar phases of DNA
  3. OBMD of a DNA molecule

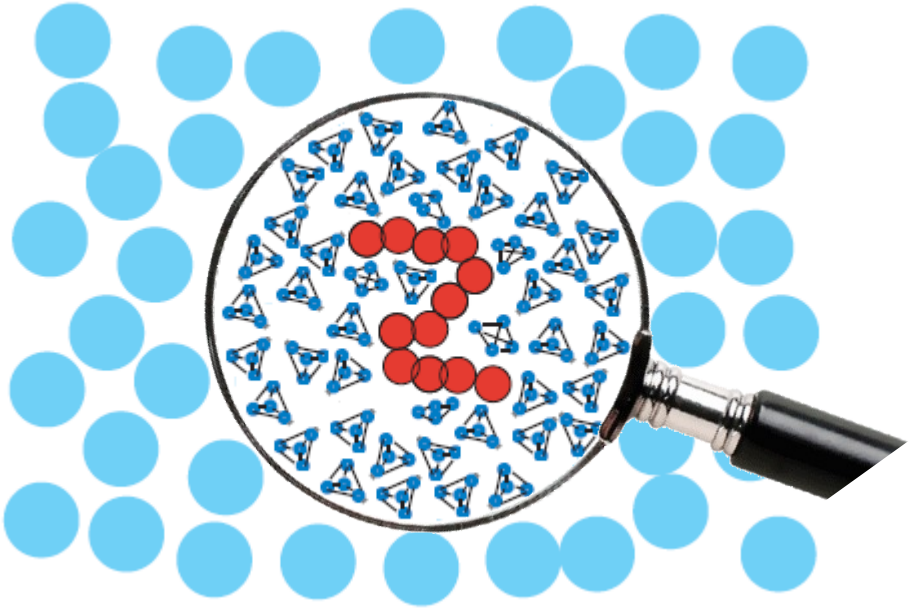
Multiscale modeling & simulation



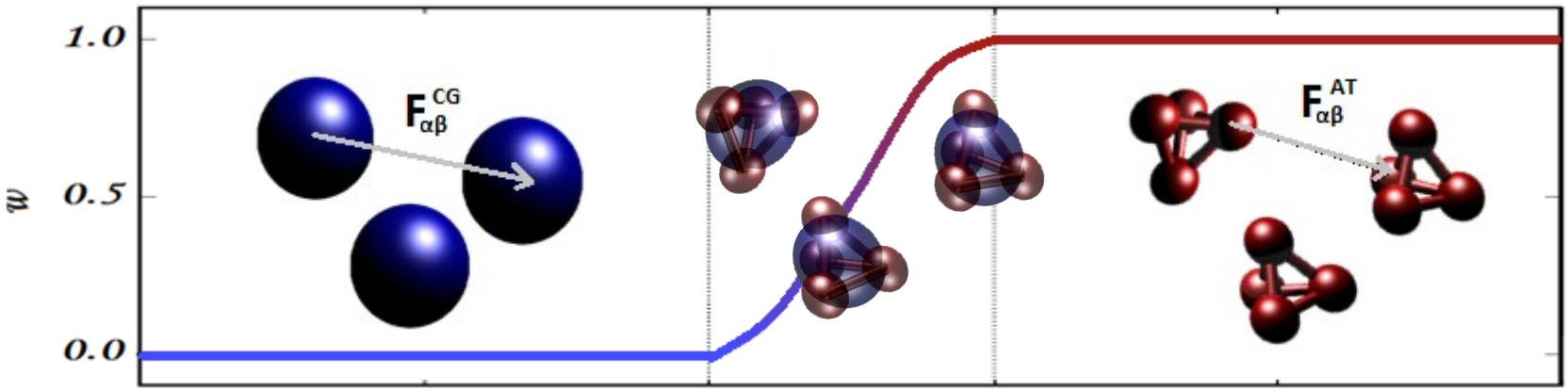
Multiscale simulation

- atomistic simulation
  - large length and time scales are difficult to capture
- coarse-grain simulation
  - atomistic details are lost
- multiscale simulation





Adaptive Resolution Scheme (AdResS)



coarse-grained (CG) hybrid (HY) atomistic (AT) region

- force between particle α and β:

$$\boldsymbol{F}_{\alpha}^{AdResS} = \sum_{\beta \neq \alpha} w(|\boldsymbol{R}_{\alpha} - \boldsymbol{R}|)\, w(|\boldsymbol{R}_{\beta} - \boldsymbol{R}|)\, \boldsymbol{F}_{\alpha\beta}^{AT} + \sum_{\beta \neq \alpha} [1 - w(|\boldsymbol{R}_{\alpha} - \boldsymbol{R}|)\, w(|\boldsymbol{R}_{\beta} - \boldsymbol{R}|)]\, \boldsymbol{F}_{\alpha\beta}^{CG} - \boldsymbol{F}_{\alpha}^{TD}(|\boldsymbol{R}_{\alpha} - \boldsymbol{R}|)$$

$w(r)$... position dependent weighting function

- above force coupling scheme obeys Newton's third law

Praprotnik, Delle Site, Kremer; Annu. Rev. Phys. Chem. (2008)

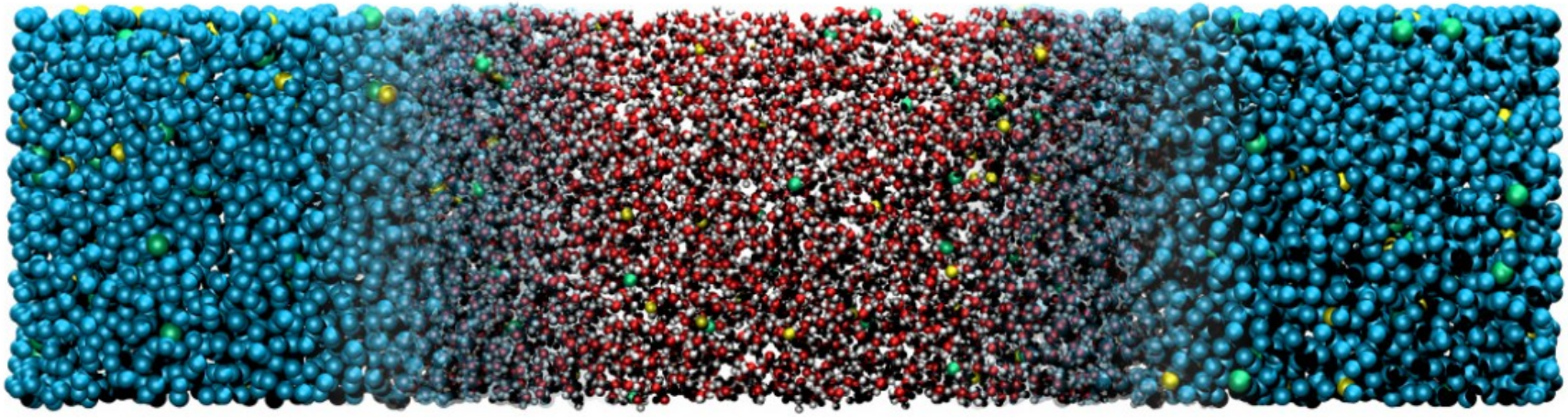
Multiscale 1M NaCl salt solution

- atomistic force field:

  TIP3P + Amber 03

- coarse-grained force field:

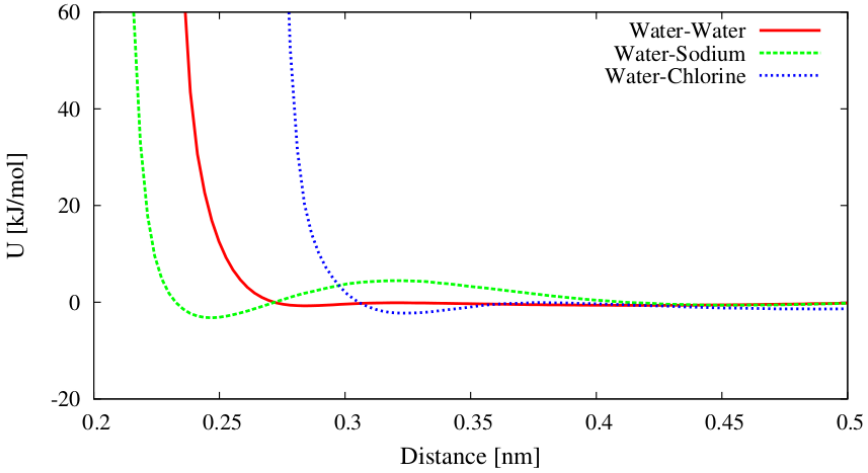
  derived with Boltzmann inversion

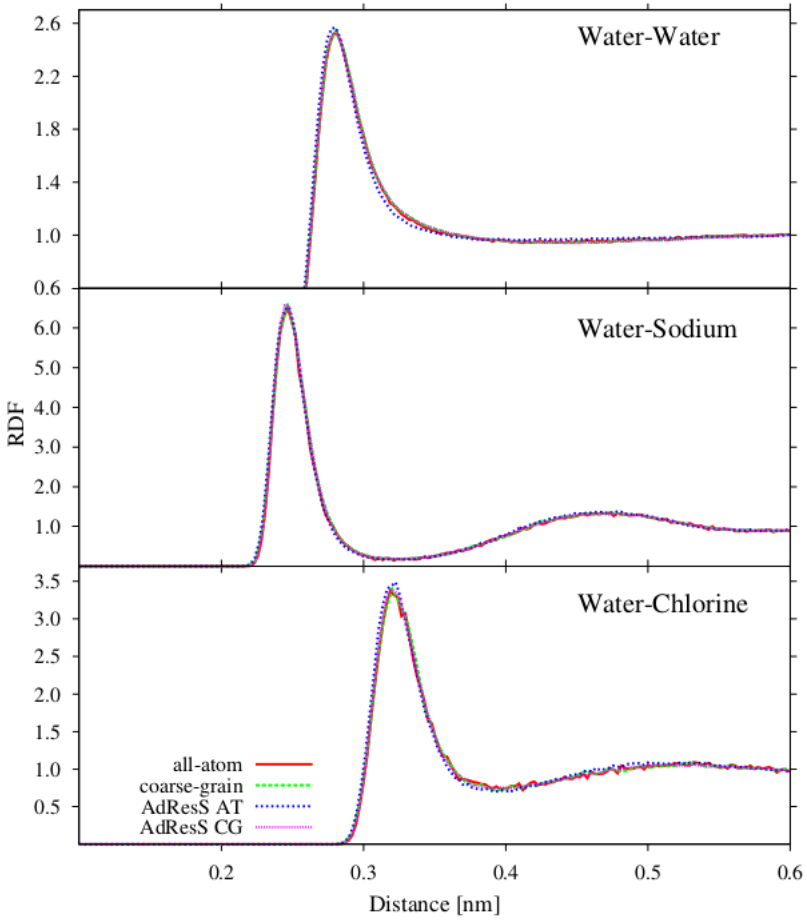


Bevc, Junghans, Kremer, Praprotnik; *New. J. Phys.* (2013)
Zavadlav, Podgornik, Praprotnik; *JCTC* (2015)

Multiscale 1M NaCl salt solution

- derived CG potential



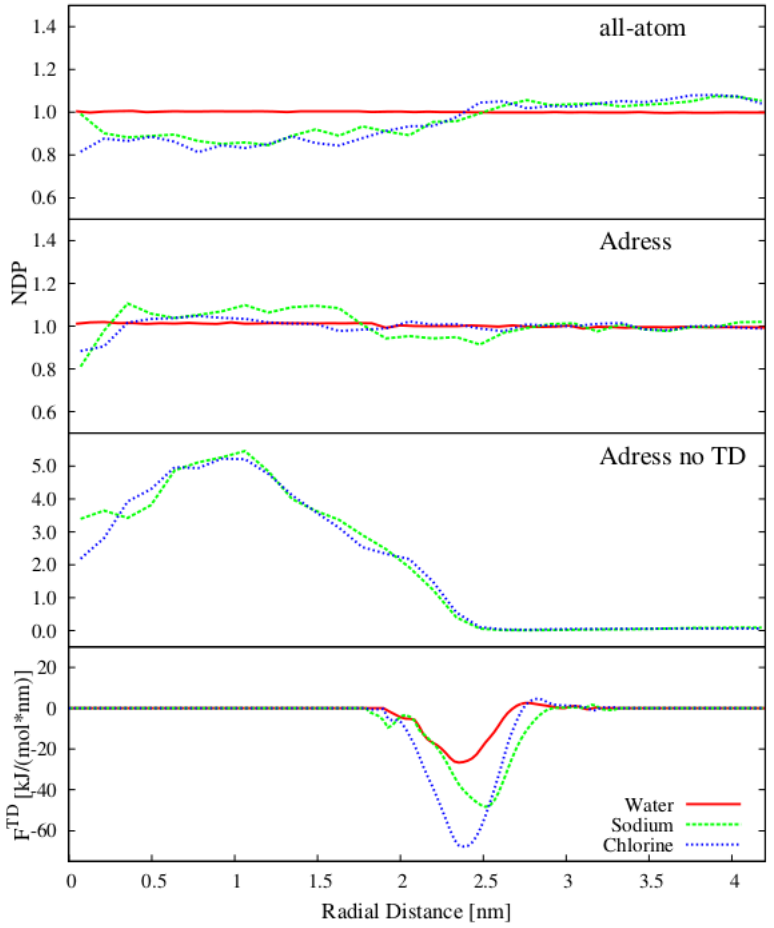


Zavadlav, Podgornik, Praprotnik; *JCTC* (2015)

Multiscale 1M NaCl salt solution

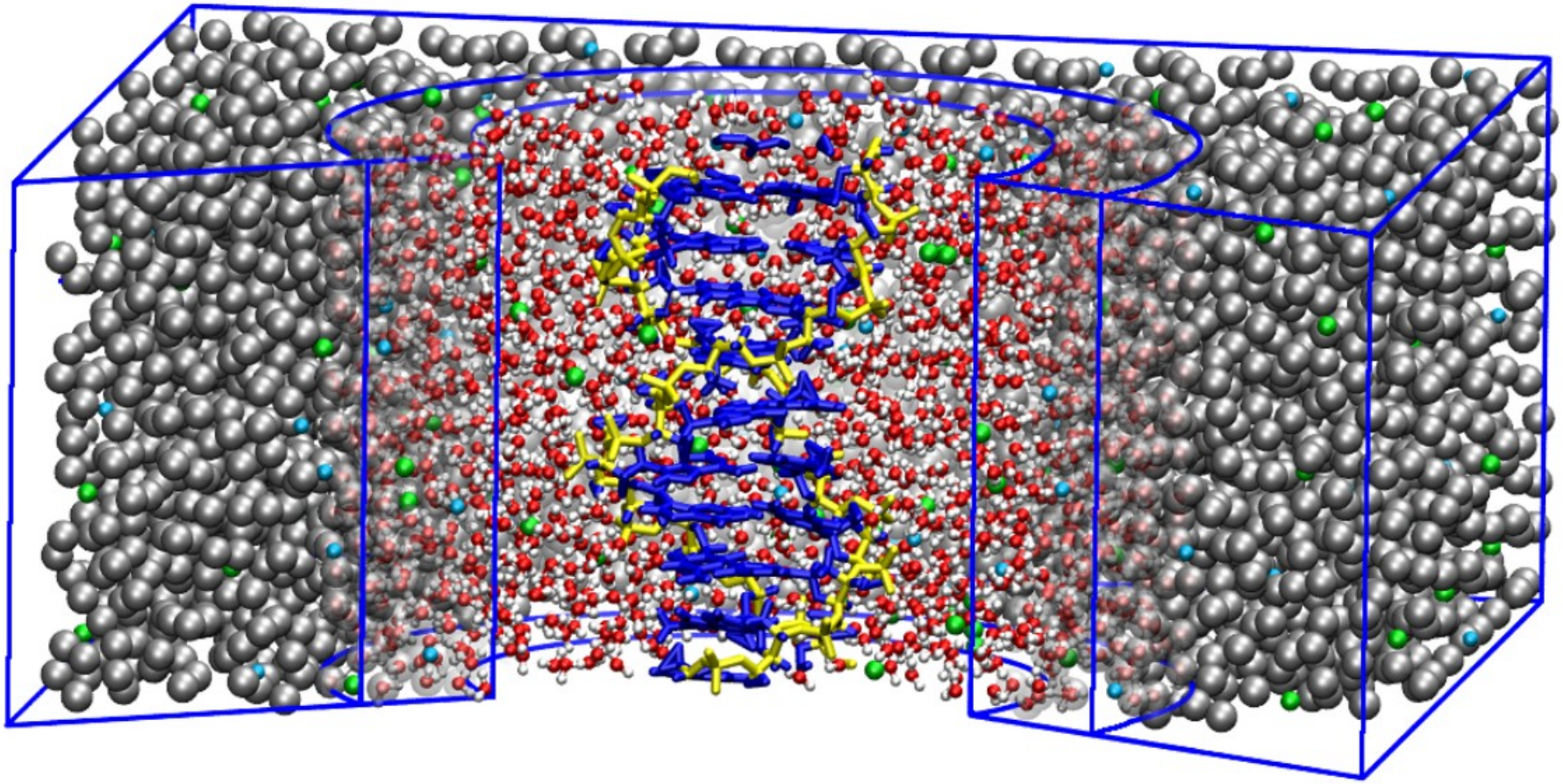
- density profile
- thermodynamic (TD) force on CG beads in HY region
- calculated iteratively

$$F_{TD}{}^{i+1} = F_{TD}{}^{i} - \frac{M_\alpha}{\rho_0{}^2 \kappa_T} \nabla \rho^i(x)$$



Zavadlav, Podgornik, Praprotnik; *JCTC* (2015)

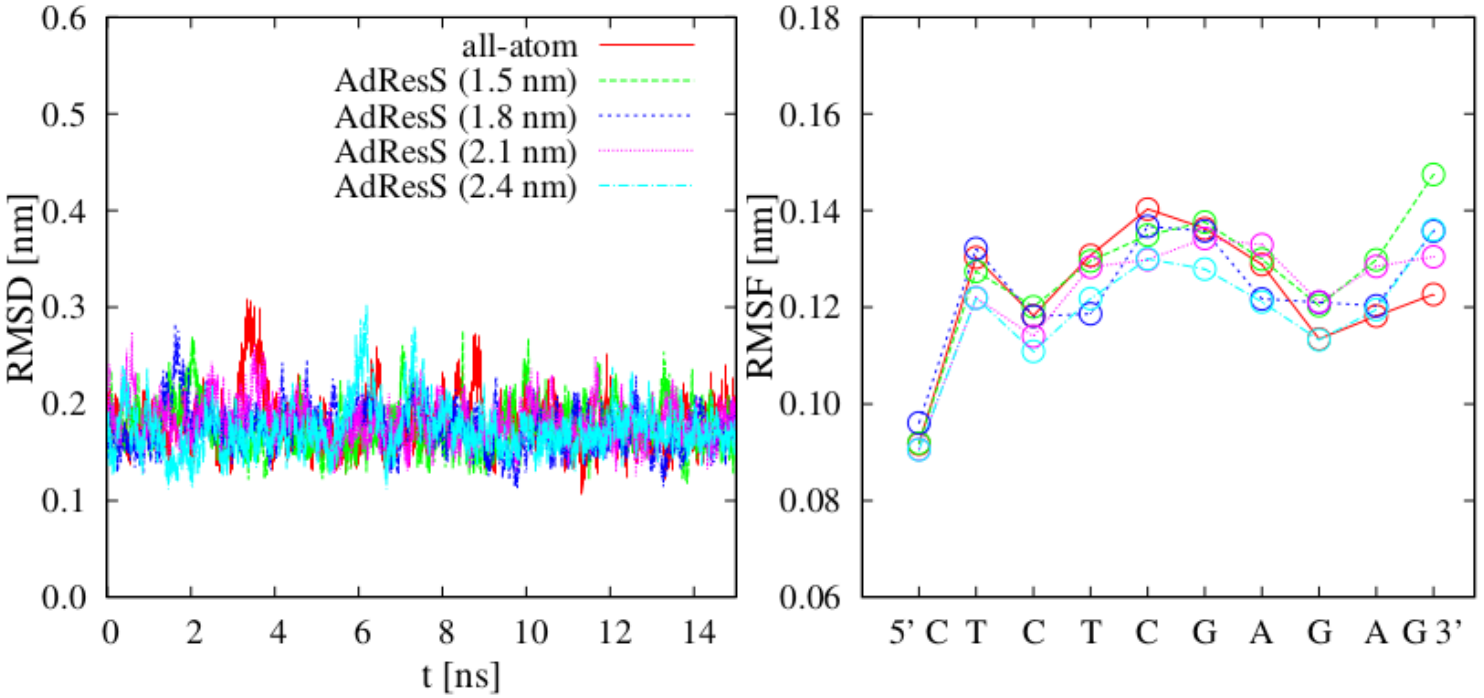
Atomistic DNA in multiscale salt solution



Zavadlav, Podgornik, Praprotnik; *J. Chem. Theory Comput.* (2015)

DNA molecule in multiscale salt solution

- structural properties of DNA molecule

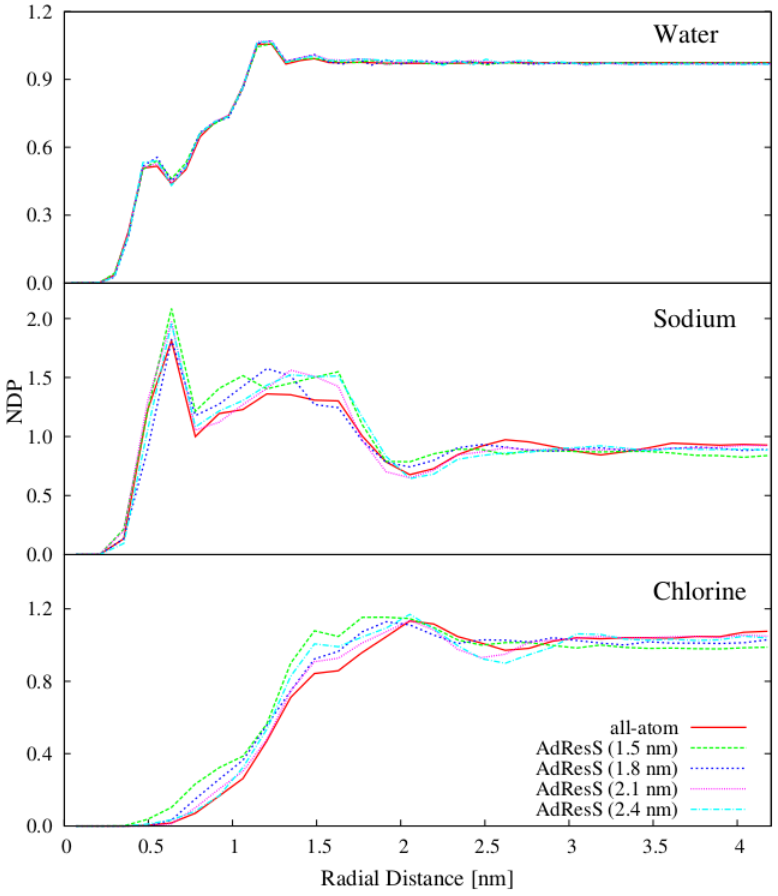


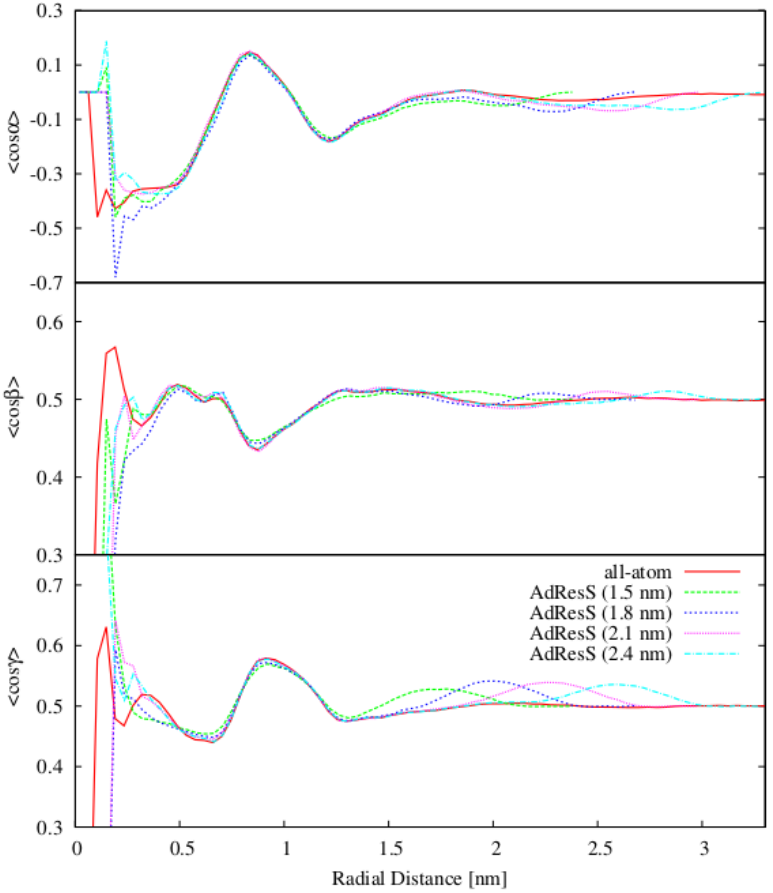
root-mean-square deviation root-mean-square fluctuations

Zavadlav, Podgornik, Praprotnik; *JCTC* (2015)

DNA molecule in multiscale salt solution

- structural properties of the surrounding solvent





Zavadlav, Podgornik, Praprotnik; *JCTC* (2015)

DNA molecule in multiscale salt solution

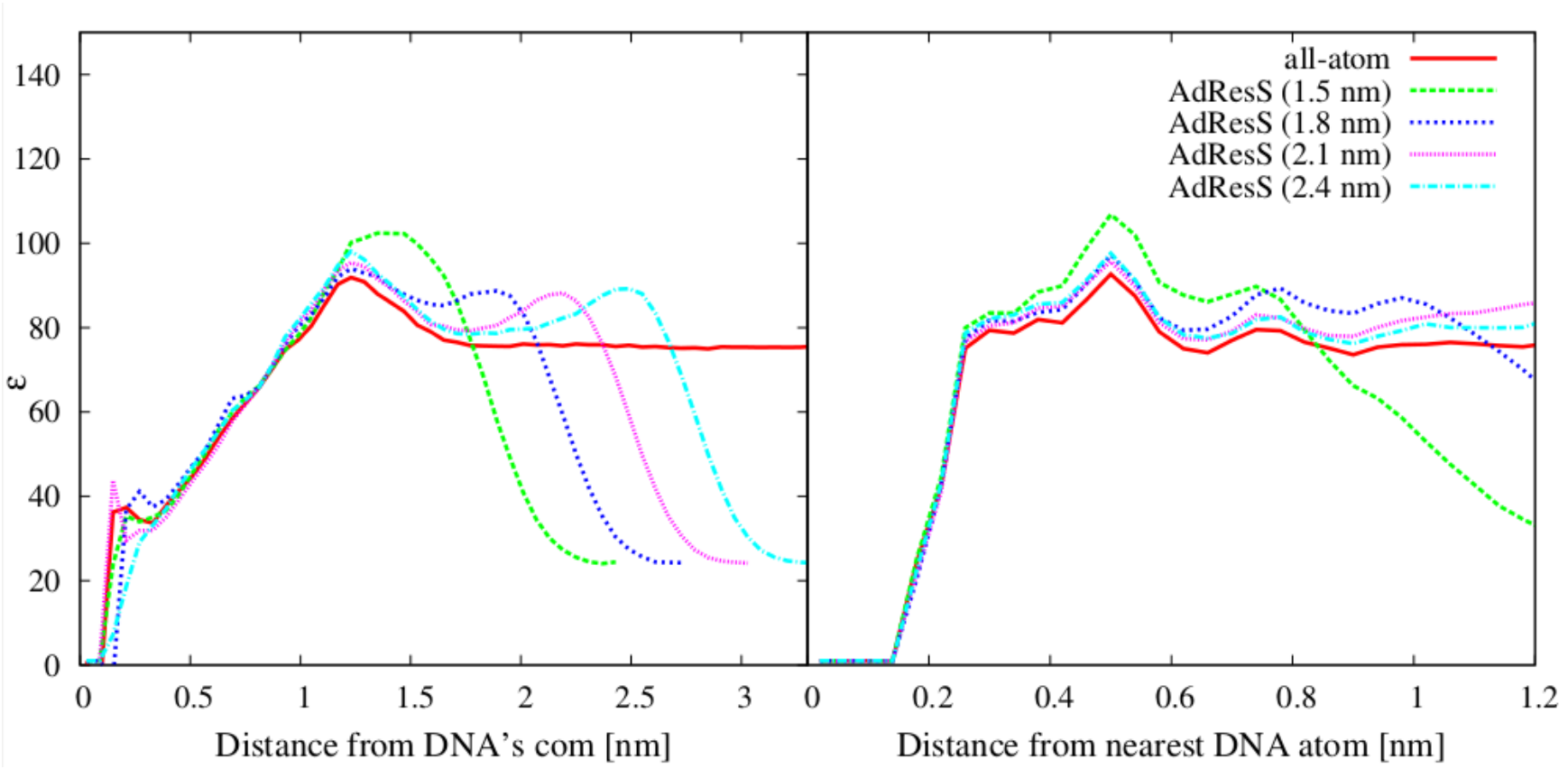
- dielectric constant of DNA molecule

Group	ε (1.5 nm)	ε (1.8 nm)	ε (2.1 nm)	ε (2.4 nm)	ε (∞)
Phosphate	18.3	21.1	17.3	15.7	17.0
Sugar	2.7	2.8	2.7	2.4	2.6
Base	2.1	2.1	2.0	2.0	2.1
DNA	5.6	5.9	5.4	4.5	5.0

Zavadlav, Podgornik, Praprotnik; *JCTC* (2015)

DNA molecule in multiscale salt solution

- dielectric constant of water

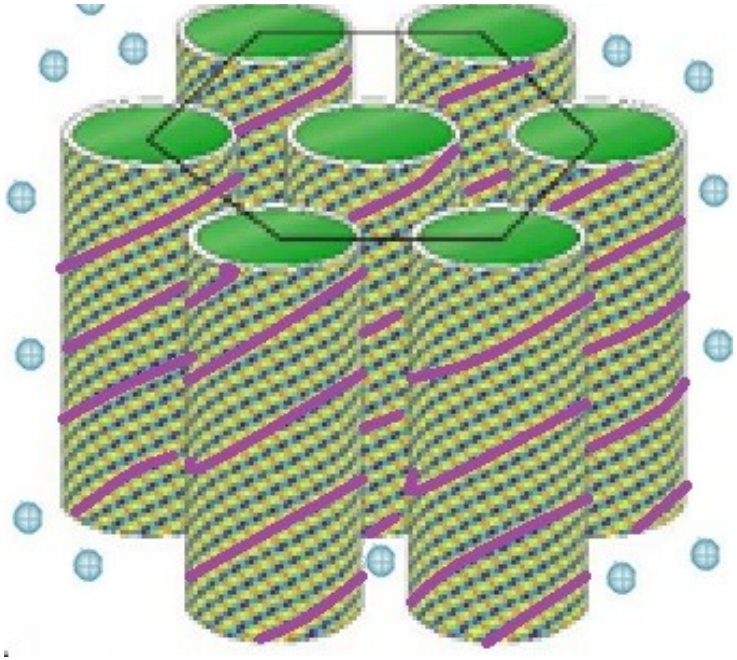


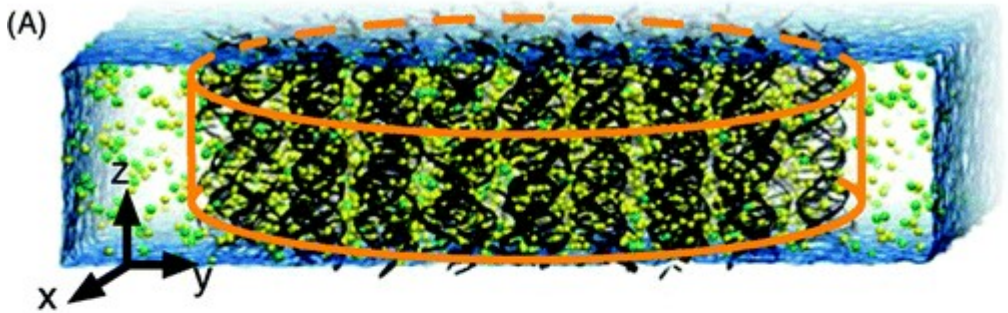
Zavadlav, Podgornik, Praprotnik; *JCTC* (2015)

Columnar phases of DNA arrays

Isotropic	Cholesteric	Hexagonal 2D progressive 3D longitudinal ordering	Orthorhombic
C(mg/ml) ≈	160 (*) 380	670	1055
	mean interhelices distance a_m 49 Å 32 Å	intermolecular distance a_H 31.5 Å 29 Å 23.7 Å	lattice parameters a = 24.09 Å a = 20.77 Å b = 39.33 Å b = 29.72 Å
		helix pitch P 34.6 Å ..... 30.2 Å	

Durand, Doucet, Livolant, *J. Phys. II France* (1992)





Lyubartsev, Nordenskiöld, *J. Phys. Chem.* (1995), Yoo, Aksimentiev, *J. Phys. Chem. Lett. (2011)*

Columnar phases of DNA arrays

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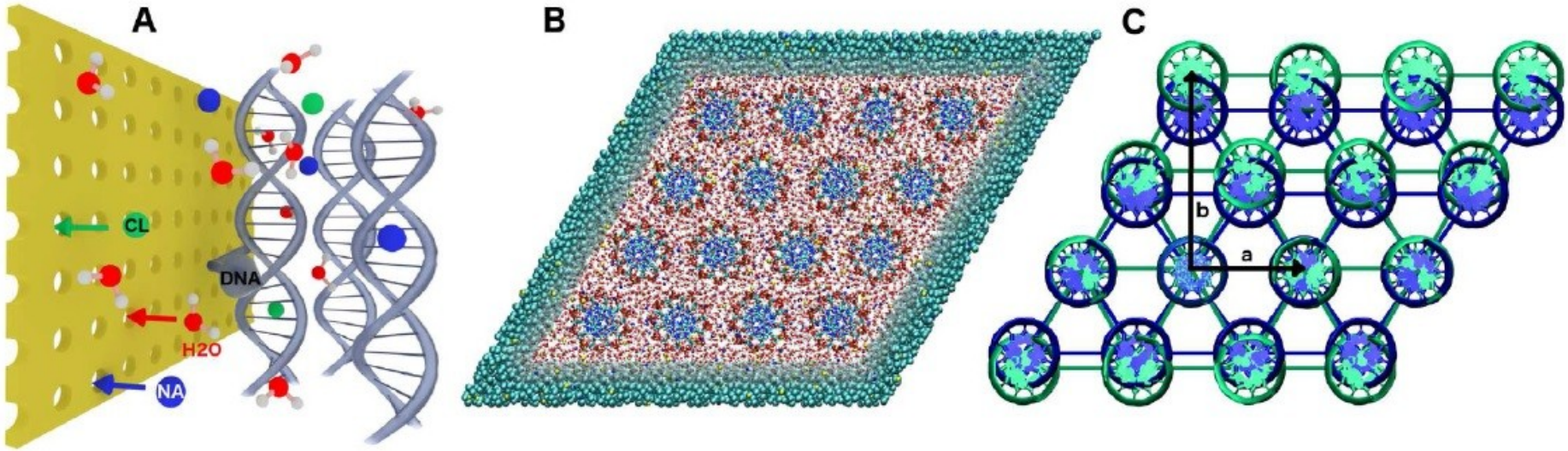
		helix pitch P 34.6 Å ..... 30.2 Å	

- system of 16 DNA molecules
- hexagonal/orthorhombic
- Na^+/Spd^{3+}

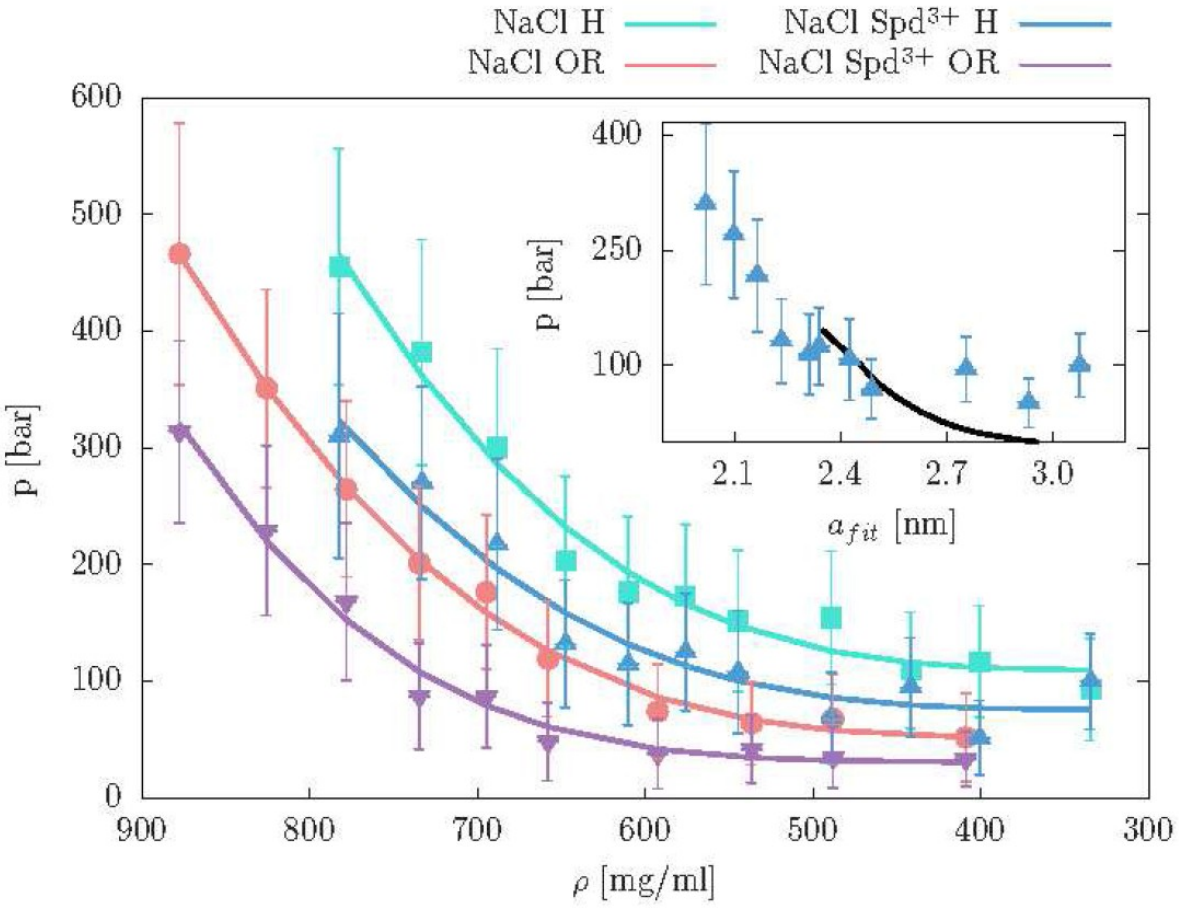
Durand, Doucet, Livolant, *J. Phys. II France* (1992)



Zavadlav, Podgornik, Praprotnik; *Sci. Rep.* (2017)

Columnar phases of DNA arrays

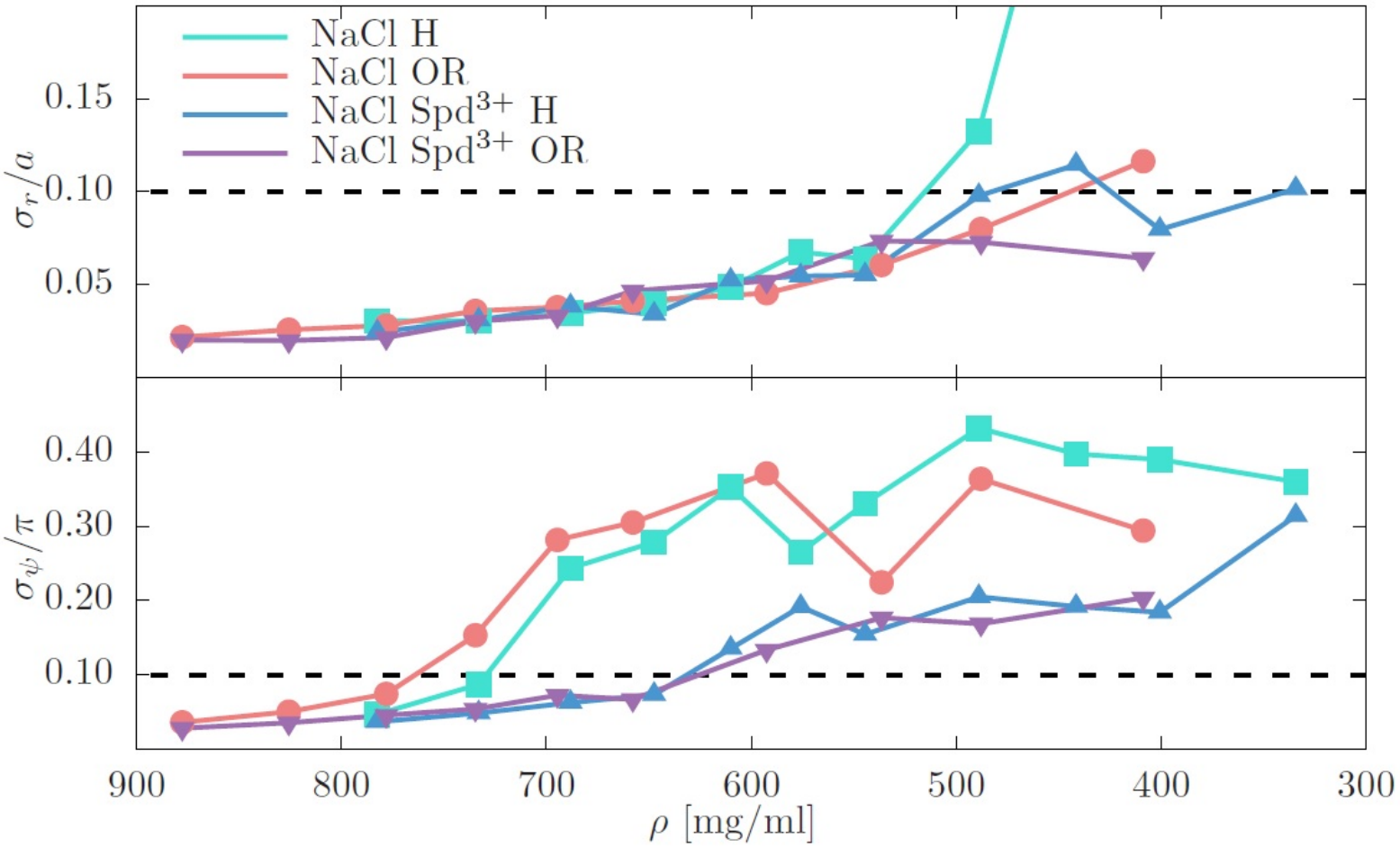
- osmotic pressure vs. DNA density



Zavadlav, Podgornik, Praprotnik; *Sci. Rep.* (2017)

Columnar phases of DNA arrays

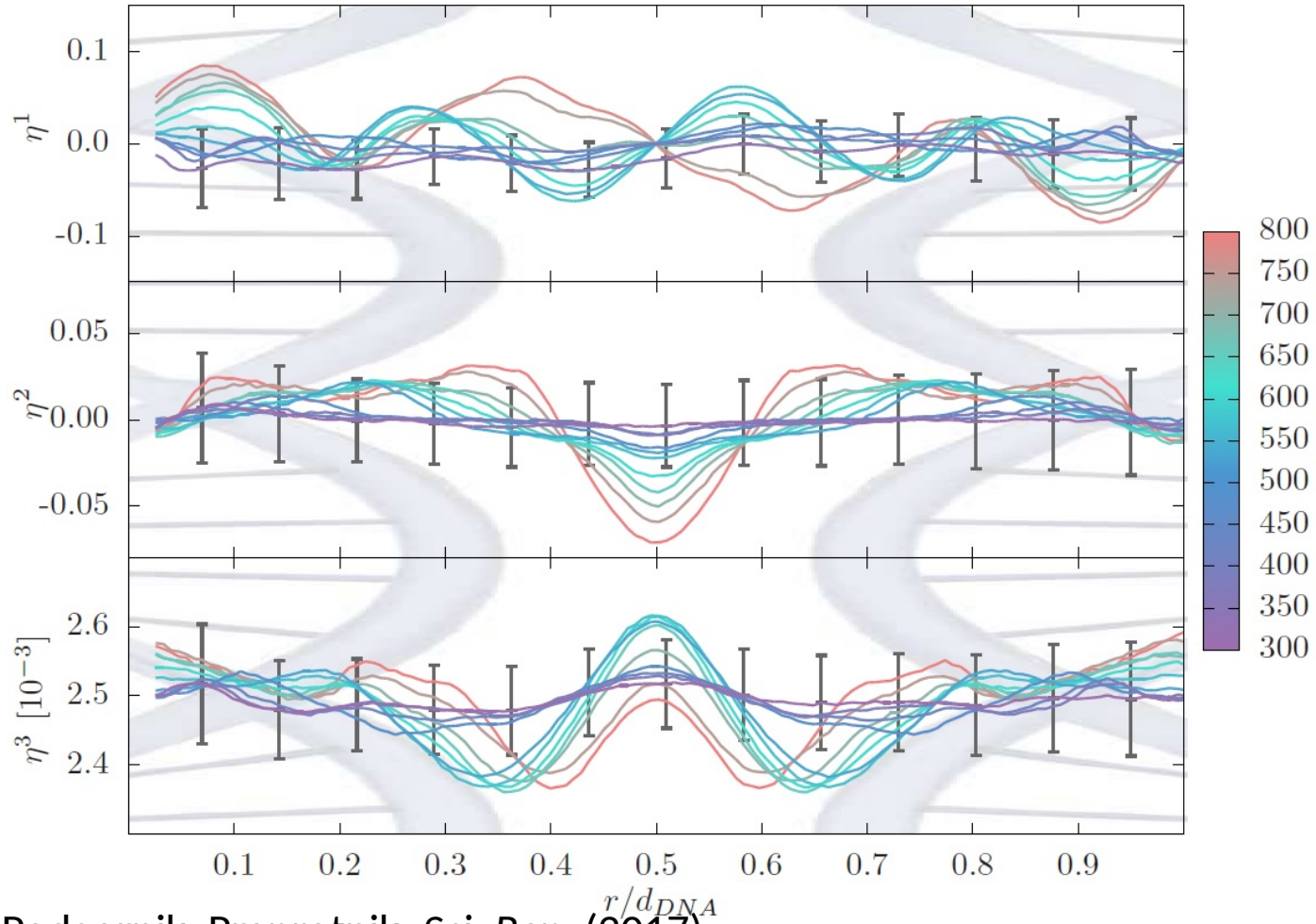
- positional and orientational correlations



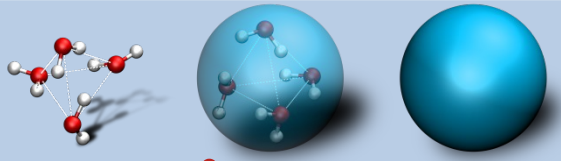
Zavadlav, Podgornik, Praprotnik; *Sci. Rep.* (2017)

Columnar phases of DNA arrays

- order parameters

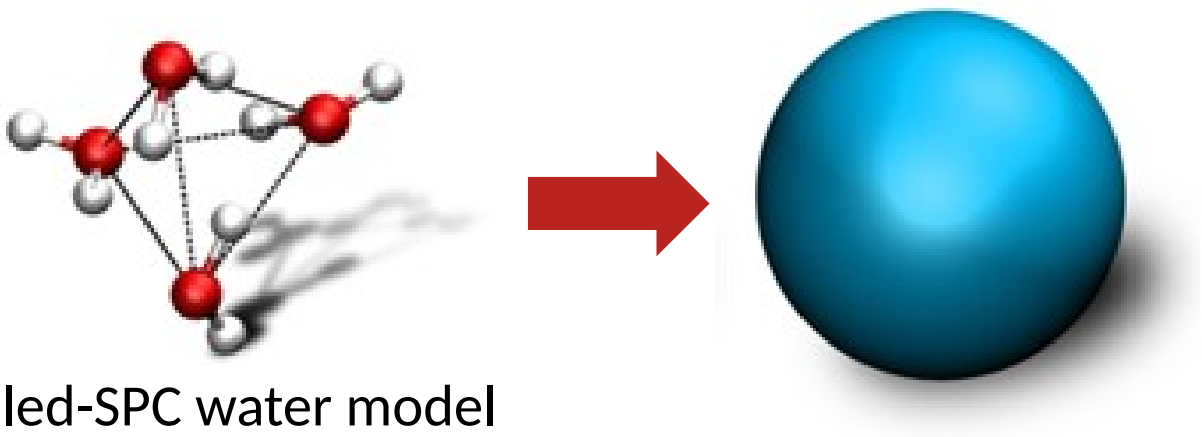


Zavadlav, Podgornik, Praprotnik; *Sci. Rep.* (2017)



Next step: supramolecular mapping

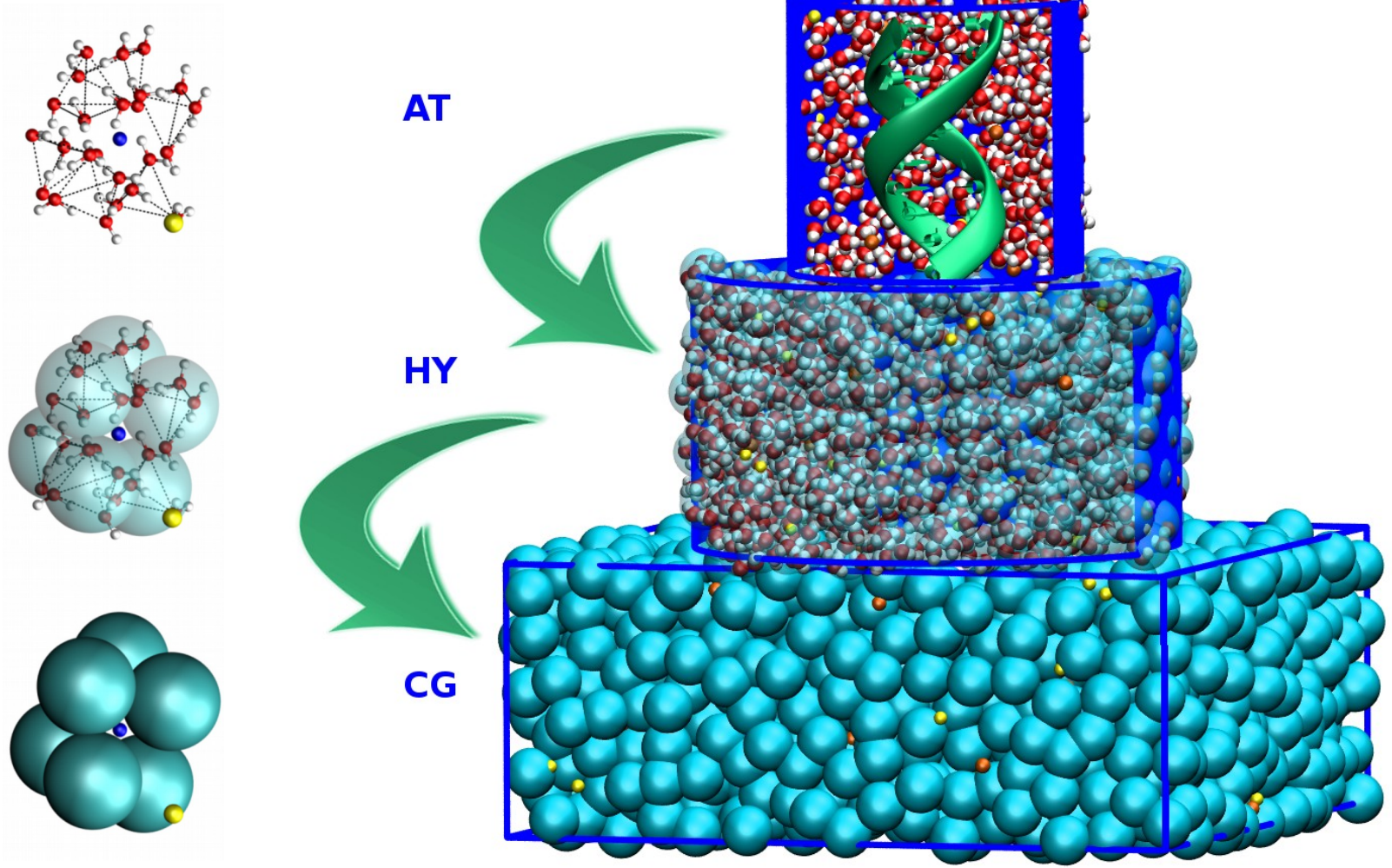
- multiple AT molecules mapped to 1 CG bead
- motivation :
  - greater computational speed-up
  - with 4-to-1 mapping the MARTINI force field can be used



- bundled-SPC water model
  - half harmonic bonds between oxygen atoms
  - different force constants -> model 1 and 2

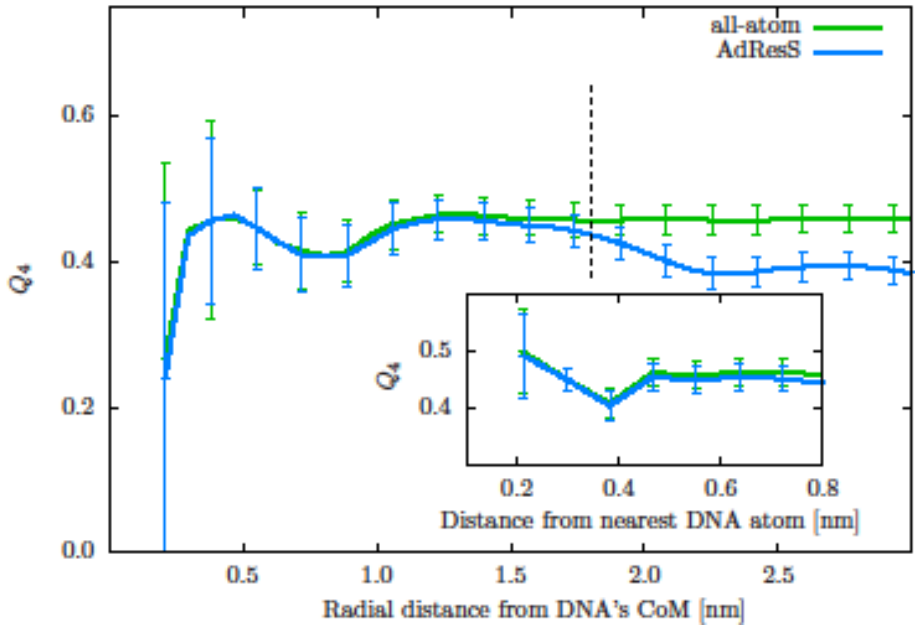
Marrink, Risselada, Yefimov, Tieleman, de Vries; Phys. Chem. B (2007)
Fuhrmans, Sanders, Marrink, de Vries; Theor. Chem. Acc. (2010)

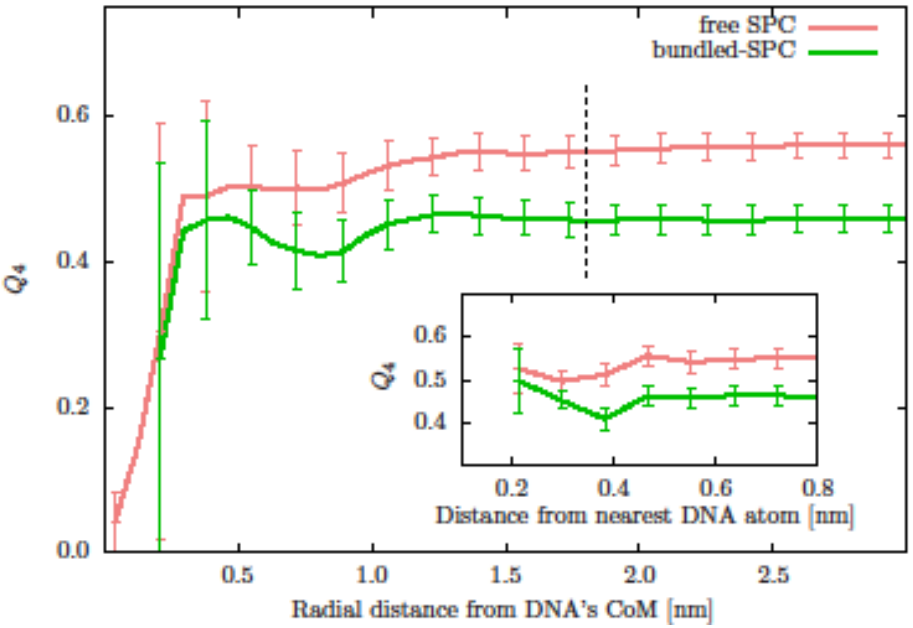
DNA molecule in bundled-SPC/MARTINI salt solution



Zavadlav, Podgornik, Melo, Marrink, Praprotnik; *EPJST* (2016)

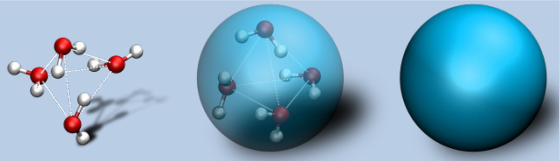
DNA molecule in bundled-SPC/MARTINI salt solution





$$Q_4 = 1 - \frac{3}{8}\sum_{i=1}^{3}\sum_{j=i+1}^{4}\left(\cos\theta_{ijk} + \frac{1}{3}\right)^2$$

Zavadlav, Podgornik, Melo, Marrink, Praprotnik; *EPJST* (2016)

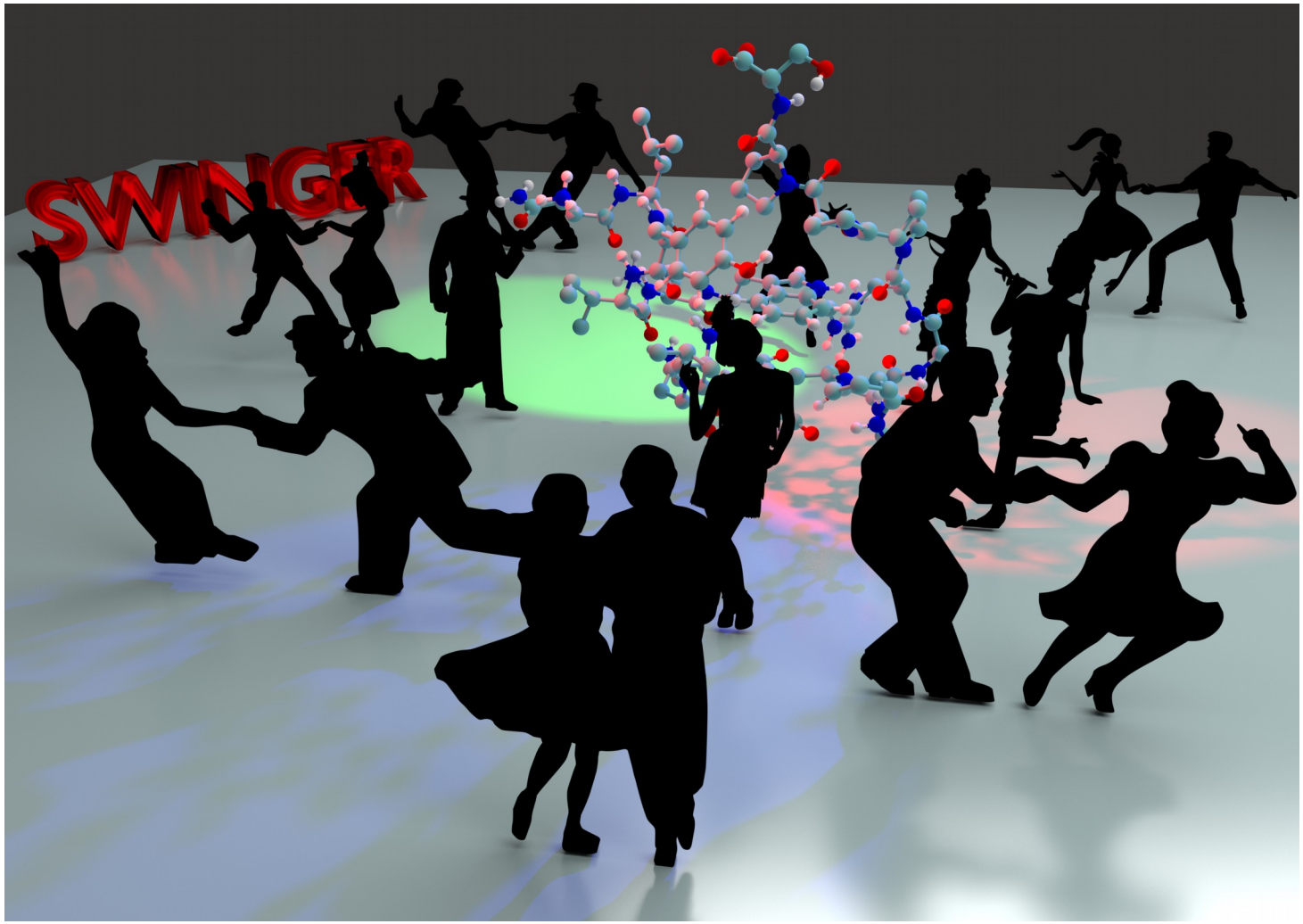


Bundled-SPC water

- pros:
  - enables multiscale simulations with multi-molecule mapping
  - interactions with non-water molecules mostly unaltered
  - can reproduce the free energy of hydration of small molecules, the PMFs between pairs of amino acid side chains
- cons:
  - bundling affects the self-interactions of the water molecules -> altered water structure & dynamics
  - slow-down in the kinetics by factor of ca. 2
  - for sensitive systems bundling can cause severe structural distortions, loss of native contacts, protein unfolding…

Fuhrmans, Sanders, Marrink, de Vries; Theor. Chem. Acc. (2010)
Gopal, Kuhn, Schäfer; PCCP (2015)

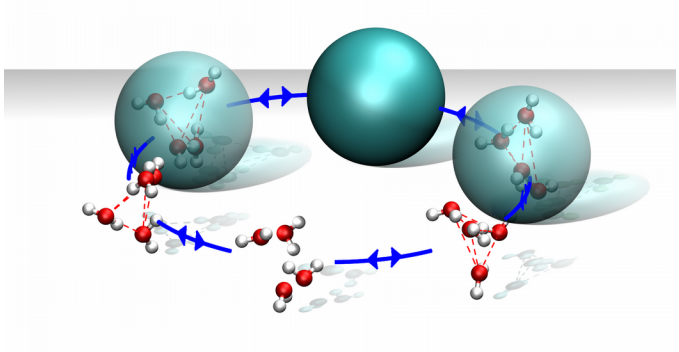
SWINGER algorithm



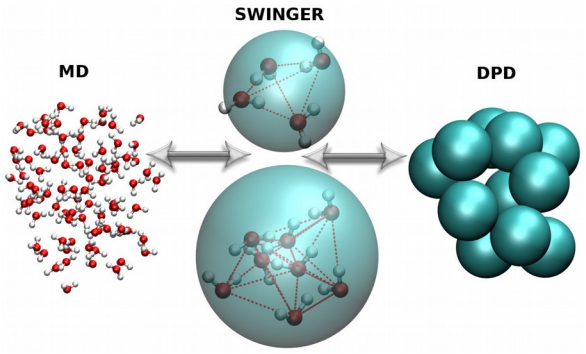
Zavadlav, Marrink, Praprotnik; *JCTC* (2018)

Free SPC/MARTINI water and DPD

- Algorithm SWINGER:
  - concurrently assembles, dissambles and reassembles water clusters

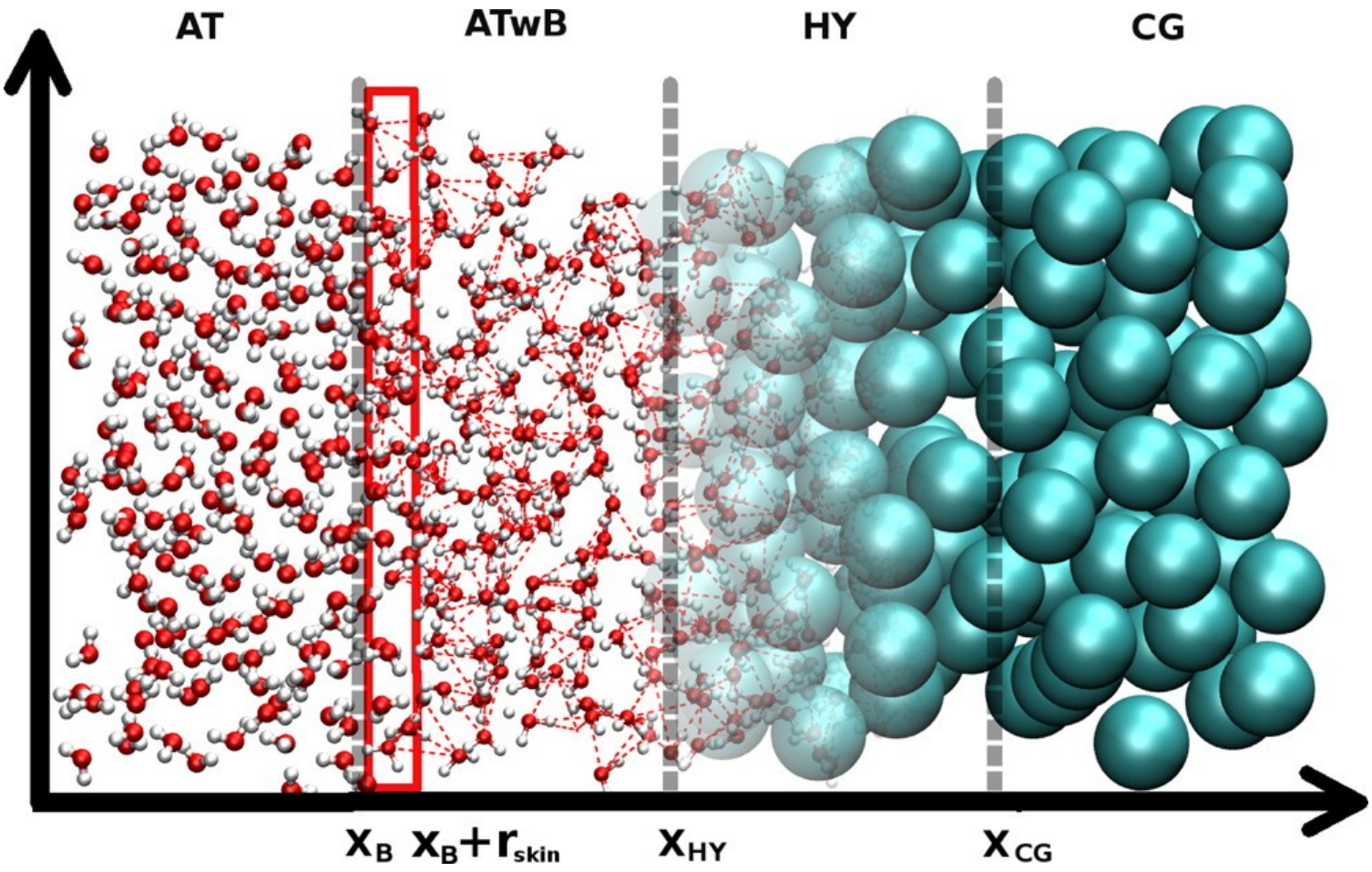


- DPD:
  - supramolecular coupling of atomistic water with DPD



Zavadlav, Marrink, Praprotnik; *J. Chem. Theory Comput*. (2016)
Zavadlav, Praprotnik; *J. Chem. Phys*. (2017)

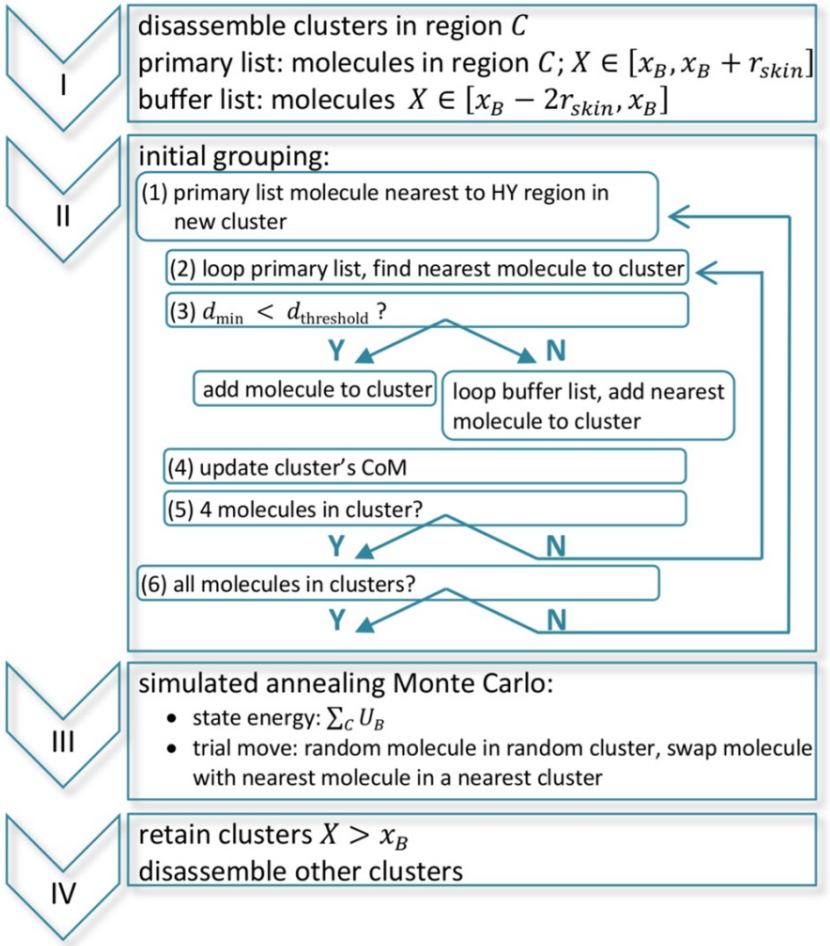
Free SPC/MARTINI water



Zavadlav, Marrink, Praprotnik; *J. Chem. Theory Comput*. (2016)

Free SPC/MARTINI water

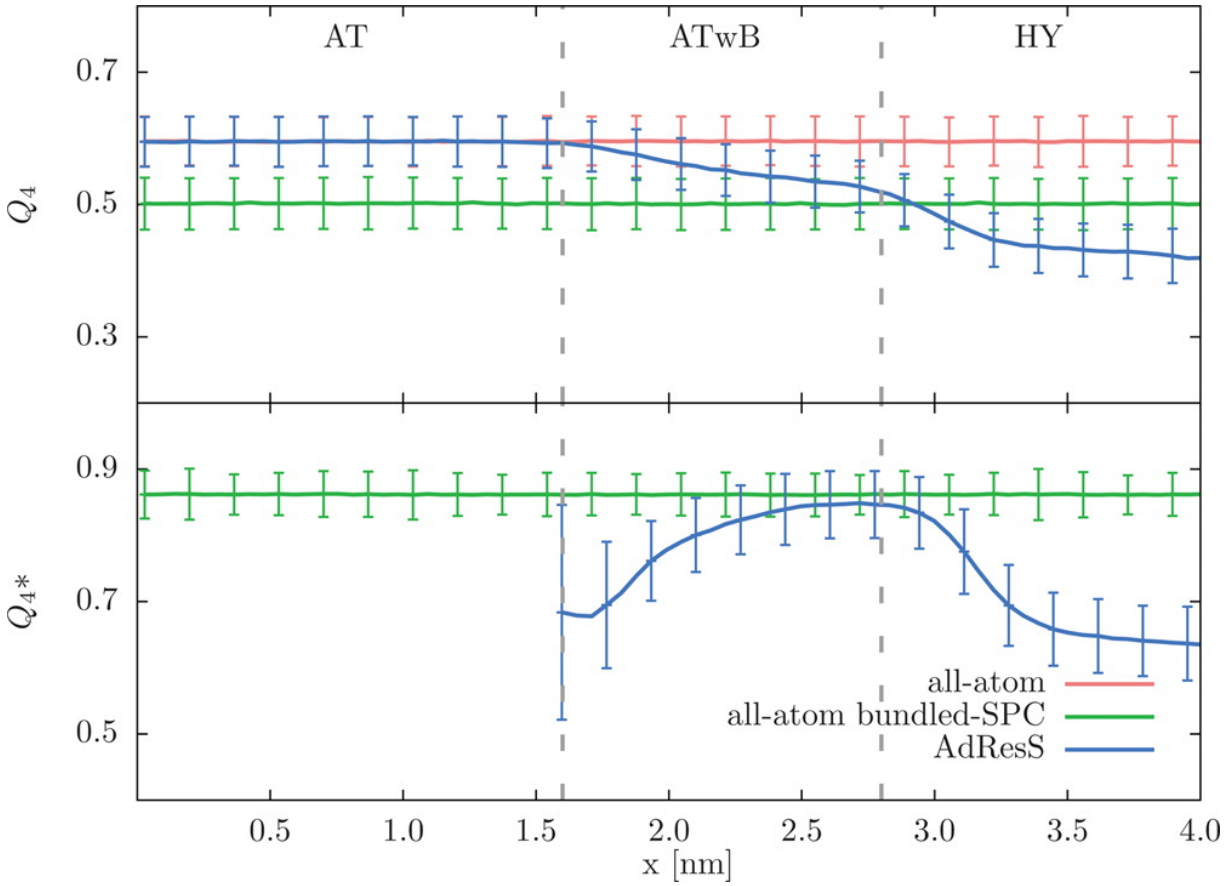
- SWINGER algorithm



Zavadlav, Marrink, Praprotnik; *J. Chem. Theory Comput*. (2016)

Free SPC/MARTINI water

- tetrahedral order

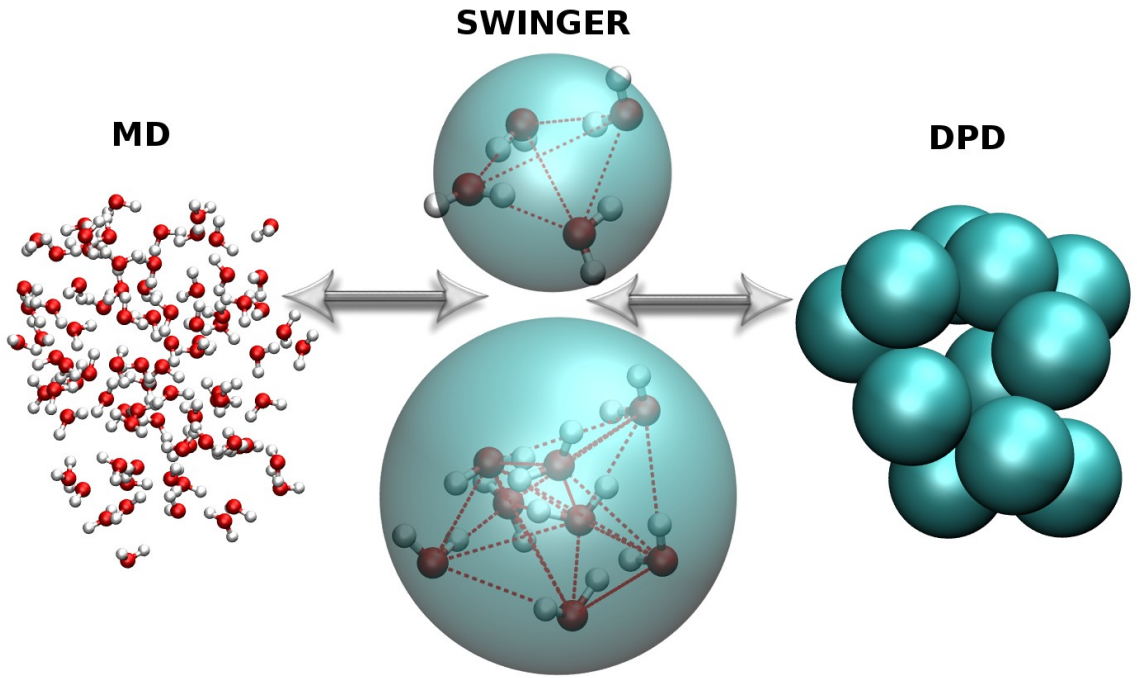


$$Q_4 = 1 - \frac{3}{8}\sum_{i=1}^{3}\sum_{j=i+1}^{4}\left(\cos\theta_{ijk} + \frac{1}{3}\right)^2$$

$$Q_4^* = 1 - \frac{3}{8}\sum_{i=1}^{3}\sum_{j=i+1}^{4}\left(\cos\Phi_{ij} + \frac{1}{3}\right)^2$$

Zavadlav, Marrink, Praprotnik; *J. Chem. Theory Comput*. (2016)

MD/DPD water



MD:

$$\mathbf{F}_{ij}^{MD,C}(\mathbf{r}_{ij}) = -\frac{\partial U^{MD}}{\partial \boldsymbol{r}_{ij}}$$

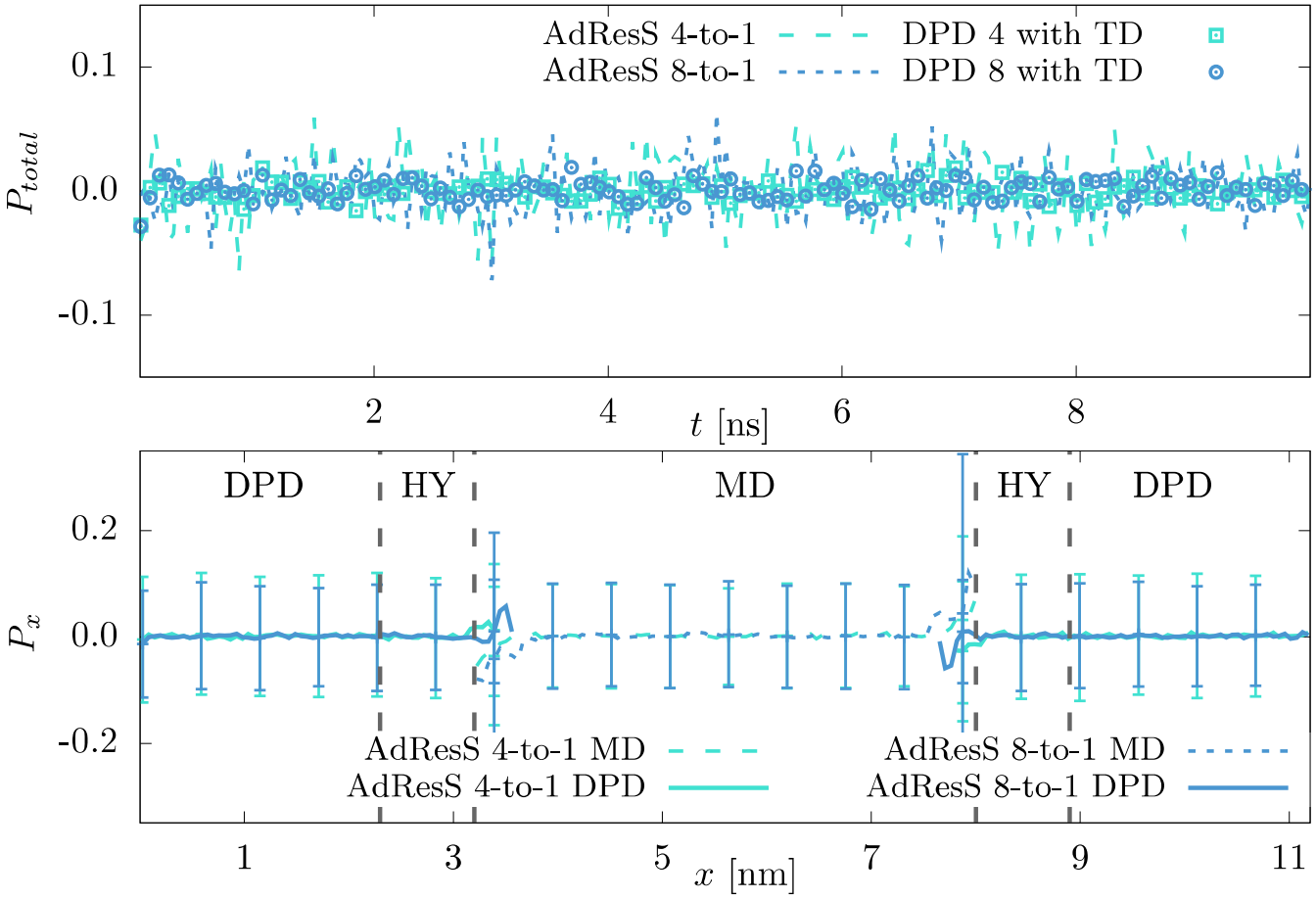
DPD:

$$\mathbf{F}_{\alpha\beta}^{DPD,C}(\mathbf{R}_{\alpha\beta}) = a_{\alpha\beta}(1 - R_{\alpha\beta}/R_c)\hat{\mathbf{R}}_{\alpha\beta}$$
$$\mathbf{F}_{\alpha\beta}^{DPD,R}(\mathbf{R}_{\alpha\beta}) = \sqrt{2\gamma_{\alpha\beta}k_BT}(1 - R_{\alpha\beta}/R_c)\zeta_{ij}\hat{\mathbf{R}}_{\alpha\beta}$$
$$\mathbf{F}_{\alpha\beta}^{DPD,D}(\mathbf{R}_{\alpha\beta}) = -\gamma_{\alpha\beta}(1 - R_{ij}/R_c)^2(\hat{\mathbf{R}}_{\alpha\beta} \cdot \mathbf{V}_{\alpha\beta})\hat{\mathbf{R}}_{\alpha\beta}$$

Zavadlav, Praprotnik; *J. Chem. Phys. (2017)*

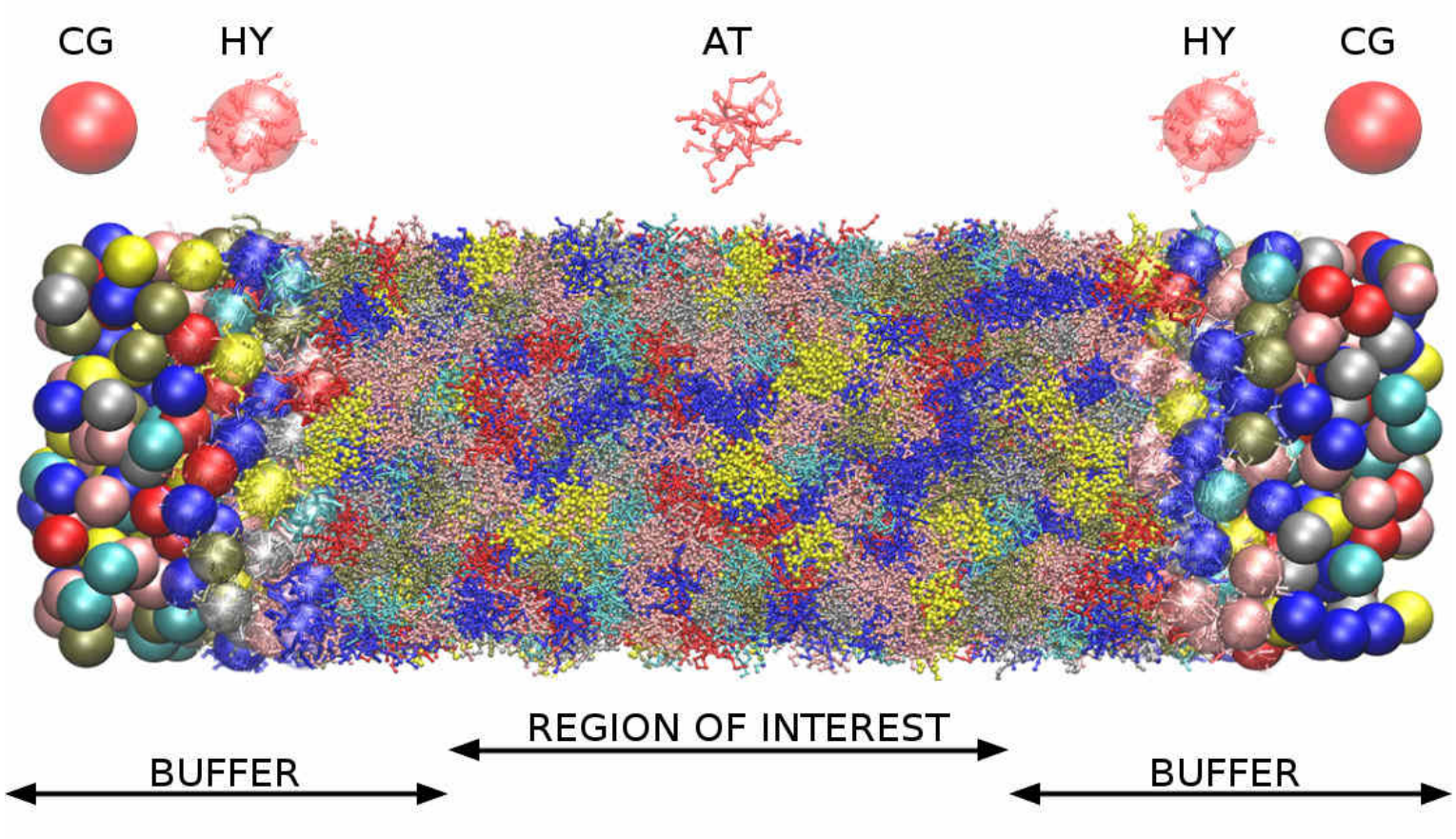
MD/DPD water

- conservation of linear momentum

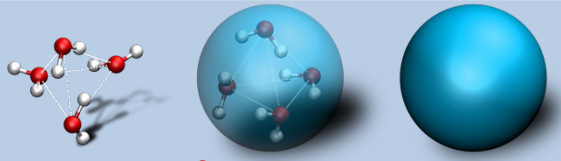


Zavadlav, Praprotnik; *J. Chem. Phys. (2017)*

Open Boundary Molecular Dynamics



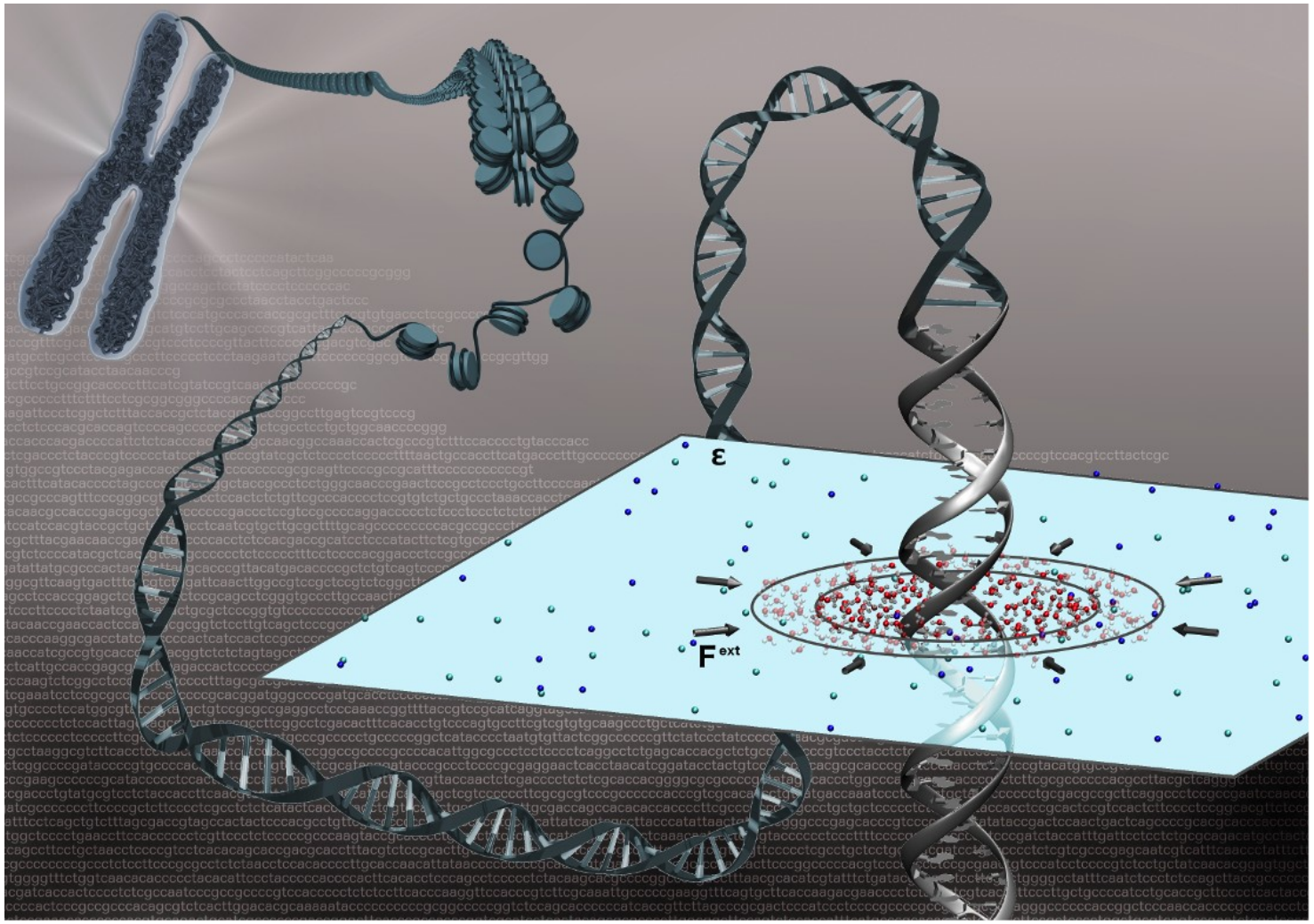
Delgado-Buscalioni, Sablić, Praprotnik; *Eur. Phys. J. Special Topics* (2015)
Sablić, Praprotnik, Delgado-Buscalioni; *Soft Matter* (2016)
Delle Site, Praprotnik; Phys. Rep. (2017)



Open Boundary Molecular Dynamics

- system exchanges mass, momentum, and energy with its surroundings
  1. Insertion of molecules: $\Delta N_B = \frac{\Delta t}{\tau_r}(\alpha\langle N_B\rangle - N_B)$
  2. Multiscale buffers -> facilitates insertion
- external boundary condition
  1. Linear momentum conservation
  2. Additional force in buffers: $\boldsymbol{F}^{ext} = \boldsymbol{J}\cdot\boldsymbol{n}_B A + \frac{\boldsymbol{P}_{out} - \boldsymbol{P}_{in}}{\Delta t} + \sum_\alpha \boldsymbol{F}_\alpha^{TD}$
- DPD thermostat: $\boldsymbol{F}_\alpha^{thermo} = \sum_{i\in\alpha, j\in\beta, \alpha\neq\beta} \sigma\omega^R(r_{ij})\zeta_{ij}\hat{\boldsymbol{r}}_{ij} - \gamma\omega^D(r_{ij})(\hat{\boldsymbol{r}}_{ij}\cdot\boldsymbol{v}_{ij})\hat{\boldsymbol{r}}_{ij}$ $\quad \omega^D(r_{ij}) = [\omega^R(r_{ij})]^2$ $\quad \sigma^2 = 2k_B T\gamma$
- total force on each particle: $\boldsymbol{F}_\alpha = \boldsymbol{F}_\alpha^{AdResS} + \boldsymbol{F}_\alpha^{ext} + \boldsymbol{F}_\alpha^{thermo}$

Open Boundary Molecular Dynamics



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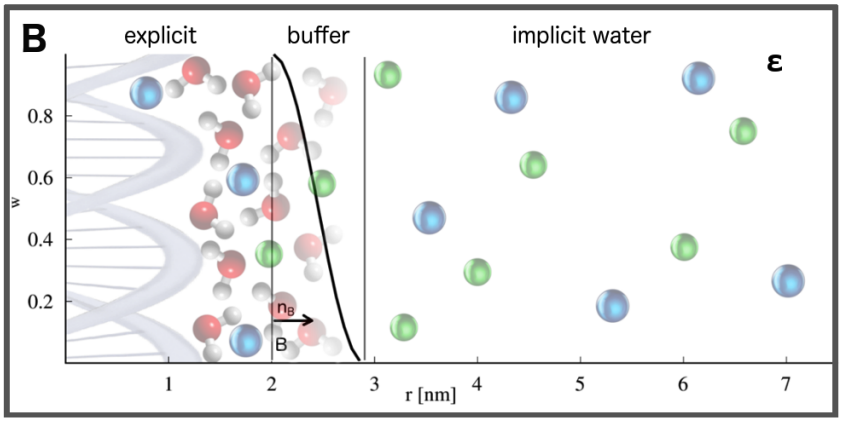
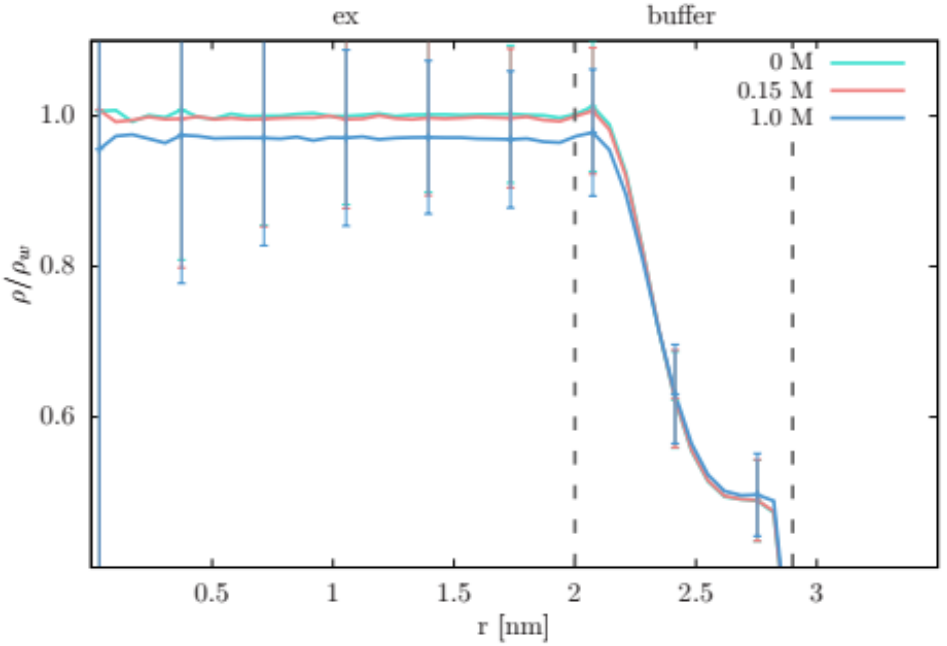
Open Boundary Molecular Dynamics





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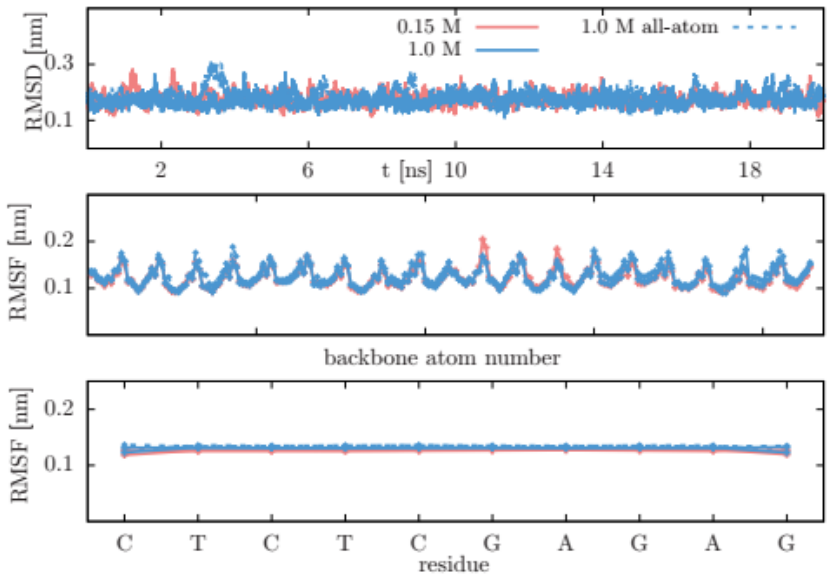
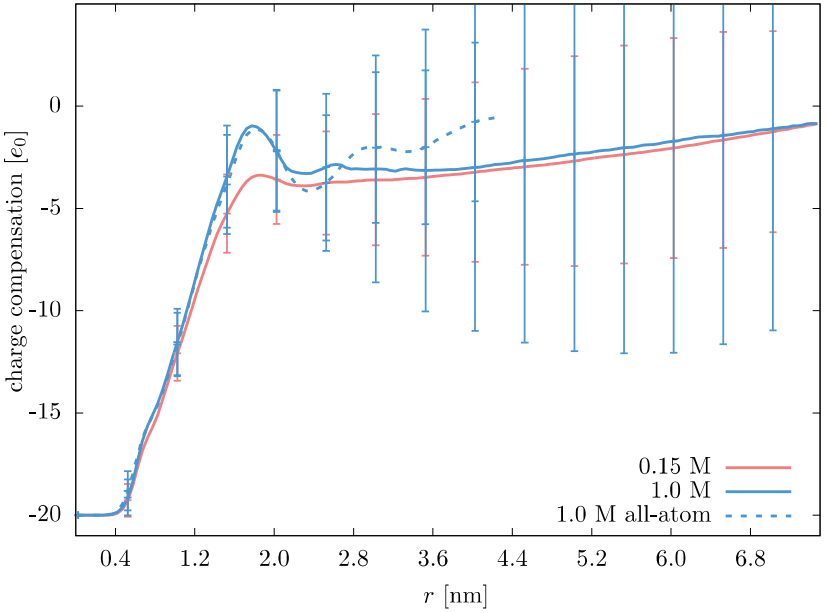
Open Boundary Molecular Dynamics





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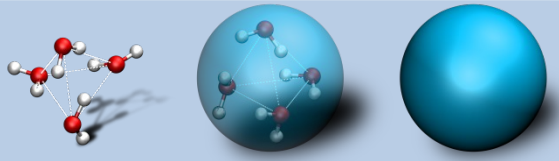
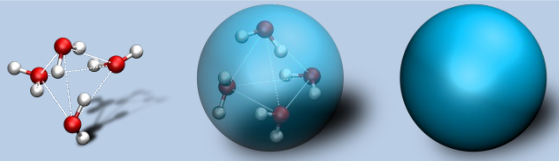
Conclusions



- OBMD:
  - Allows for simulation of open systems that can exchange mass, energy, and linear momentum with the environment.
  - Enables us to perform effiecient molecular dynamics simulations of molecular liquids in the grand-canonical ensemble or under non-equilibrium flows.
  - In the explicit domain, the water molecules and ions are both overtly present in the system, whereas in the implicit water domain, only the ions are explicitly present and the water is described as a continuous dielectric medium.
  - Water molecules are inserted and deleted into/from the system in the intermediate buffer domain that acts as a water reservoir to the explicit domain, with both water molecules and ions free to enter or leave the explicit domain.
  - Our approach is general and allows for efficient molecular simulations of biomolecules solvated in bathing salt solutions at any ionic strength condition.



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