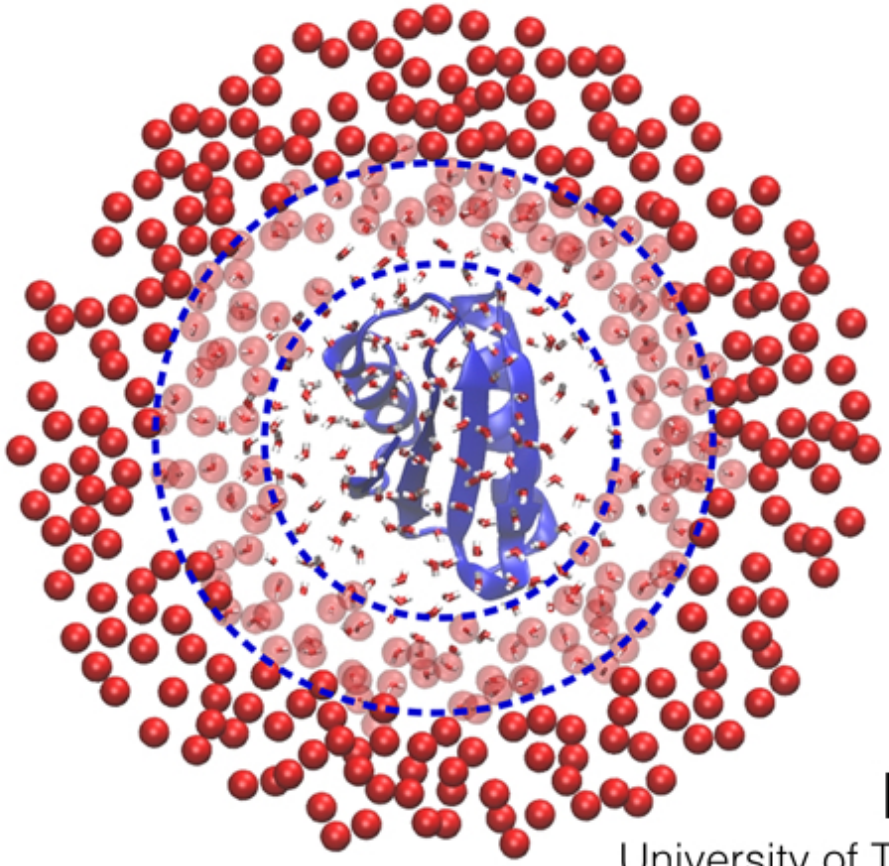
The devil is in the atomistic detail

Problems and solutions in computational soft matter



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Università degli Studi di Pavia - Physics Dept. I March 8, 2018

Acknowledgements

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Ralf Everaers (Lyon)
Mark E. Tuckerman (New York)
Paolo Carloni (Jülich)

Funding and support

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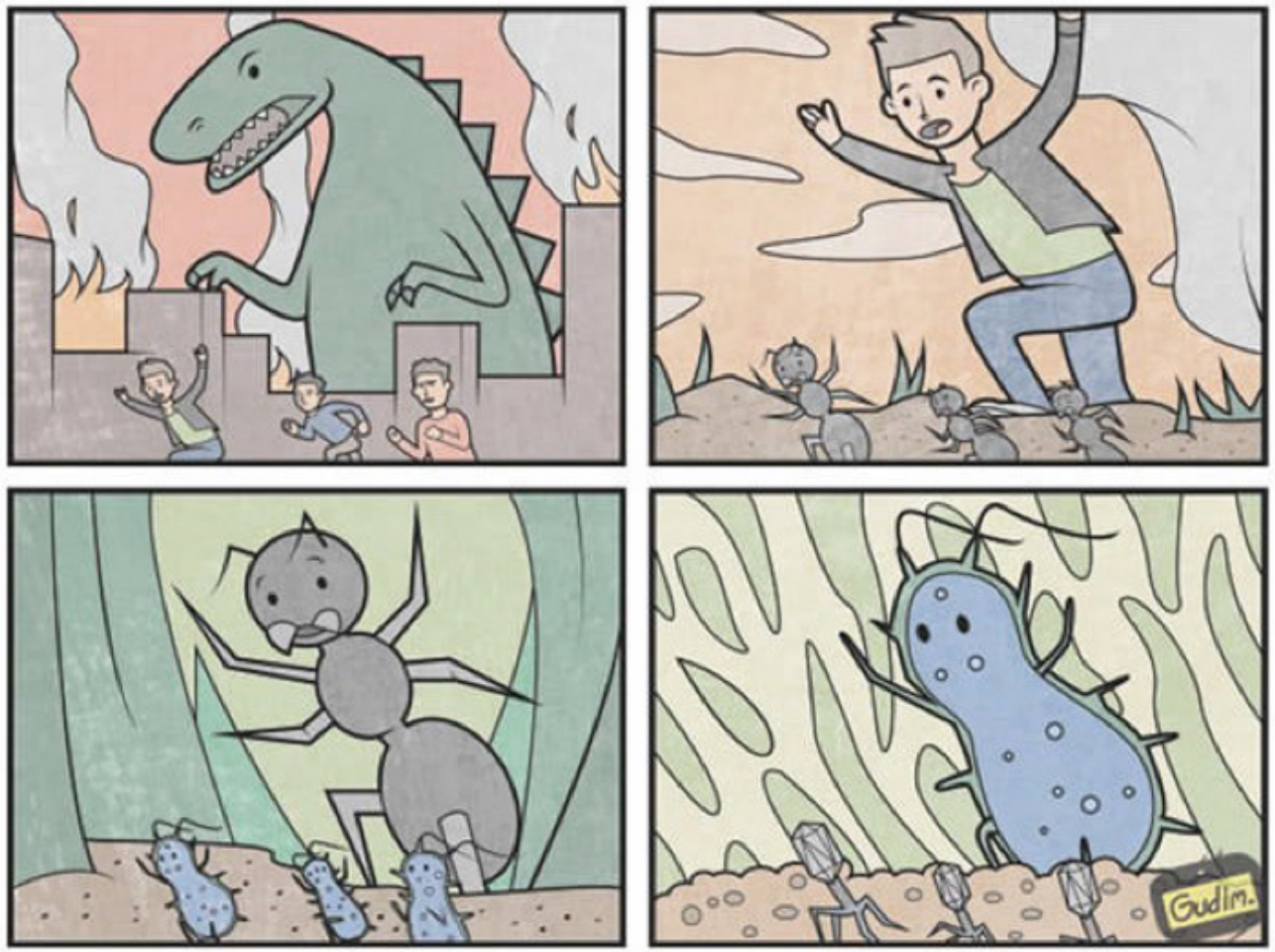
Motivation:
the multiscale challenge in biological systems



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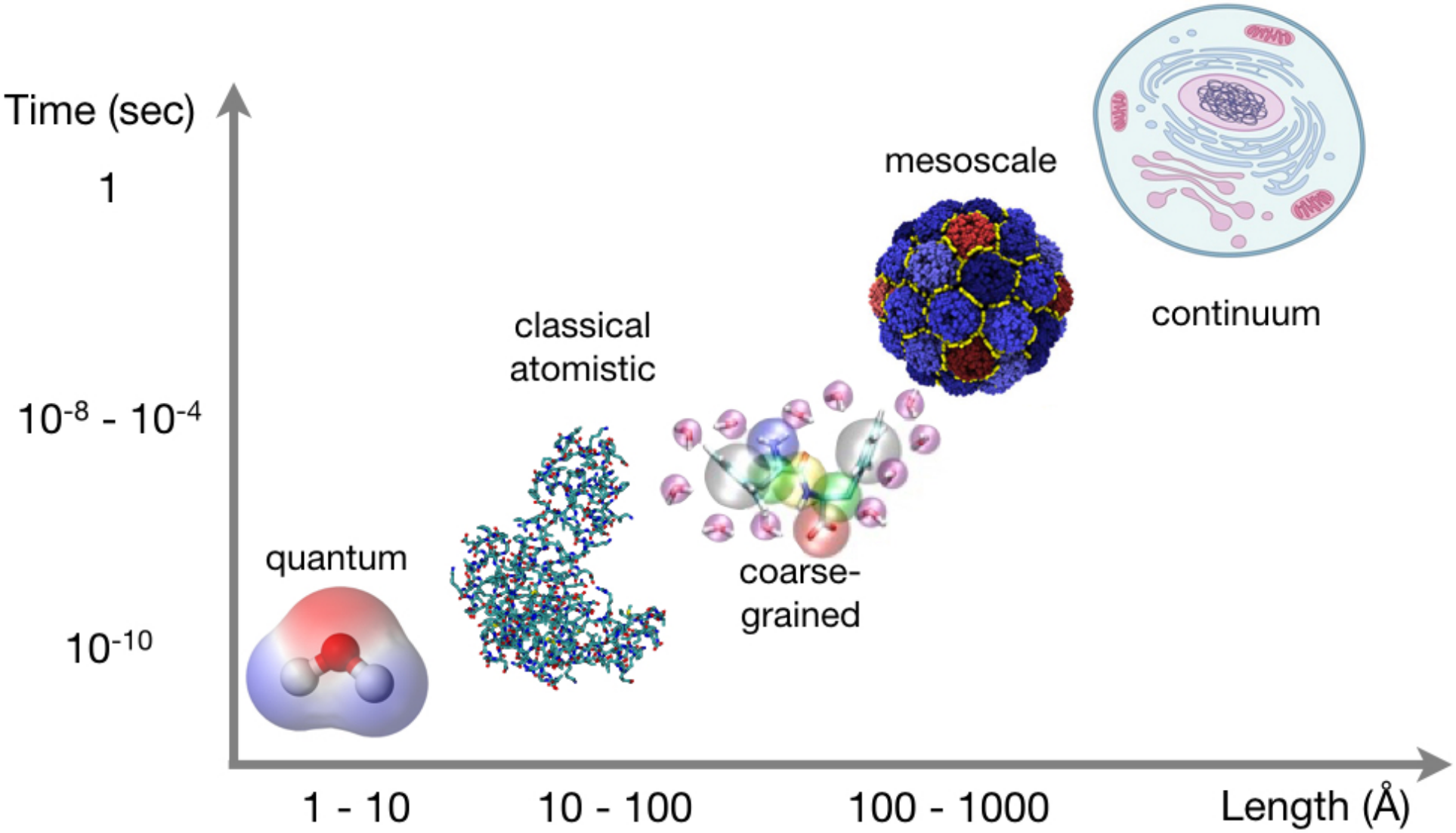

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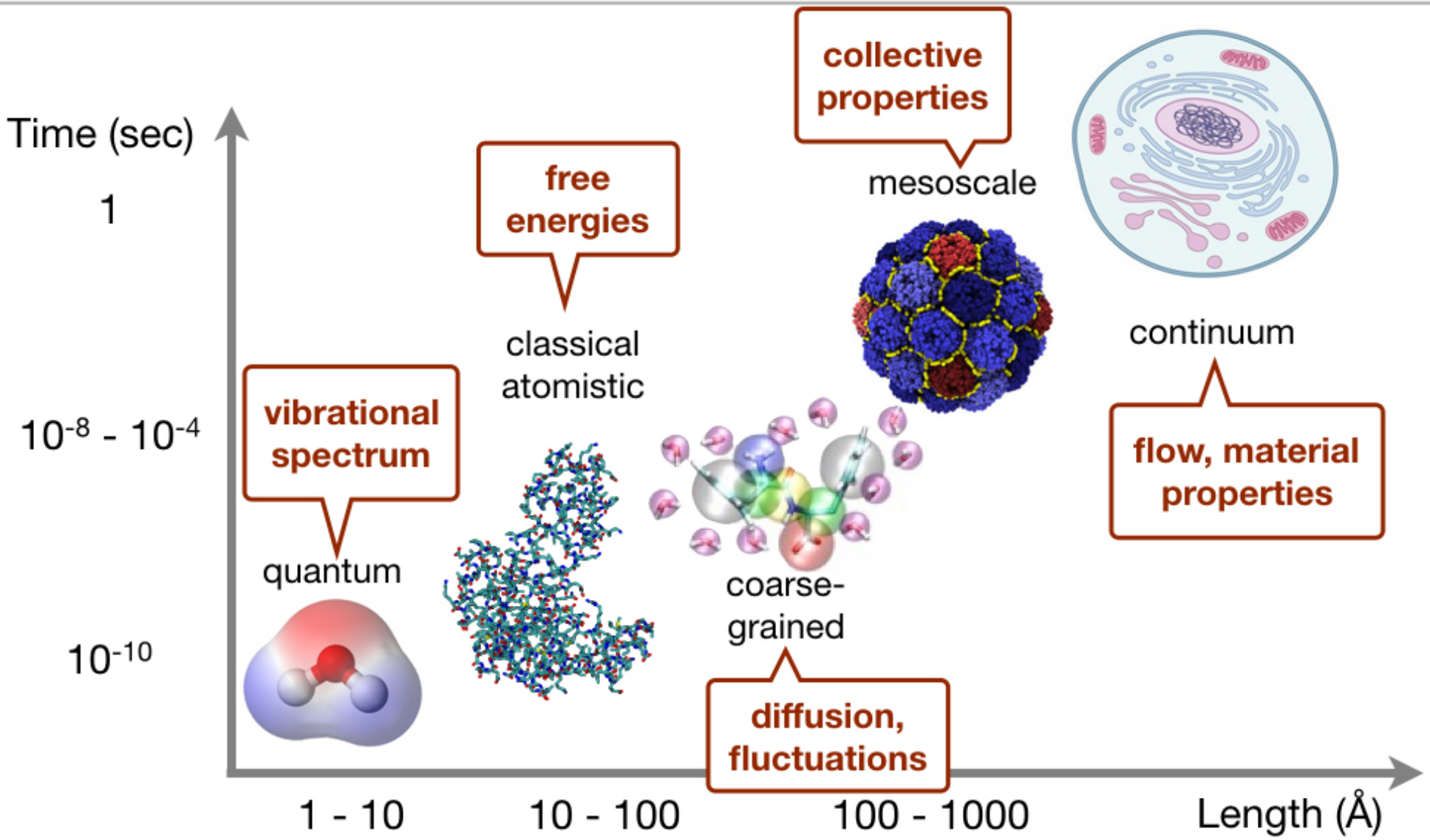

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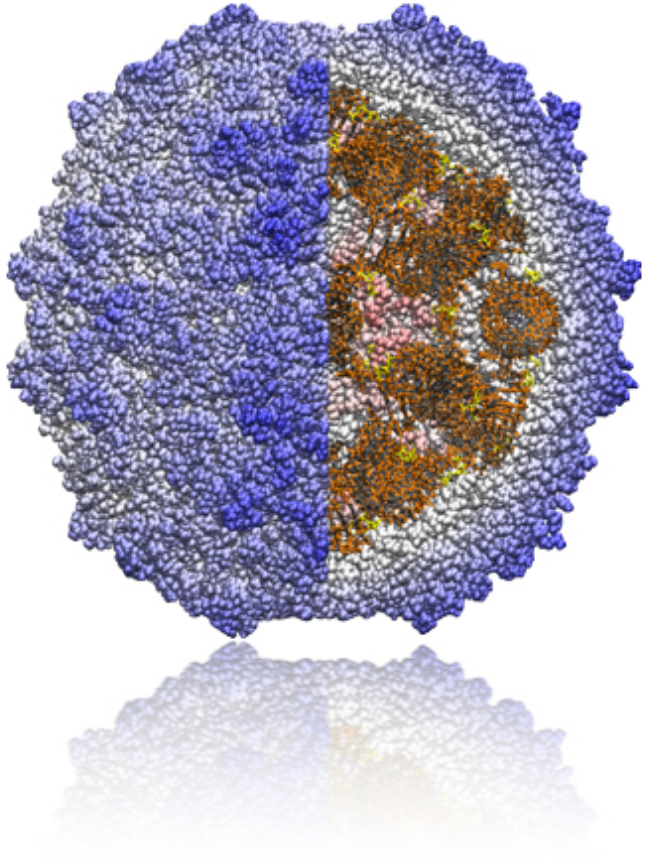

Fully atomistic simulation
of viral capsids (e.g. [1])

-10^6 atoms
-simulation duration: ~100ns

[1] P.L. Freddolino, A.S. Arkhipov, S.B. Larson, A. McPherson, K. Schulten, Structure 14, 2006

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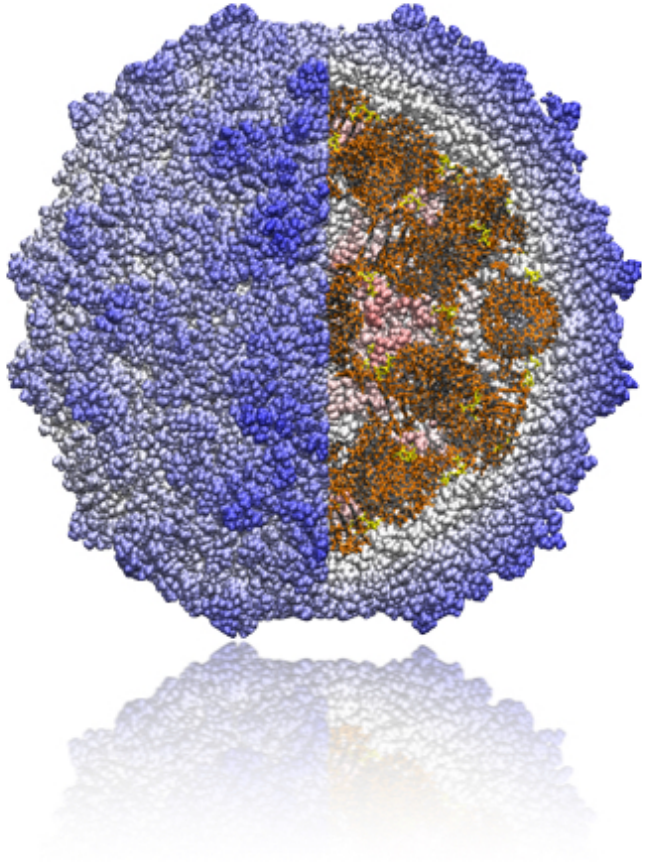

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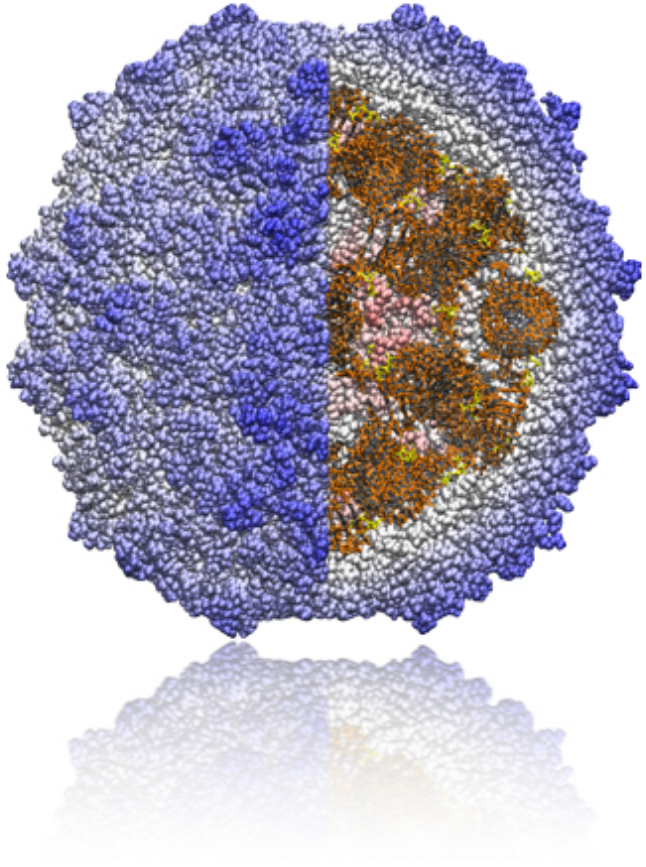

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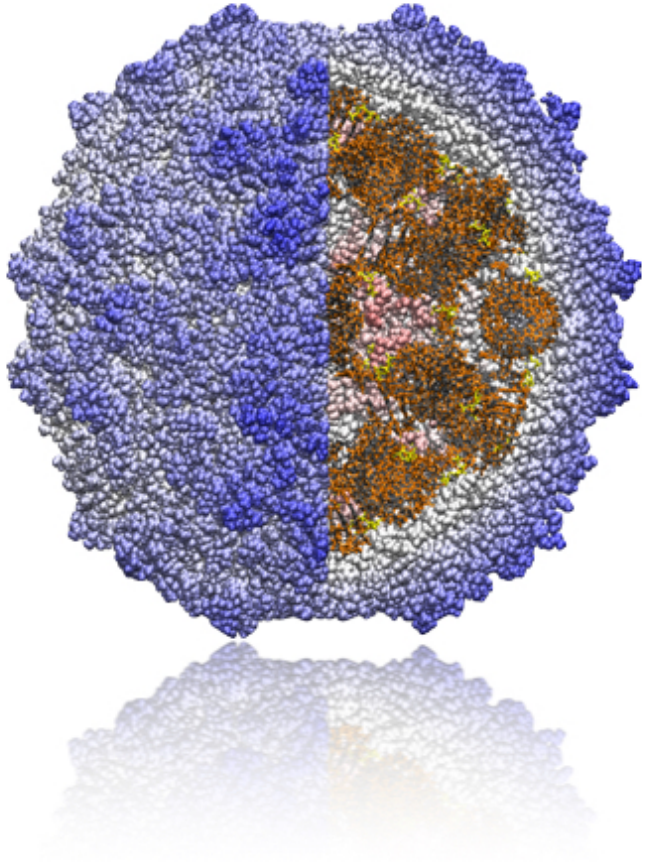

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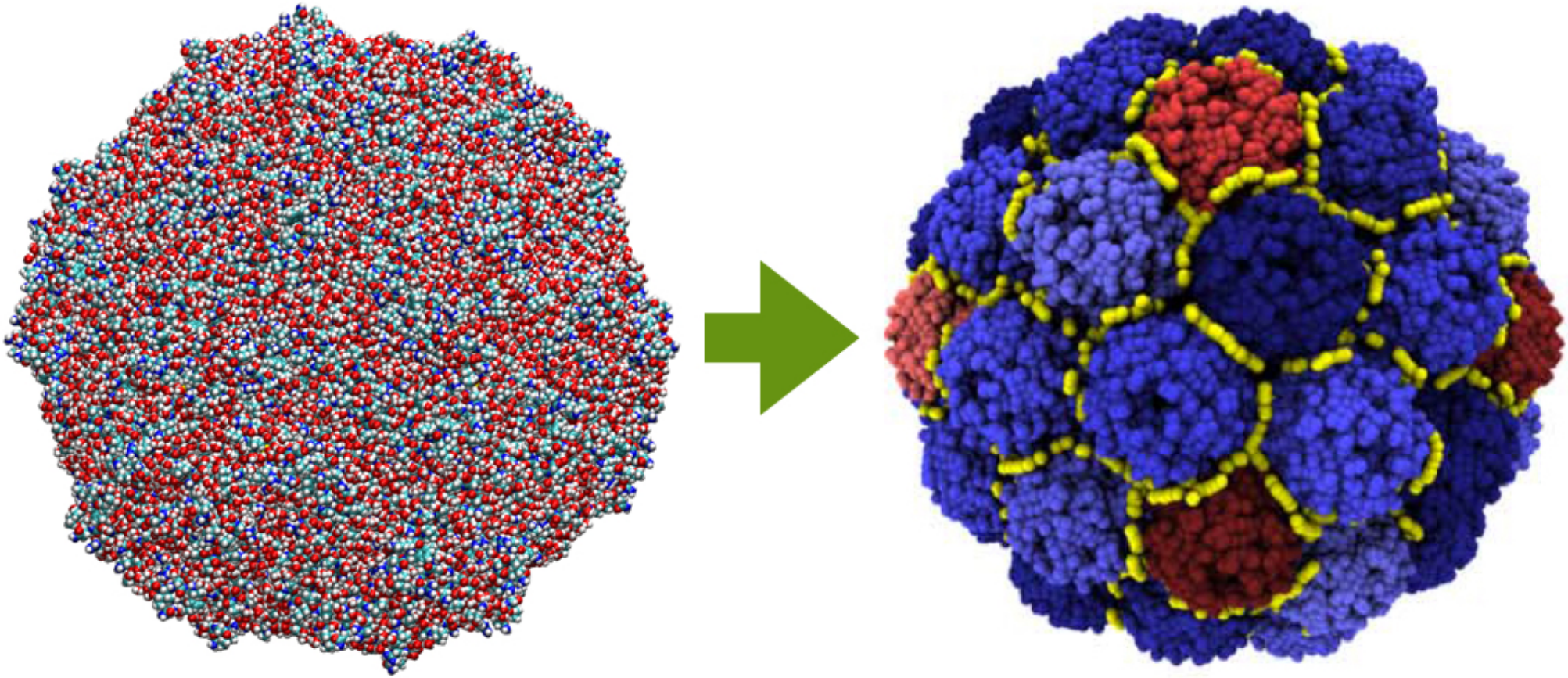
- Get more insight at modeling stage
- Explore the parameter space

[1] P.L. Freddolino, A.S. Arkhipov, S.B. Larson, A. McPherson, K. Schulten, Structure 14, 2006

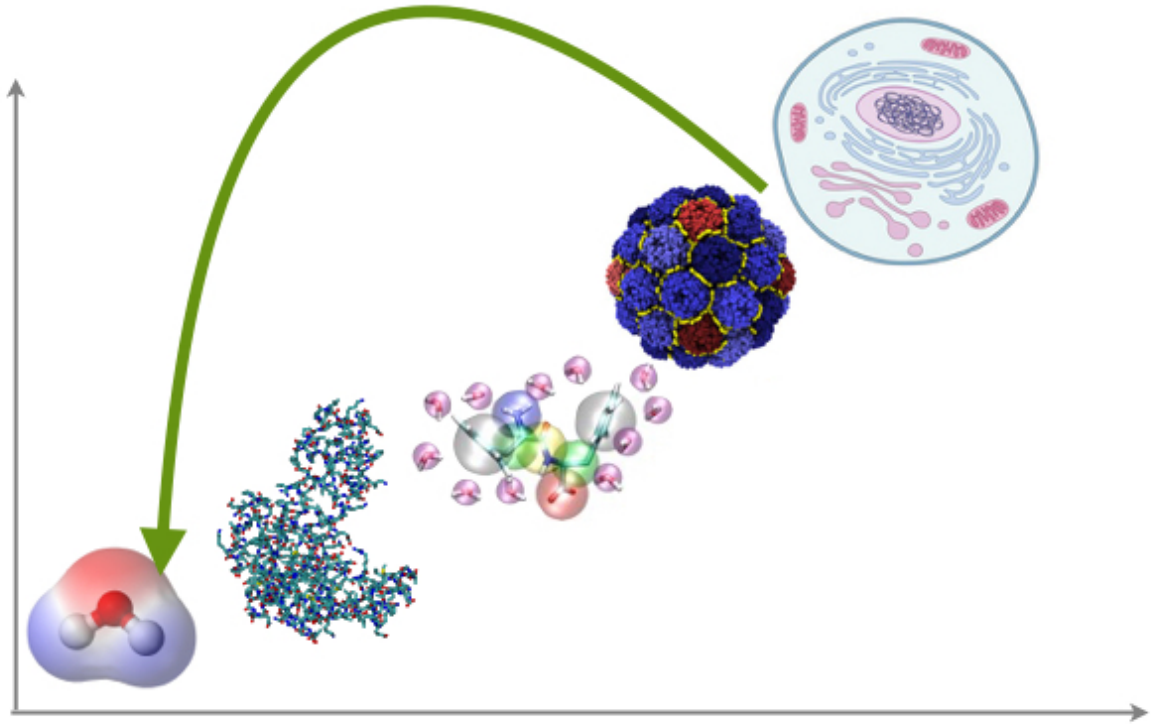
Modelling as a source of insight

**"It is nice to know that the computer understands the problem.
But I would like to understand it, too."
[Eugene Wigner]**



Coarse-graining methods in soft matter

TOP-DOWN APPROACHES
Higher-level knowledge is employed
to parametrize system interactions



Coarse-graining methods in soft matter

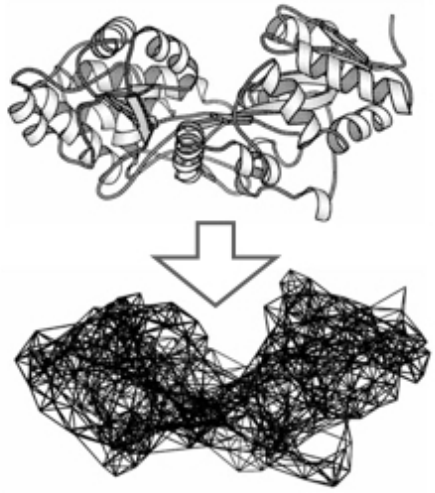
TOP-DOWN APPROACHES
Higher-level knowledge is employed
to parametrize system interactions

Elastic Network Models

The collective dynamics emerges from
a large number of small-scale interactions

$$E_p = \frac{1}{2}\sum_{\text{bonds}} K_b(b - b_0)^2 + \frac{1}{2}\sum_{\text{angles}} K_\theta(\theta - \theta_0)^2 + \frac{1}{2}\sum_{\text{dihedrals}} K_\phi[1 + \cos(n\phi - \delta)] + \sum_{\text{nonbonded pairs}}\left[\frac{A}{r^{12}} - \frac{B}{r^6} + \frac{q_1 q_2}{Dr}\right]. \quad (1)$$

$$E(\mathbf{r}_a, \mathbf{r}_b) = \frac{C}{2}\left(\frac{\mathbf{r}^0_{a,b} \cdot \Delta\mathbf{r}_{a,b}}{|\mathbf{r}^0_{a,b}|}\right)^2$$



M. Tirion, PRL (1996)
Figure by YH Sanejouand, from Monticelli and Saonen, Springer

Go Models

"Teleological" approach: interaction strength
determined by the folded 3D structure

Taketomi, Ueda, Go, Int J Pept ProteinRes, 7, 445 (1975)

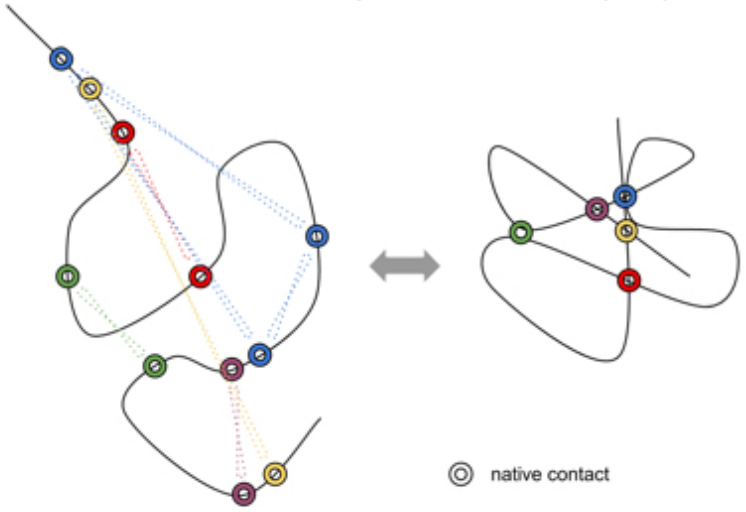
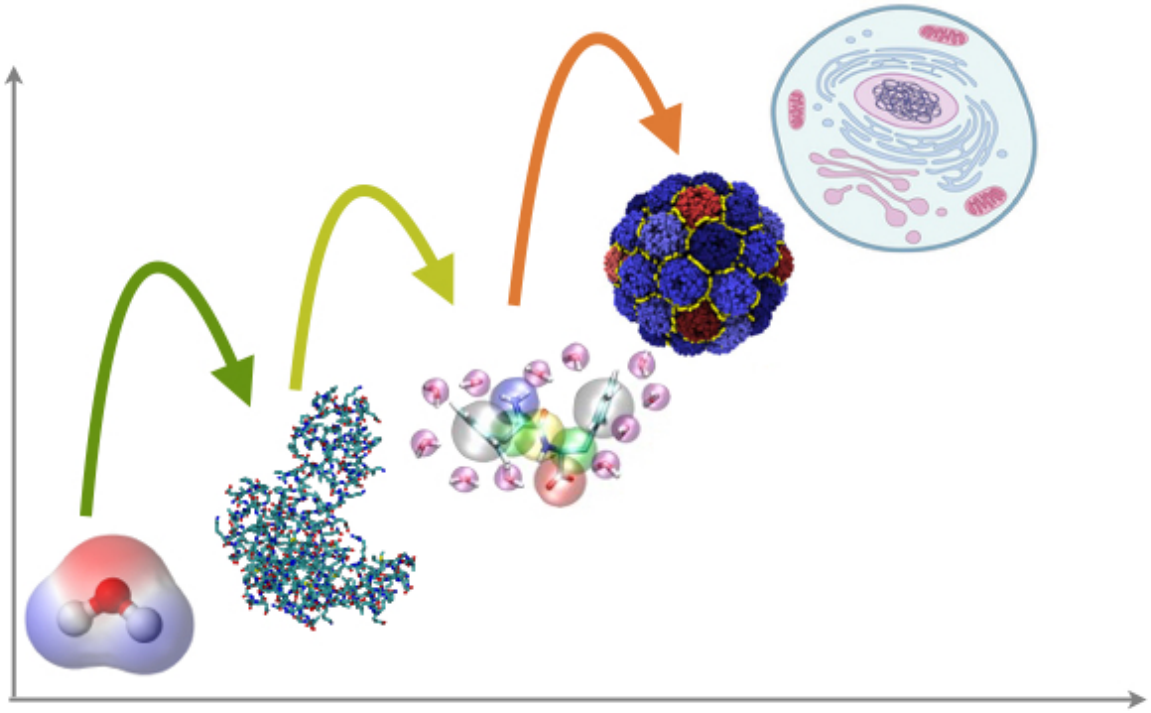


Figure by S. Demharter http://www.blopig.com/blog/2014/03/journal-club-the-role-of-native-contacts-in-folding-of-small-proteins/

Coarse-graining methods in soft matter

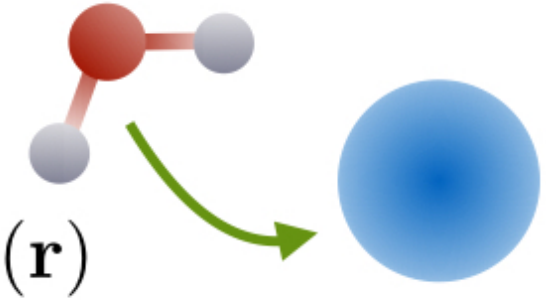
BOTTOM-UP APPROACHES
OR SYSTEMATIC COARSE-GRAINING

Systematic inclusion of higher-resolution details into effective interactions among coarse-grained sites



Coarse-graining methods in soft matter

Systematic CG'ing requires:



- **a mapping function** $\mathbf{R}_I = M(\mathbf{r})$

- **a consistency criterion** $p_R(\mathbf{R}) = \langle \delta(M(\mathbf{r}) - \mathbf{R}) \rangle$

$$P_R(\mathbf{R}) = p_R(\mathbf{R})$$

Multi-body PMF $U(\mathbf{R}) = -k_B T \ln z(\mathbf{R})$

$$z(\mathbf{R}) = \int d\mathbf{r} \ \exp[-u(\mathbf{r})/k_B T] \ \delta(M(\mathbf{r}) - \mathbf{R})$$

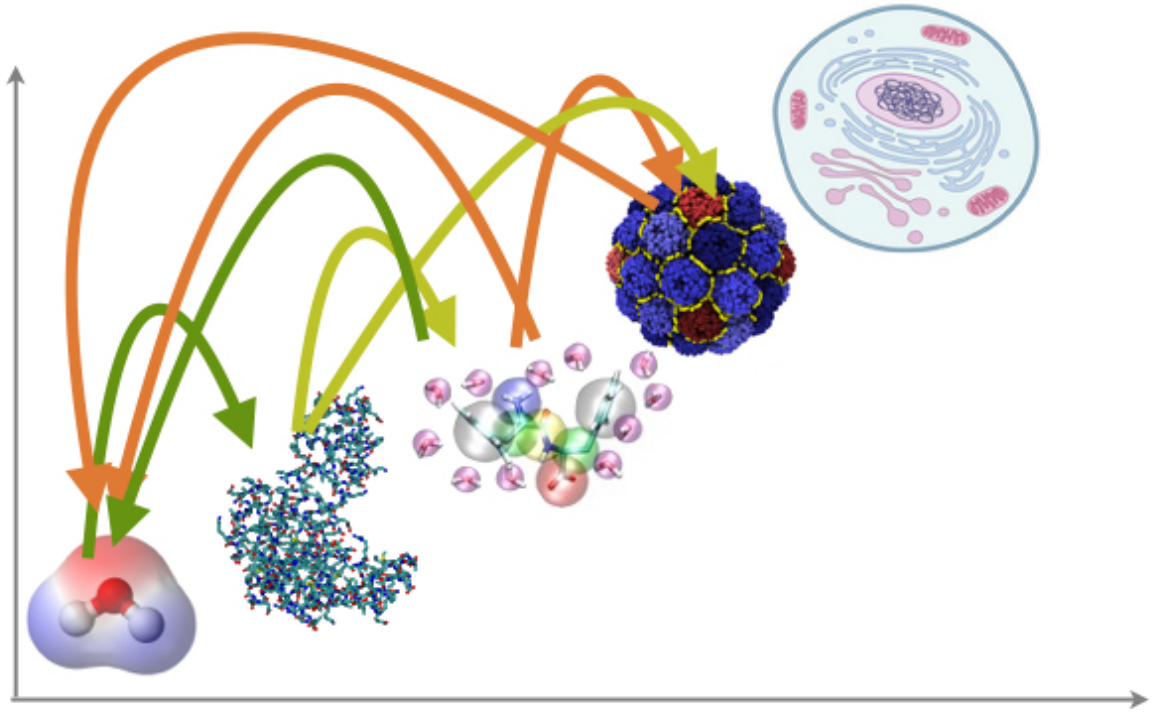
The big issue: approximate the MB PMF

Coarse-graining methods in soft matter

CONCURRENT MULTI-RESOLUTION APPROACHES

Interplay and feedback between different scales

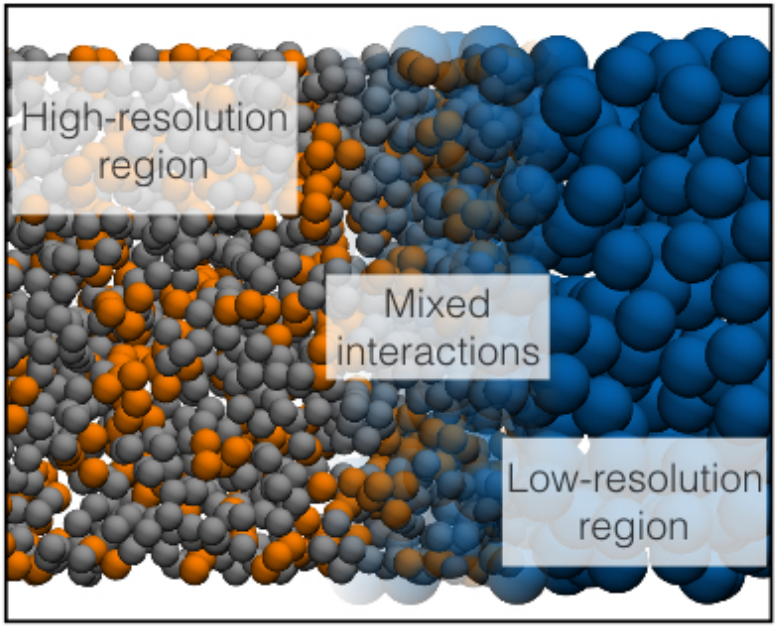
No effective decoupling possible

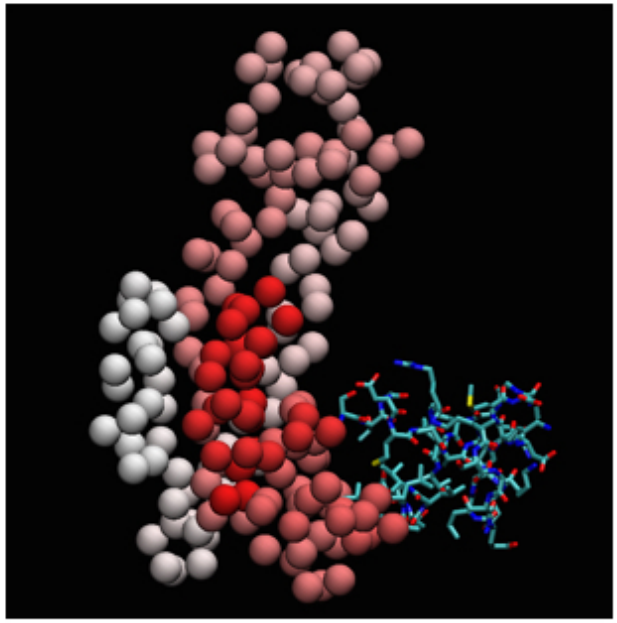


Concurrent multi-resolution approaches

In principle the **highest resolution level** has to be retained

Alternative solution available if there is a **spatial separation** between the **interesting** and the **necessary** DoFs



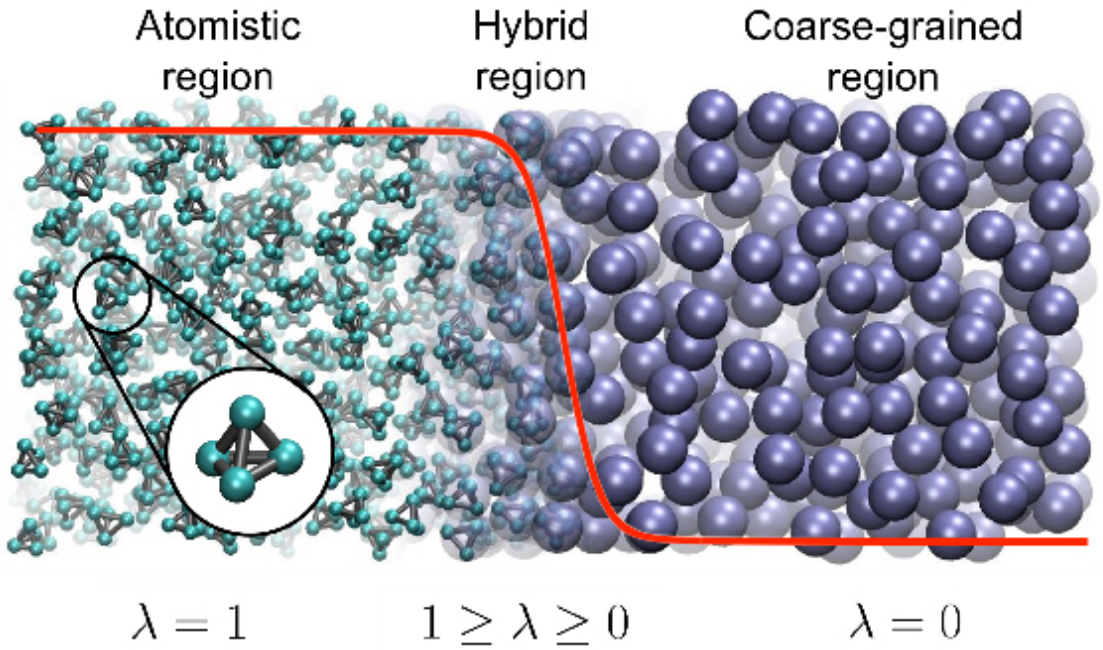


Models at different resolution are concurrently employed in different parts of the systems

AdResS
Adaptive Resolution Simulation scheme

Interpolation of the two-body force

$$\mathbf{F}_{\alpha\beta} = \lambda(\mathbf{R}_\alpha)\lambda(\mathbf{R}_\beta)\mathbf{F}^{AA}_{\alpha\beta} + (1 - \lambda(\mathbf{R}_\alpha)\lambda(\mathbf{R}_\beta))\mathbf{F}^{CG}_{\alpha\beta}$$

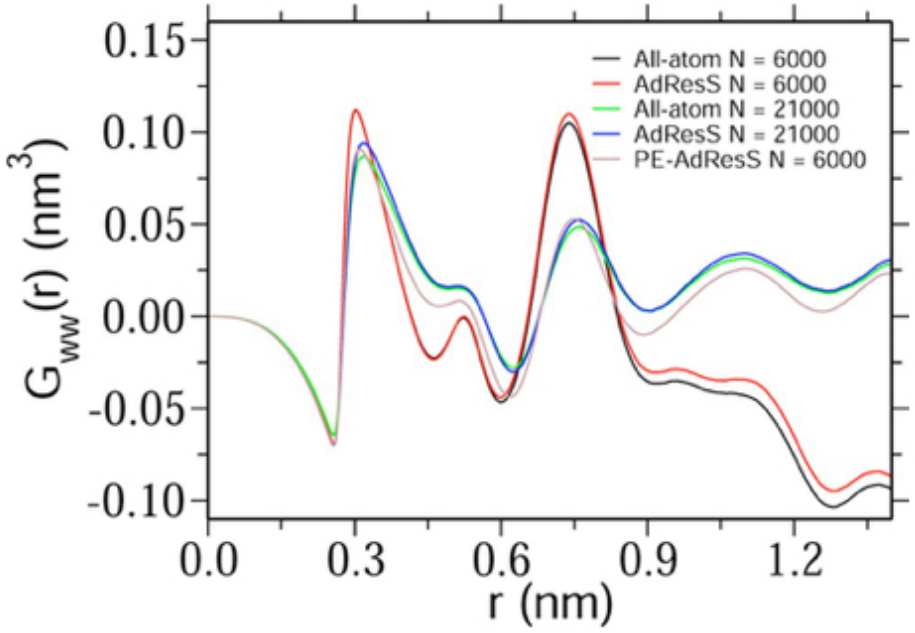


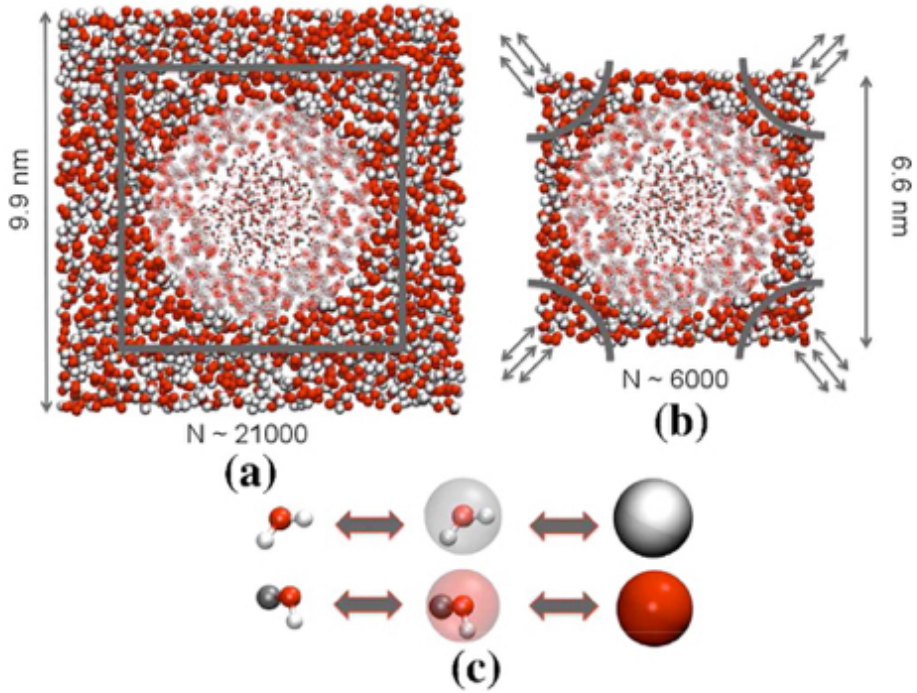
M. Praprotnik, L. Delle Site, and K. Kremer, J. Chem. Phys. 123, 2005

Quasi-Grand Canonical simulations

PNIPAm conformational transition as a function of cosolvent concentration

System size effects impact the cosolvent molecule number fluctuations





In the CG region the solvent/cosolvent identity is swapped via a Metropolis algorithm

The AA region behaves as an open system
Smaller system sizes can be employed

D. Mukherji, K. Kremer, Macromolecules 46, 2013

AdResS force-based interpolation: pros & cons

- Simplest strategy possible
- Newton's Third Law is preserved (antisymmetric force)
- No force containing derivatives of the switch function
- No Hamiltonian function exists
- A local thermostat is needed for stable simulations
- No NVE or Monte Carlo simulations
- No theory based on the partition function

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Is a Hamiltonian formulation viable?

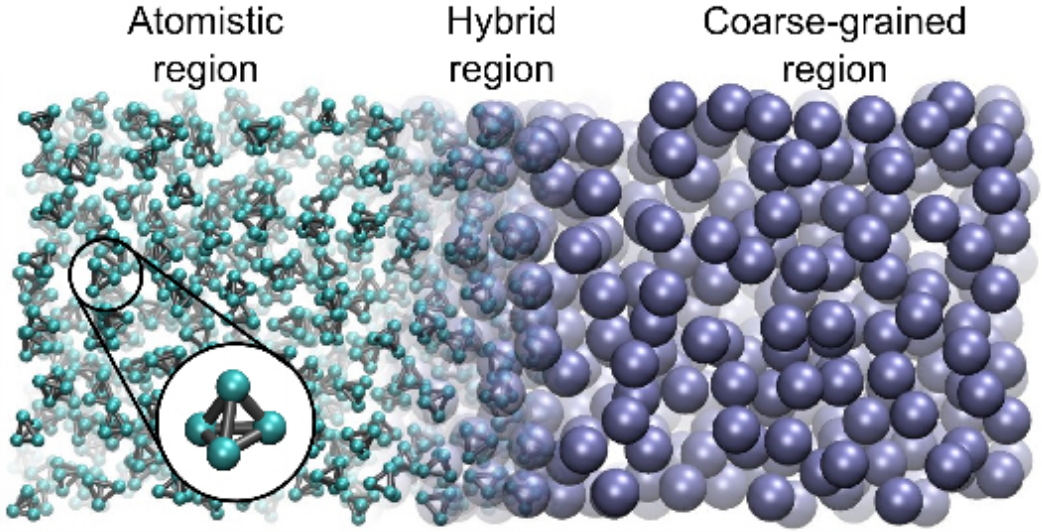
H-AdResS
Hamiltonian Adaptive Resolution Simulation

$$H = \mathcal{K} + V^{int} + \sum_{\alpha} \left\{ \lambda_\alpha V_\alpha^{AA} + (1-\lambda_\alpha) V_\alpha^{CG} \right\}$$

$$V_\alpha^{\mathrm{AA}} \equiv \frac{1}{2} \sum_{\beta,\beta\neq\alpha}^{N} \sum_{ij} V^{AA}(|\mathbf{r}_{\alpha i} - \mathbf{r}_{\beta j}|)$$

$$V_\alpha^{\mathrm{CG}} \equiv \frac{1}{2} \sum_{\beta,\beta\neq\alpha}^{N} V^{CG}(|\mathbf{R}_\alpha - \mathbf{R}_\beta|)$$

$$\lambda_\alpha = \lambda(\mathbf{R}_\alpha)$$



RP, S. Fritsch, P. Español, R. Delgado-Buscalioni, K. Kremer, R. Everaers and D. Donadio, Phys. Rev. Lett. 110, 108301 (2013)

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$$\begin{aligned} \mathbf{F}_\alpha &= \mathbf{F}_\alpha^{int} + \sum_{\beta, \beta \neq \alpha} \left\{ \frac{\lambda_\alpha + \lambda_\beta}{2} \mathbf{F}_{\alpha|\beta}^{AA} + \left(1 - \frac{\lambda_\alpha + \lambda_\beta}{2} \right) \mathbf{F}_{\alpha|\beta}^{CG} \right\} \\ &- \left[V_\alpha^{AA} - V_\alpha^{CG} \right] \nabla_\alpha \lambda_\alpha \end{aligned}$$

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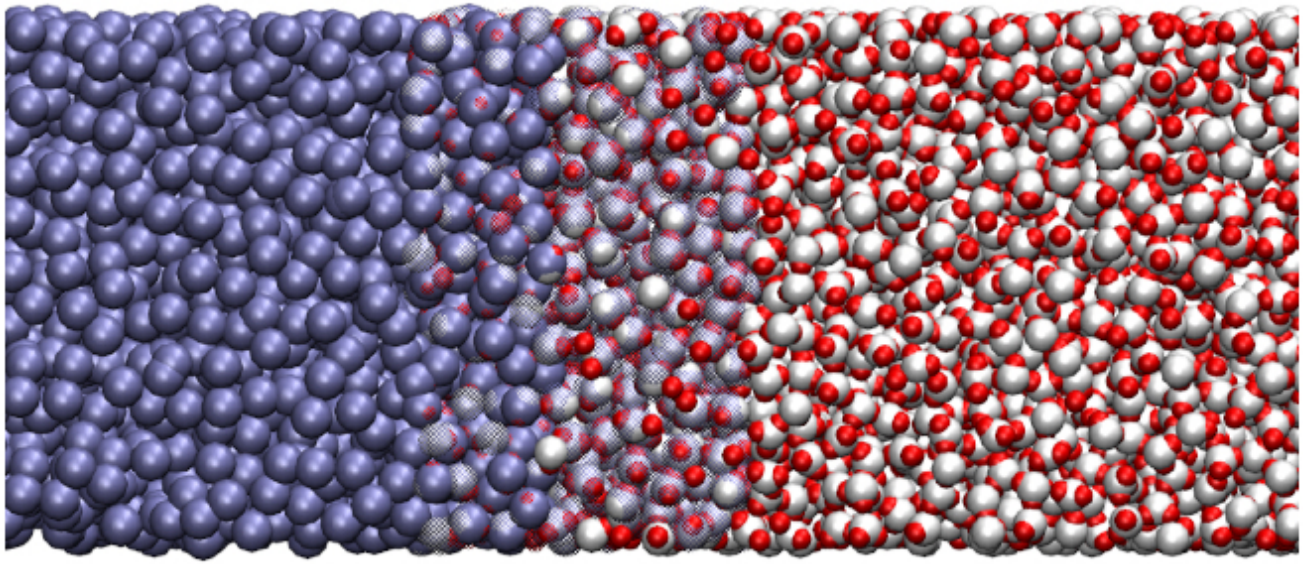
Drift force and density imbalance compensation



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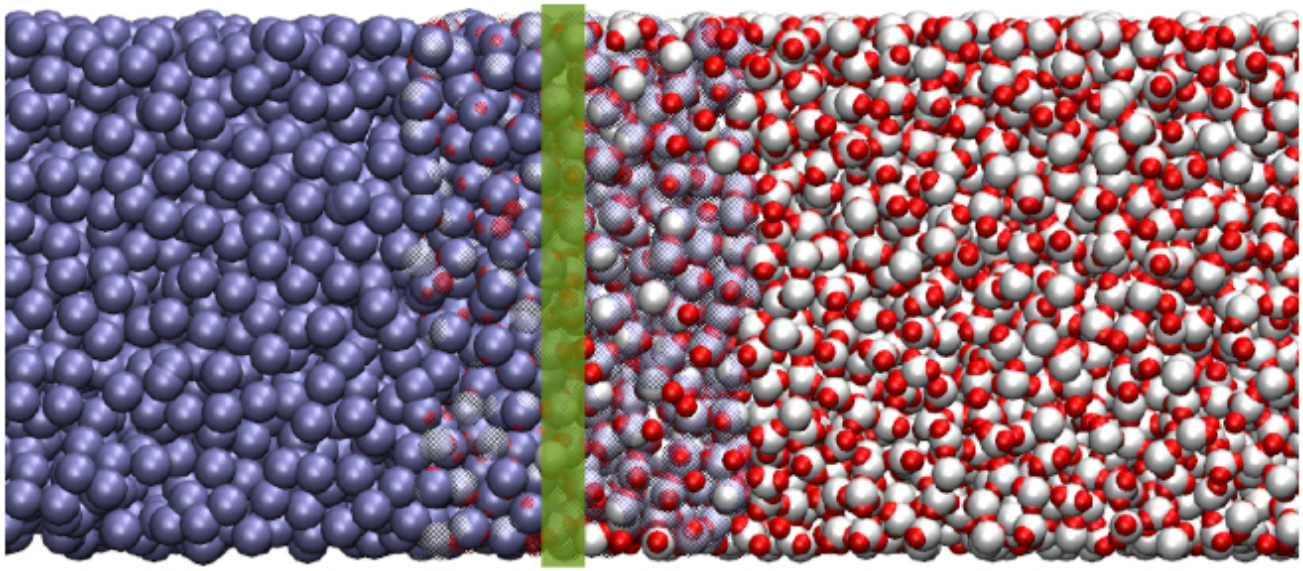
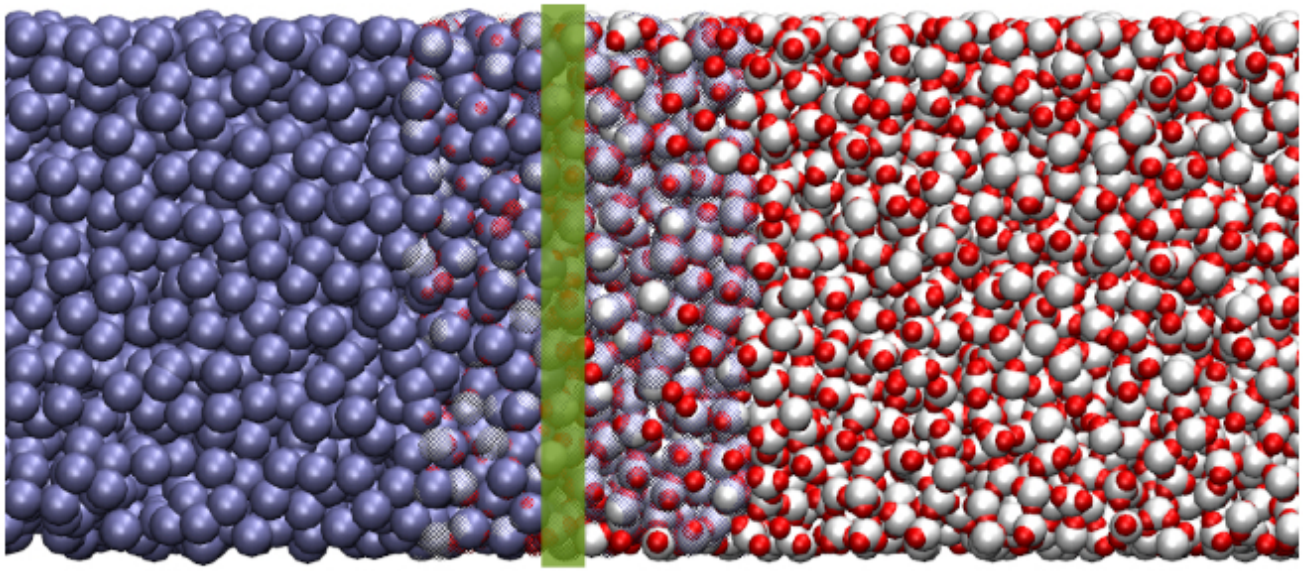


$$\mathbf{R}_\alpha, \lambda_\alpha$$

Drift force and density imbalance compensation



$$\mathbf{R}_\alpha, \lambda_\alpha$$

$$\left\langle \mathbf{F}_\alpha^\nabla \right\rangle = -\left\langle [V_\alpha^{AA} - V_\alpha^{CG}] \right\rangle_{\mathbf{R}_\alpha} \nabla\lambda(\mathbf{R}_\alpha)$$

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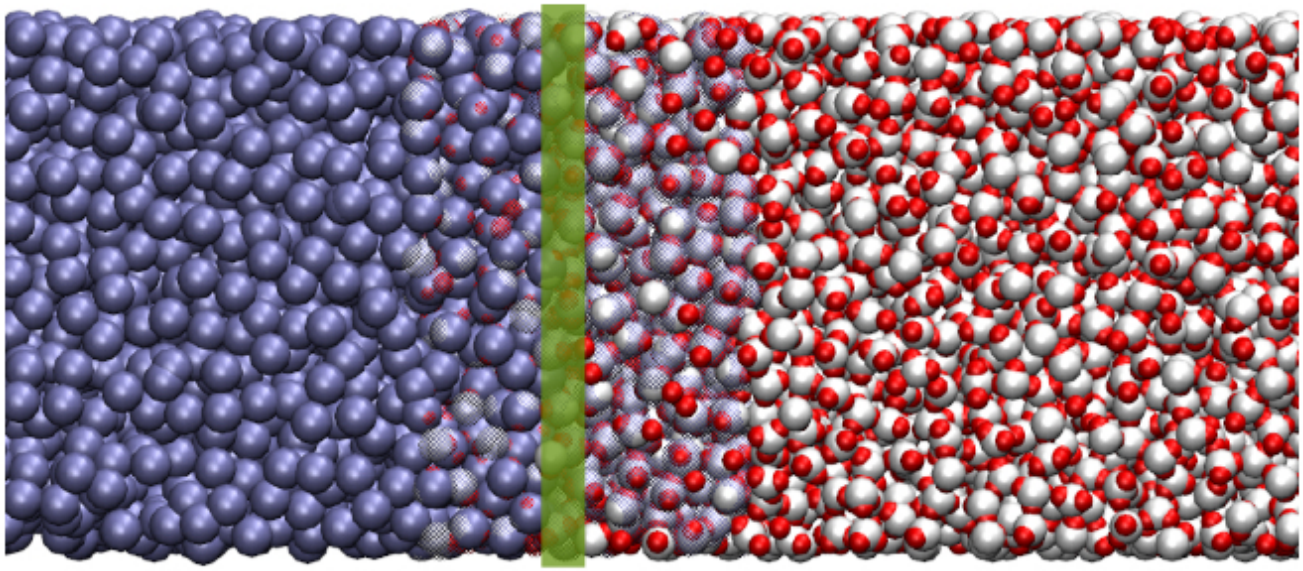

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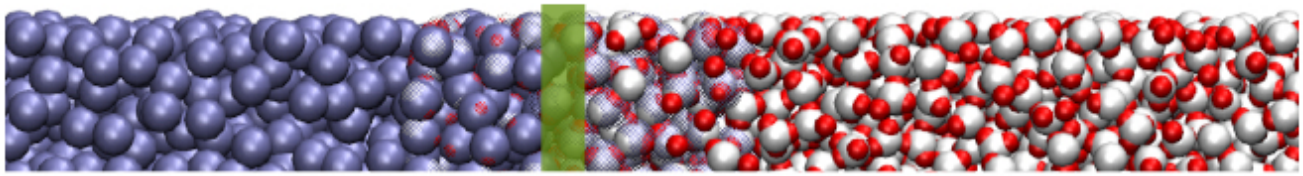
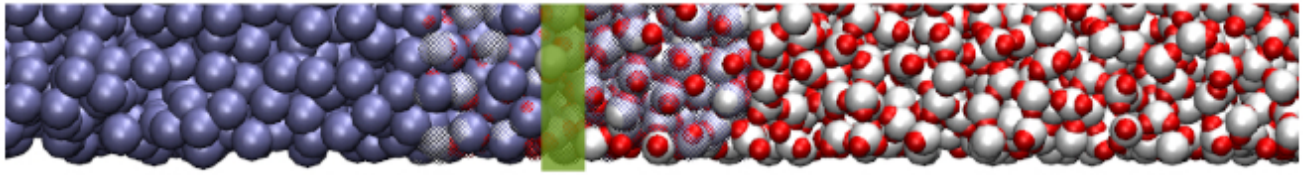


The force in the hybrid region is proportional
to the gradient of Helmholtz free energy
as a function of the resolution



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Drift force and density imbalance compensation

Modify the Hamiltonian introducing a compensation term

$$H_\Delta = H - \sum_{\alpha=1}^{N} \Delta H(\lambda(\mathbf{R}_\alpha))$$

$$\left\langle [V_\alpha^{AA} - V_\alpha^{CG}] \right\rangle_{\mathbf{R}_\alpha} \simeq \frac{1}{N} \frac{dF(\lambda)}{d\lambda}$$

$$\Delta H(\lambda) \equiv \frac{\Delta F(\lambda)}{N}$$

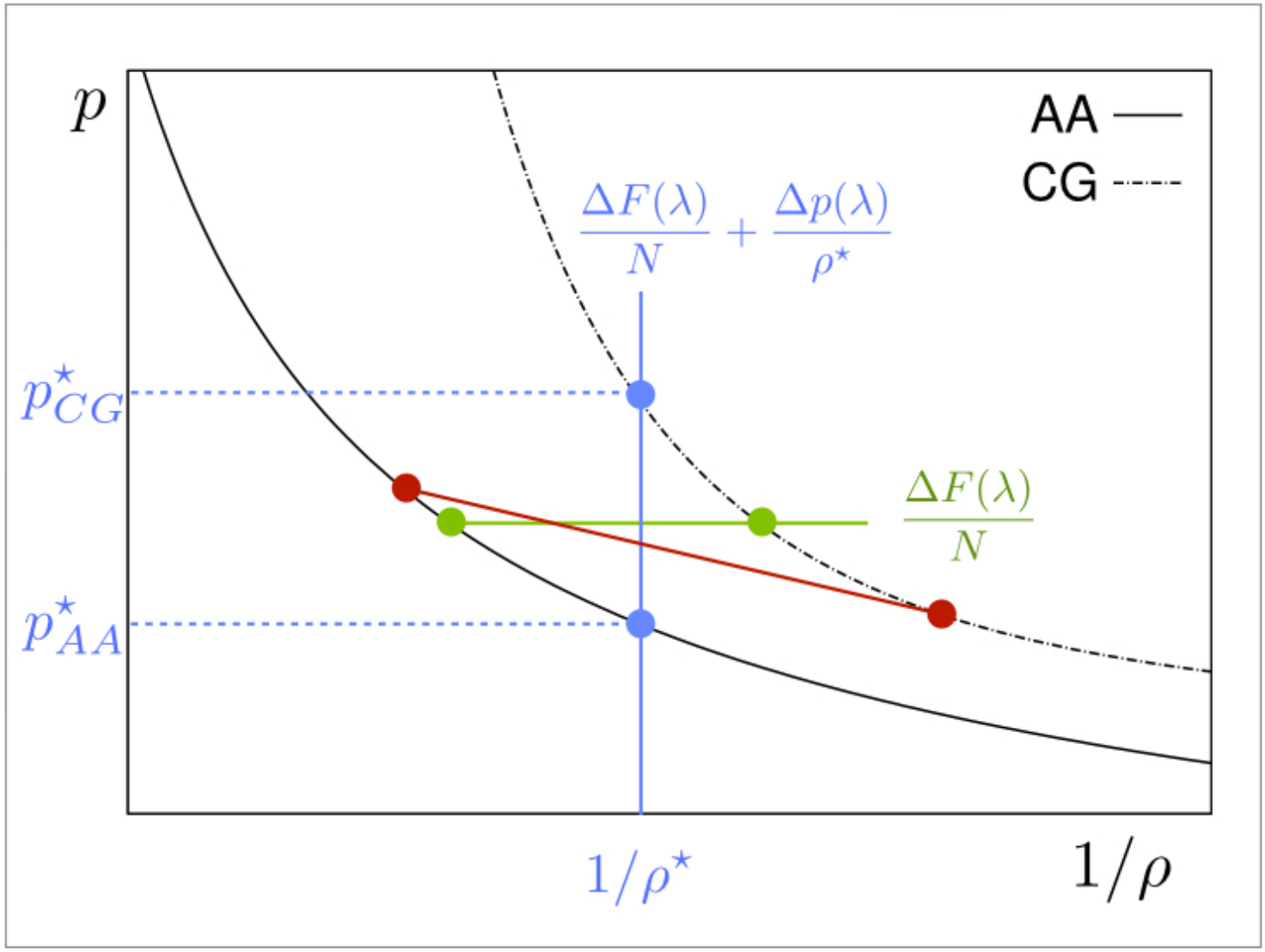
Helmholtz free energy cancels the drift force in the hybrid region

Gibbs free energy removes also the density imbalance between AA and CG

$$\Delta H(\lambda) \equiv \Delta\mu(\lambda) = \frac{\Delta F(\lambda)}{N} + \frac{\Delta p(\lambda)}{\rho^\star}$$

M. Heidari, R. Cortes Huerto, D. Donadio and RP, EPJ ST (2016)

H-AdResS: the big picture



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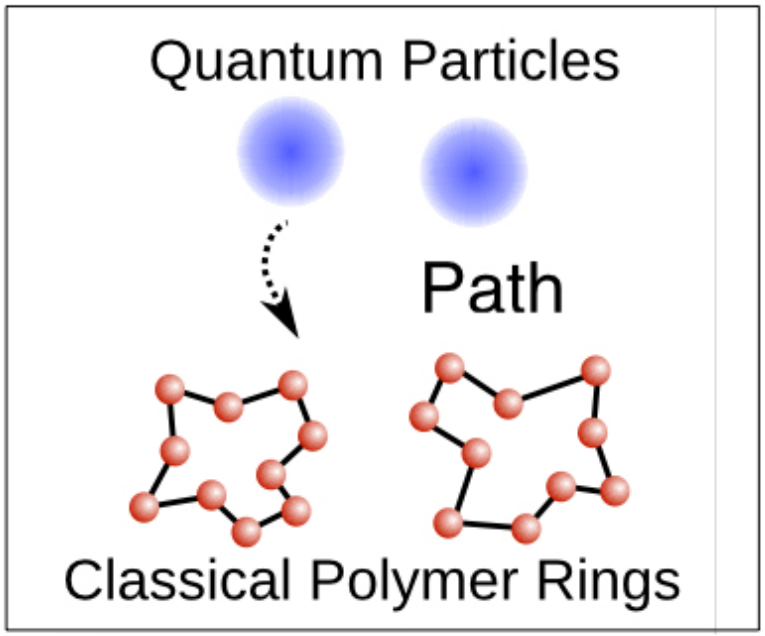
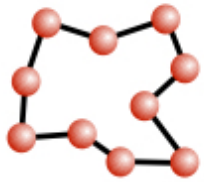
H-AdResS Quantum/Classical coupling



$$m \rightarrow \mu(\lambda) = \lambda m + (1-\lambda) M$$

$$\mu(\lambda = 1) = m$$



$$\mu(\lambda = 0) = M$$

$$V_P^{\mu} = \sum_{l=1}^{P} \sum_{\alpha=1}^{N} \left\{ \frac{\mu_{\alpha,l}\ \omega_P^2}{2} |\mathbf{r}_{\alpha,l} - \mathbf{r}_{\alpha,l+1}|^2 - \frac{3}{2\beta} \log \frac{\mu_{\alpha,l}}{m} + \frac{1}{P} \left[\lambda_{\alpha,l} V_{\alpha,l}^1 + (1-\lambda_{\alpha,l}) V_{\alpha,l}^0 - \Delta H(\lambda_{\alpha,l}) \right] \right\}$$

K. Kreis, M. E. Tuckerman, D. Donadio, K. Kremer and RP, JCTC (2016)
K. Kreis, K. Kremer, RP, M. E. Tuckerman, JCP (2017)

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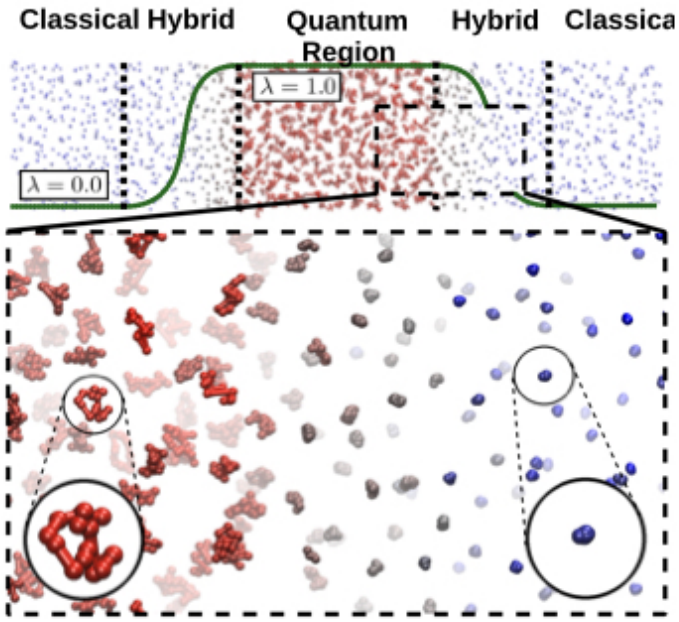

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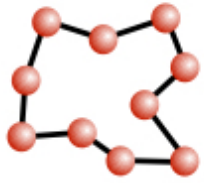
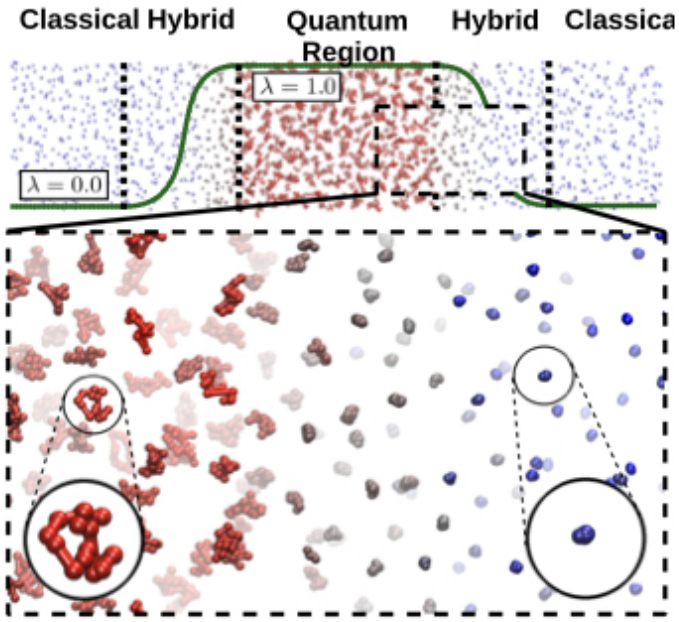


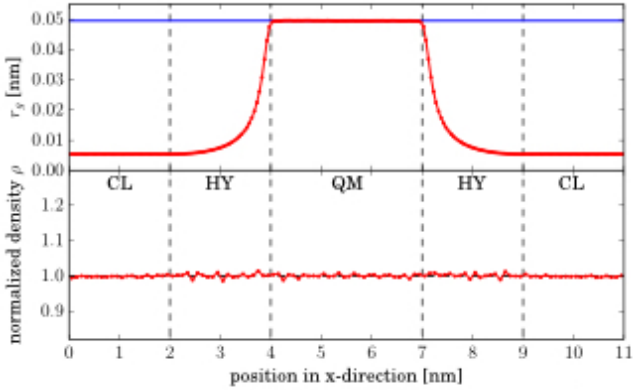
$$\mu(\lambda = 0) = M$$

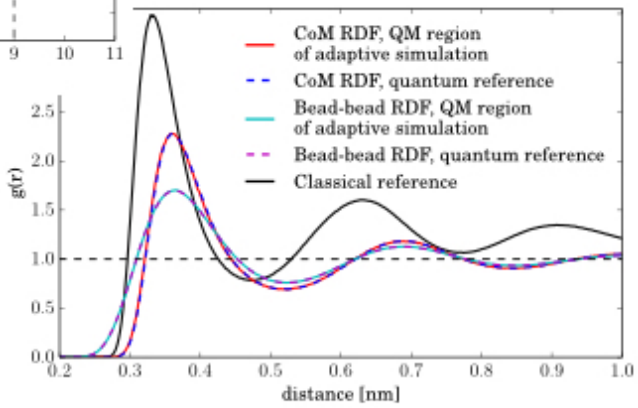
$$V_P^{\mu} = \sum_{l=1}^{P} \sum_{\alpha=1}^{N} \left\{ \frac{\mu_{\alpha,l}\ \omega_P^2}{2} |\mathbf{r}_{\alpha,l} - \mathbf{r}_{\alpha,l+1}|^2 - \frac{3}{2\beta} \log \frac{\mu_{\alpha,l}}{m} + \frac{1}{P} \left[\lambda_{\alpha,l} V_{\alpha,l}^1 + (1-\lambda_{\alpha,l}) V_{\alpha,l}^0 - \Delta H(\lambda_{\alpha,l}) \right] \right\}$$

K. Kreis, M. E. Tuckerman, D. Donadio, K. Kremer and RP, JCTC (2016)
K. Kreis, K. Kremer, RP, M. E. Tuckerman, JCP (2017)

H-AdResS Quantum/Classical coupling







$$V_P^\mu = \sum_{l=1}^{P} \sum_{\alpha=1}^{N} \left\{ \frac{\mu_{\alpha,l}\ \omega_P^2}{2} |\mathbf{r}_{\alpha,l} - \mathbf{r}_{\alpha,l+1}|^2 - \frac{3}{2\beta} \log \frac{\mu_{\alpha,l}}{m} + \frac{1}{P} \left[\lambda_{\alpha,l} V_{\alpha,l}^1 + (1 - \lambda_{\alpha,l}) V_{\alpha,l}^0 - \Delta H(\lambda_{\alpha,l}) \right] \right\}$$

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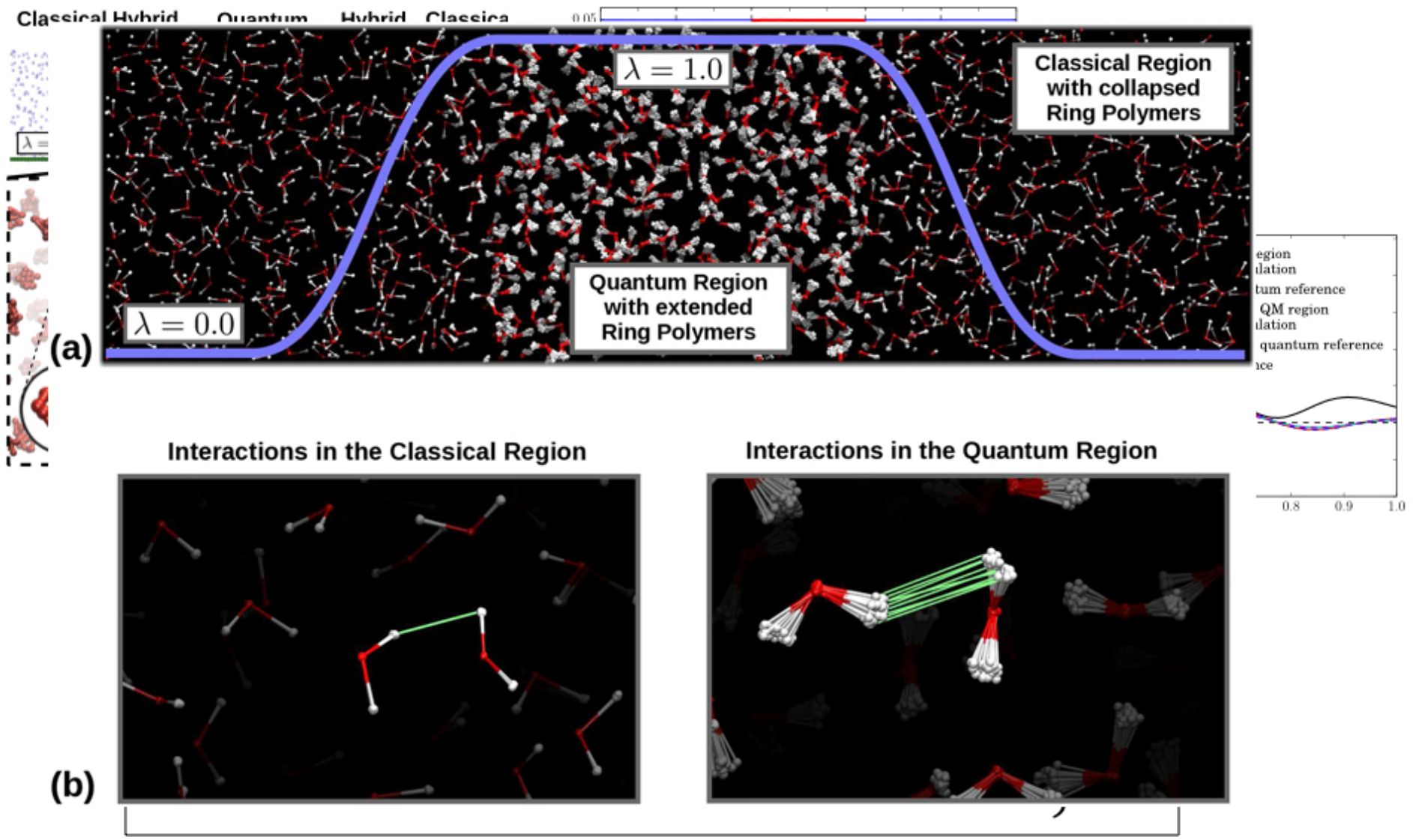

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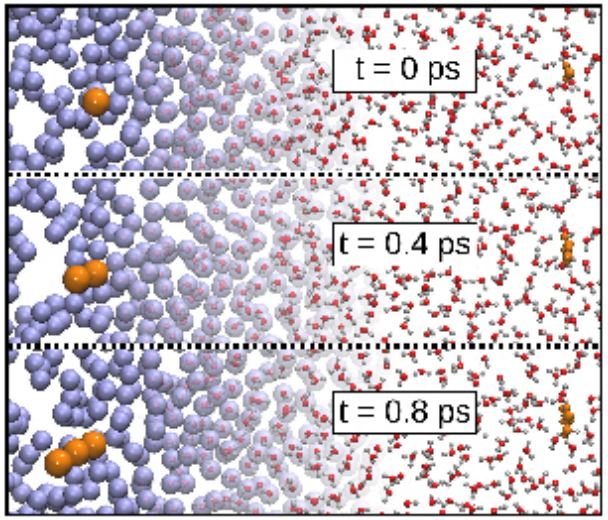
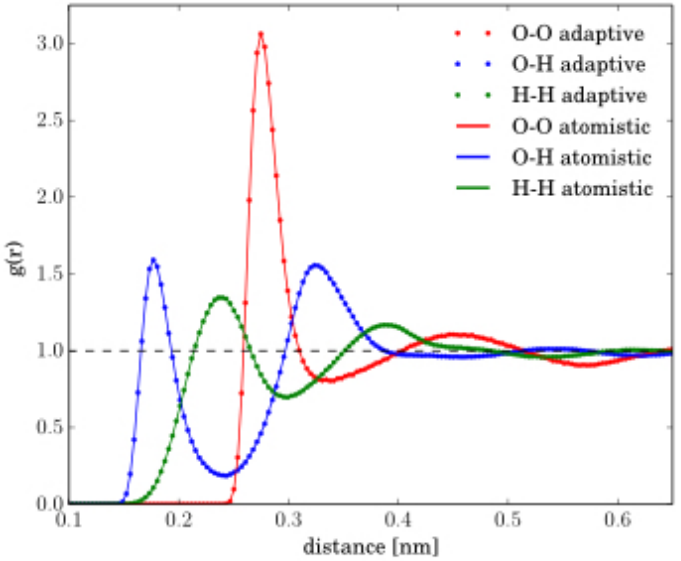
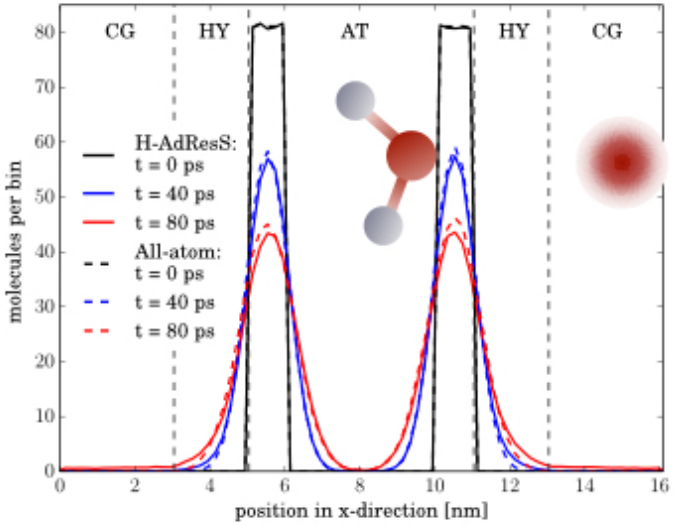
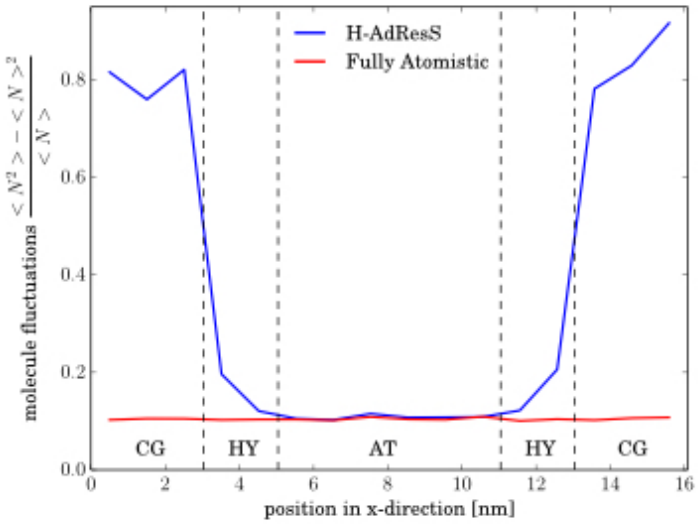
H-AdResS water/ideal gas coupling



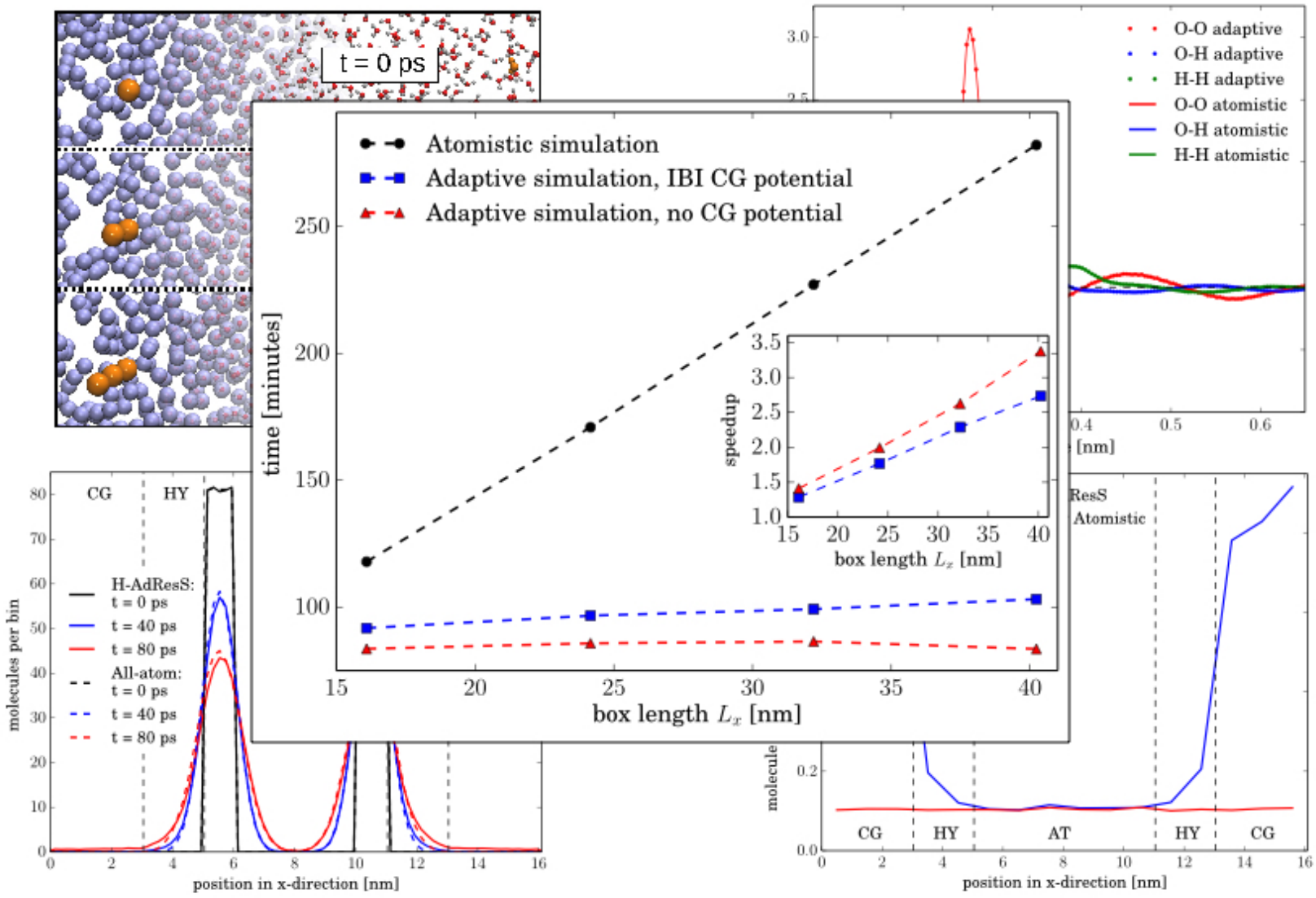






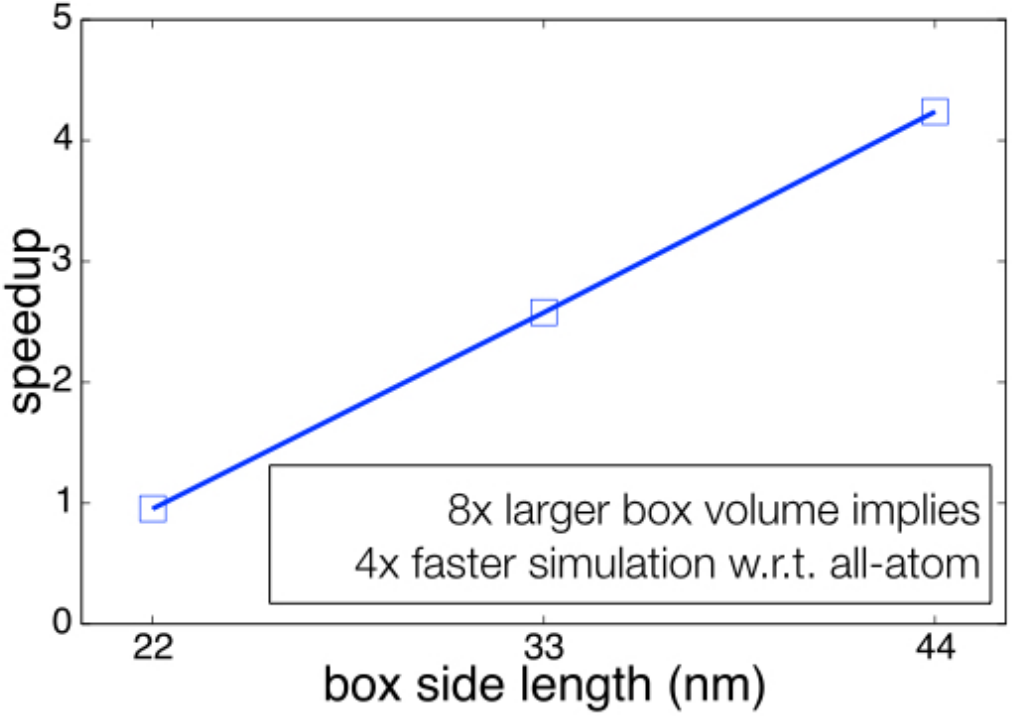
K. Kreis, A.C. Fogarty, K. Kremer, RP, EPJ-ST 2015

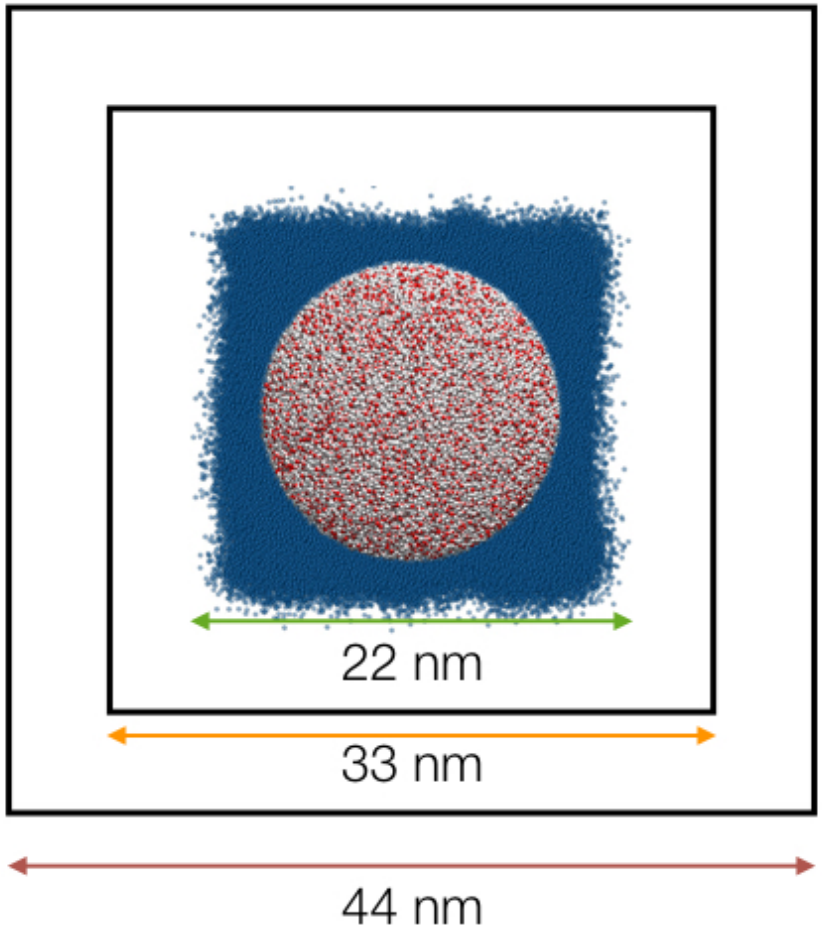
H-AdResS water/ideal gas coupling



K. Kreis, A.C. Fogarty, K. Kremer, RP, EPJ-ST 2015

Coupling all-atom and ideal gas models



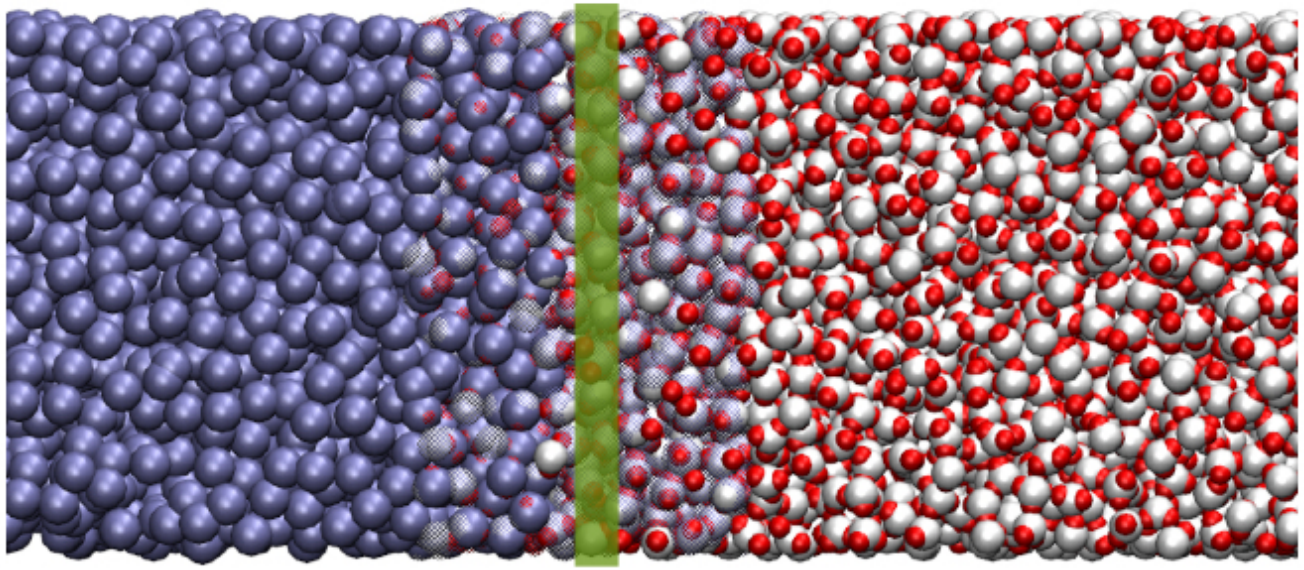


System setup

- Water in cubic box
- H-AdResS adaptive resolution simulation
- All-atom SPC/E water model coupled to ideal gas
- Spherical atomistic region of 9 nm radius *(kept fixed)*
- Box side of 22, 33, 44 nm (reps. 902286, 3090900, 7218309 atoms)
- 1000 time steps (dt = 1 fs)
- Single core runs on Intel(R) Core(TM) i5-4690 CPU @ 3.50GHz
- Spherical atomistic region size compatible with solvated STMV viral capsid

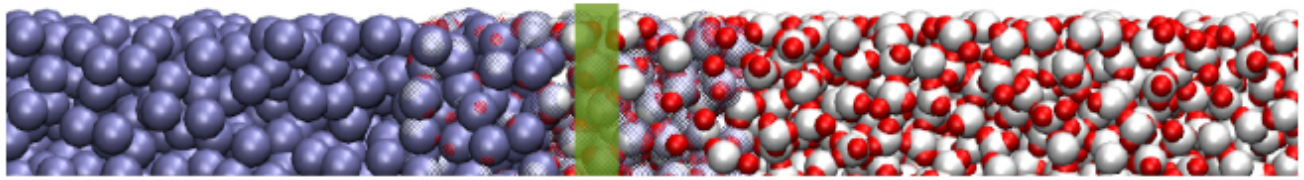
Simulations by M. Heidari, MPIP

Dual-res simulations for chemical physics

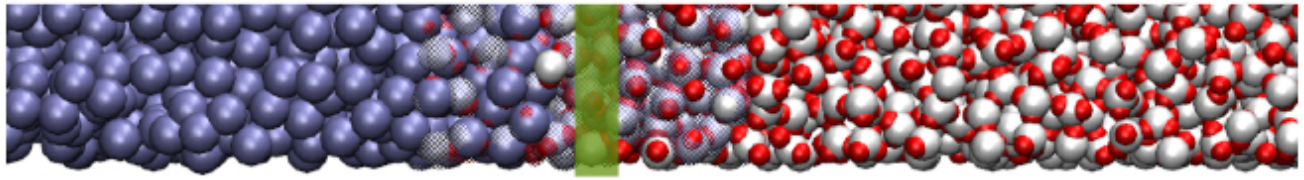


$$\mathbf{R}_\alpha, \lambda_\alpha$$

Dual-res simulations for chemical physics



The drift force in the hybrid region
pushes molecules where the free energy is lower



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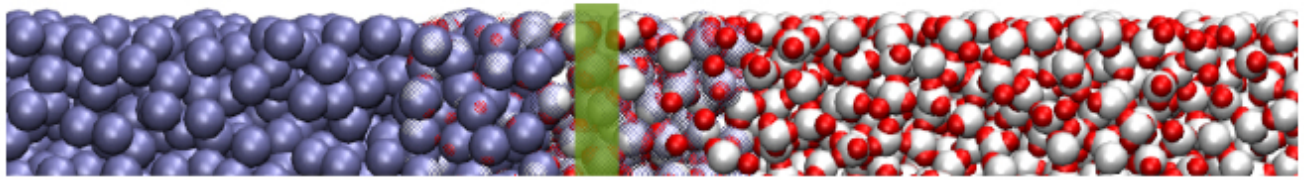

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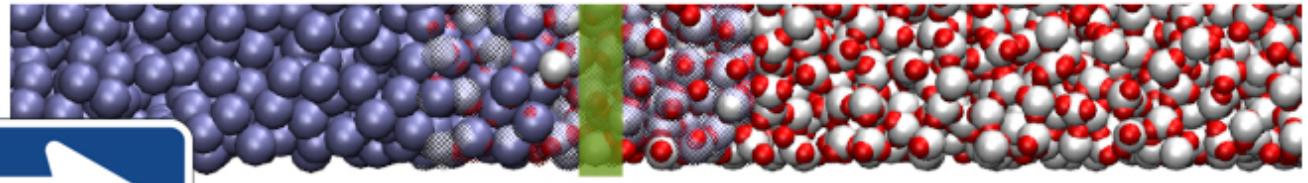
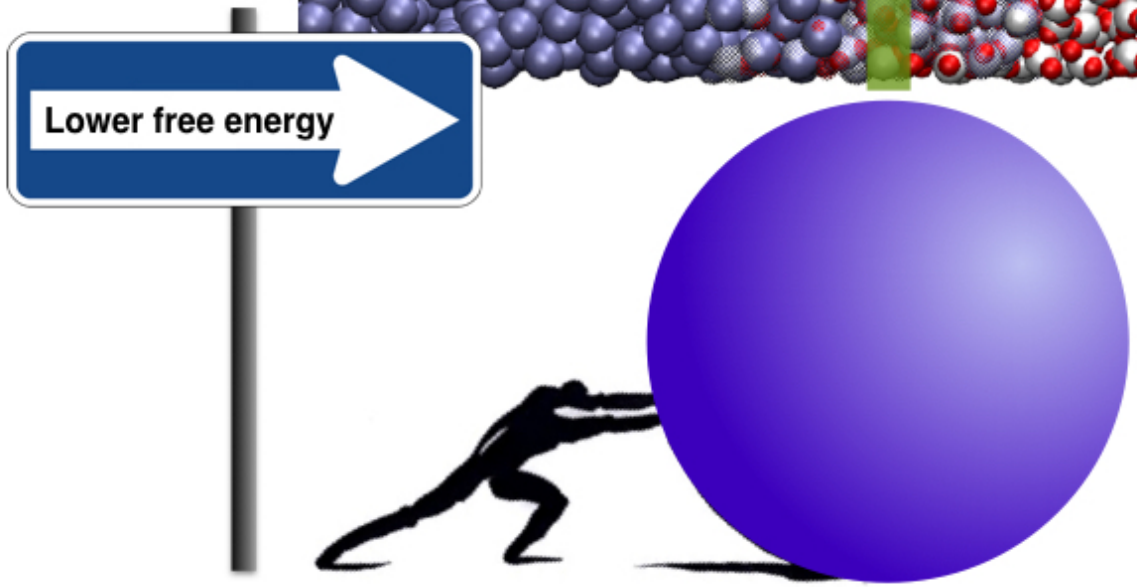
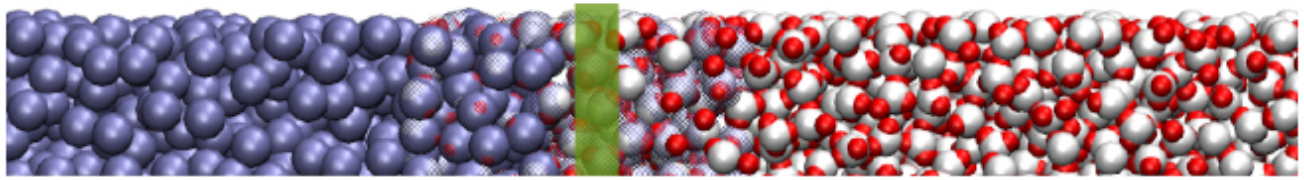




Dual-res simulations for chemical physics



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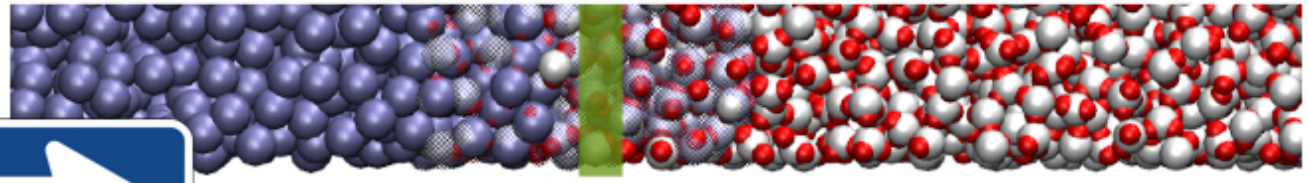
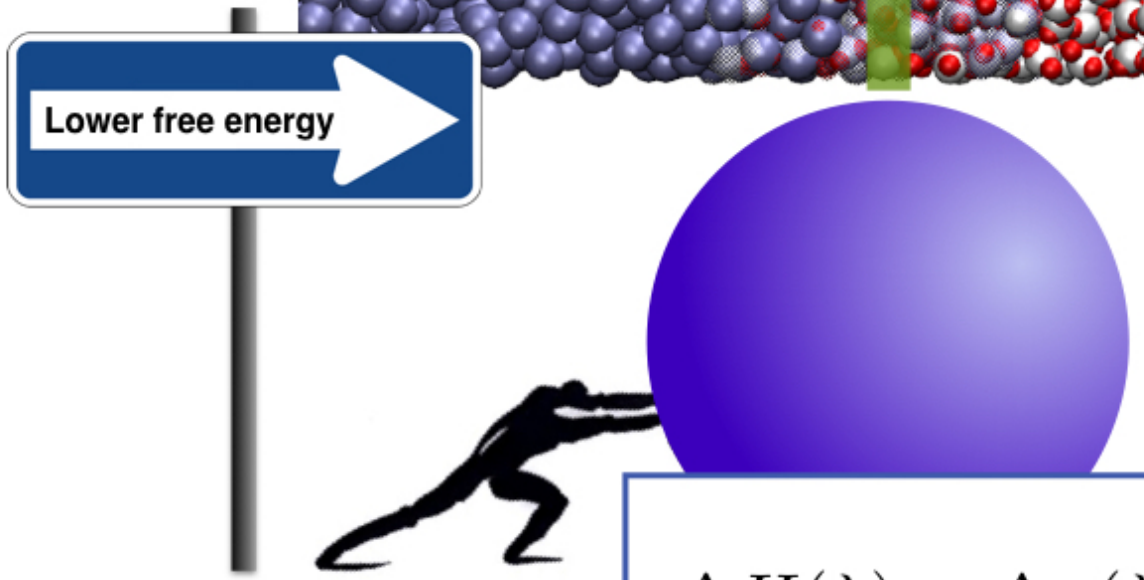
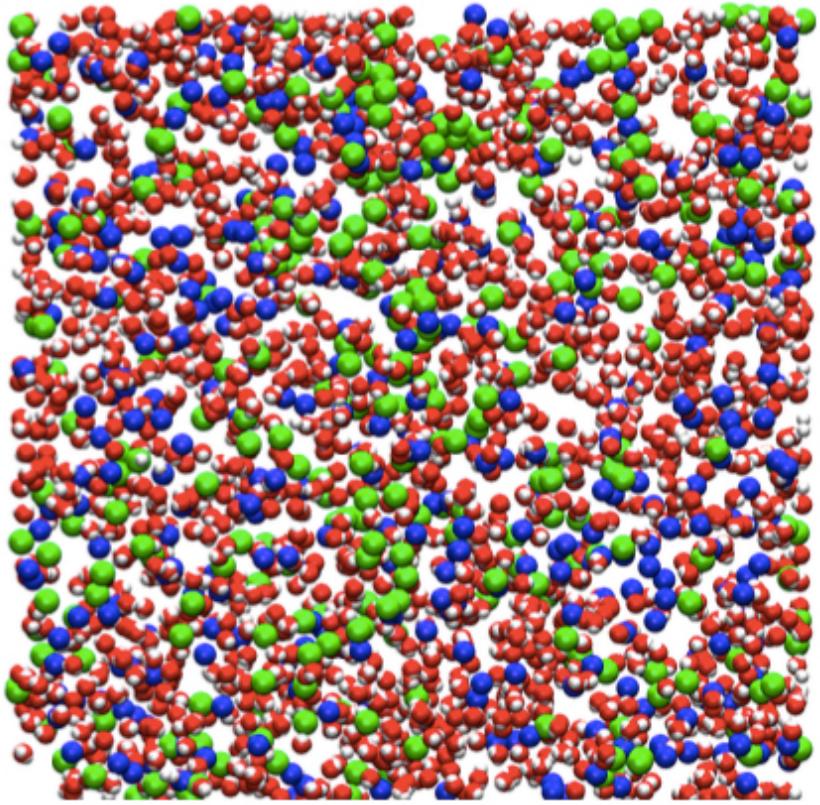




$$\Delta H(\lambda) \equiv \Delta\mu(\lambda) = \frac{\Delta F(\lambda)}{N} + \frac{\Delta p(\lambda)}{\rho^\star}$$

Fast calculation of chemical potentials



M. Heidari, K. Kremer, R. Cortes-Huerto and RP, submitted

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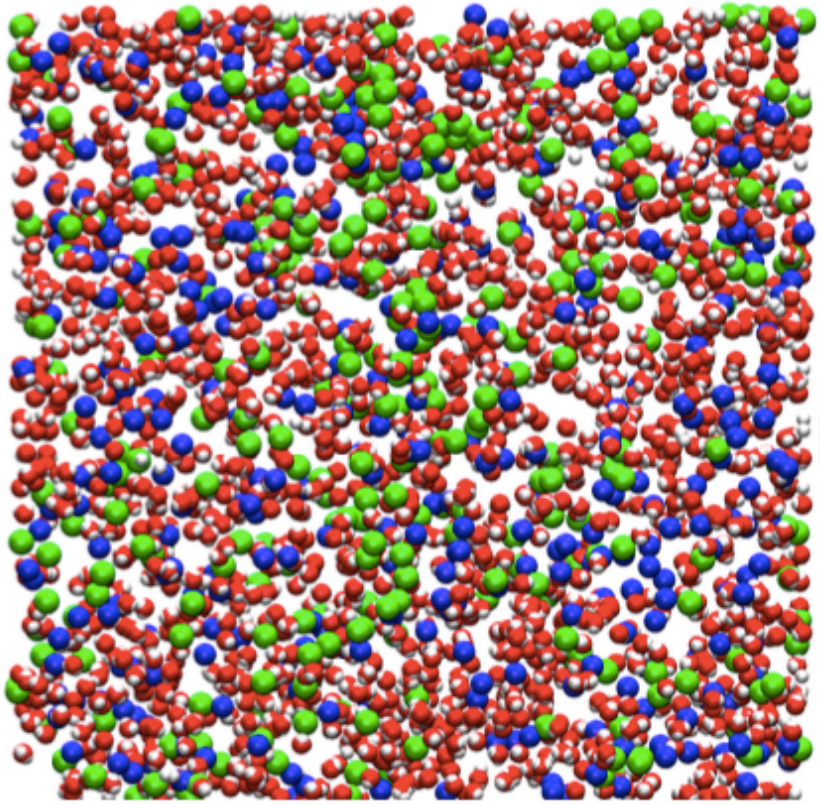

NaCl in water

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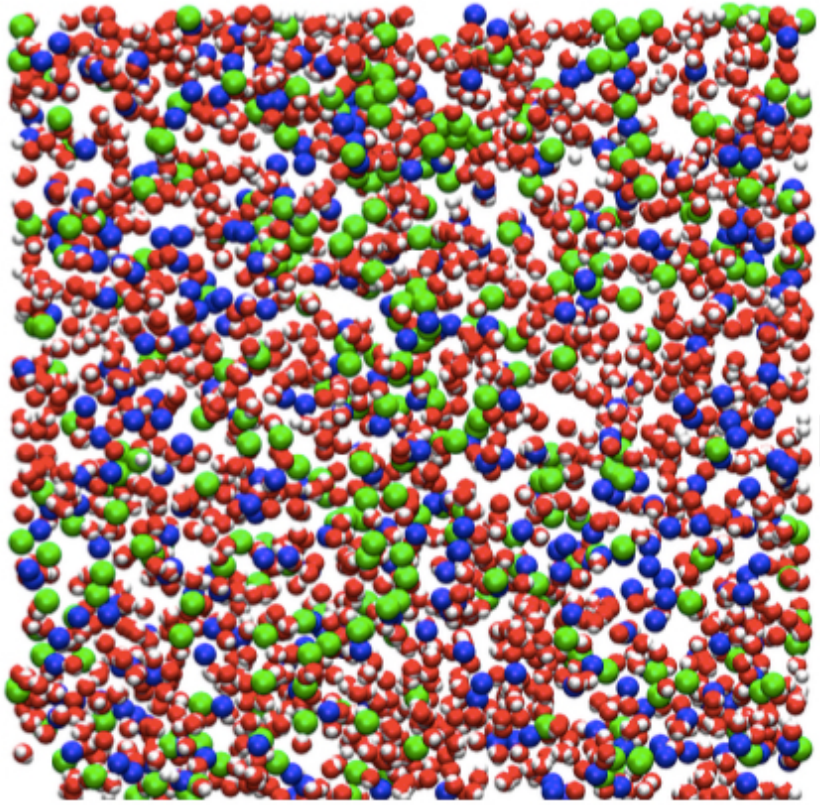
Fast calculation of chemical potentials

Ben Widom



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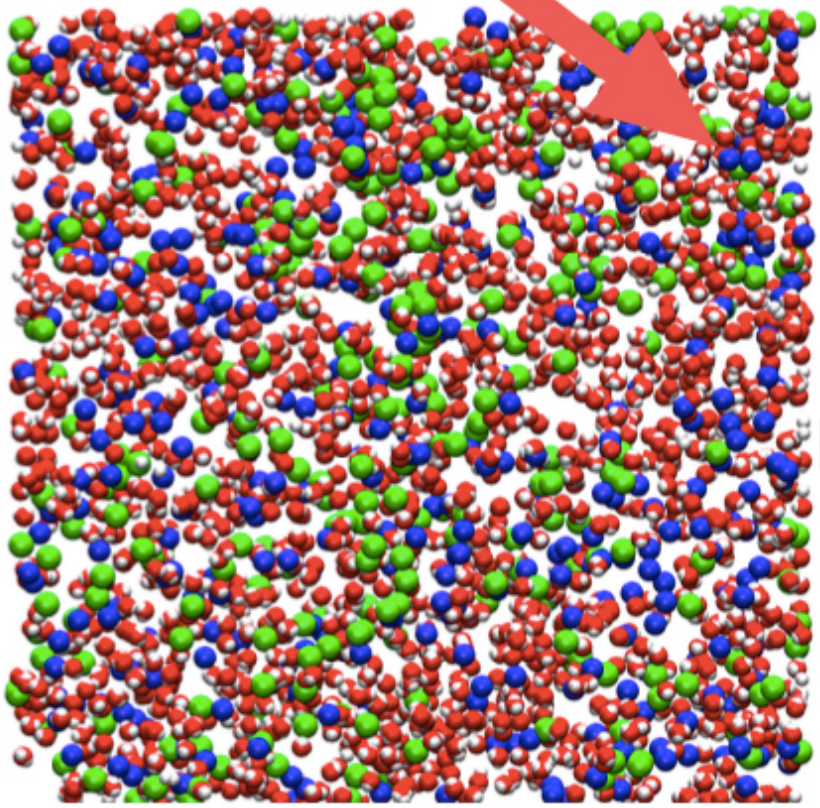

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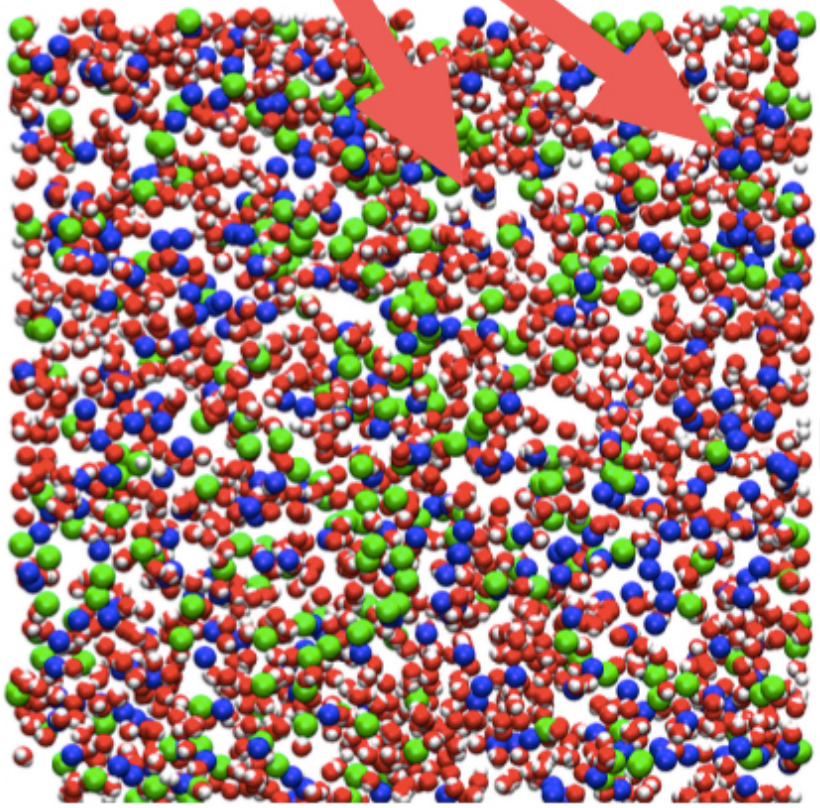

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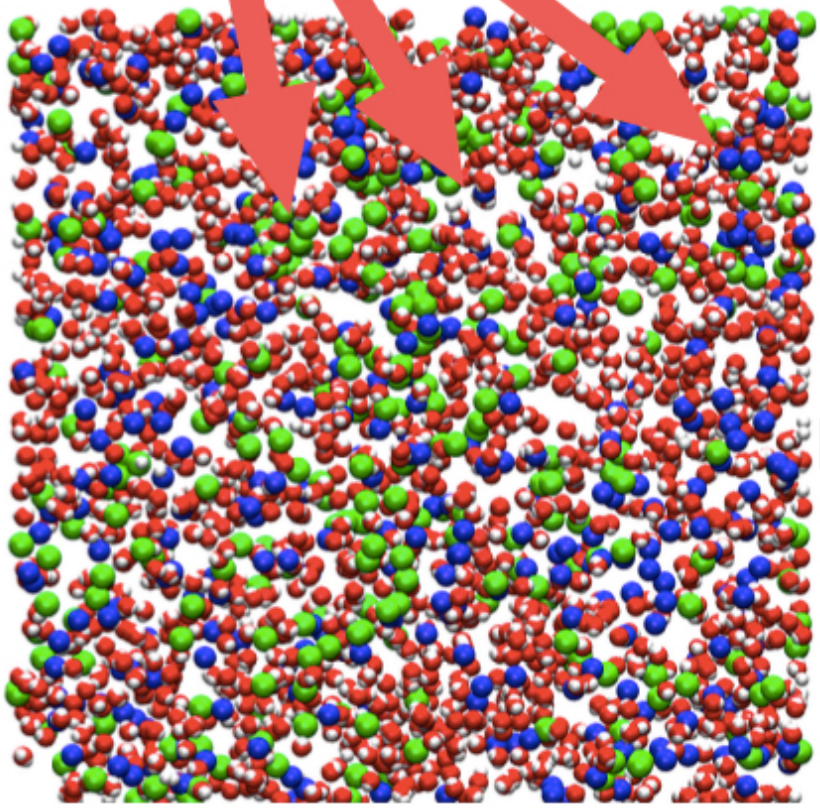

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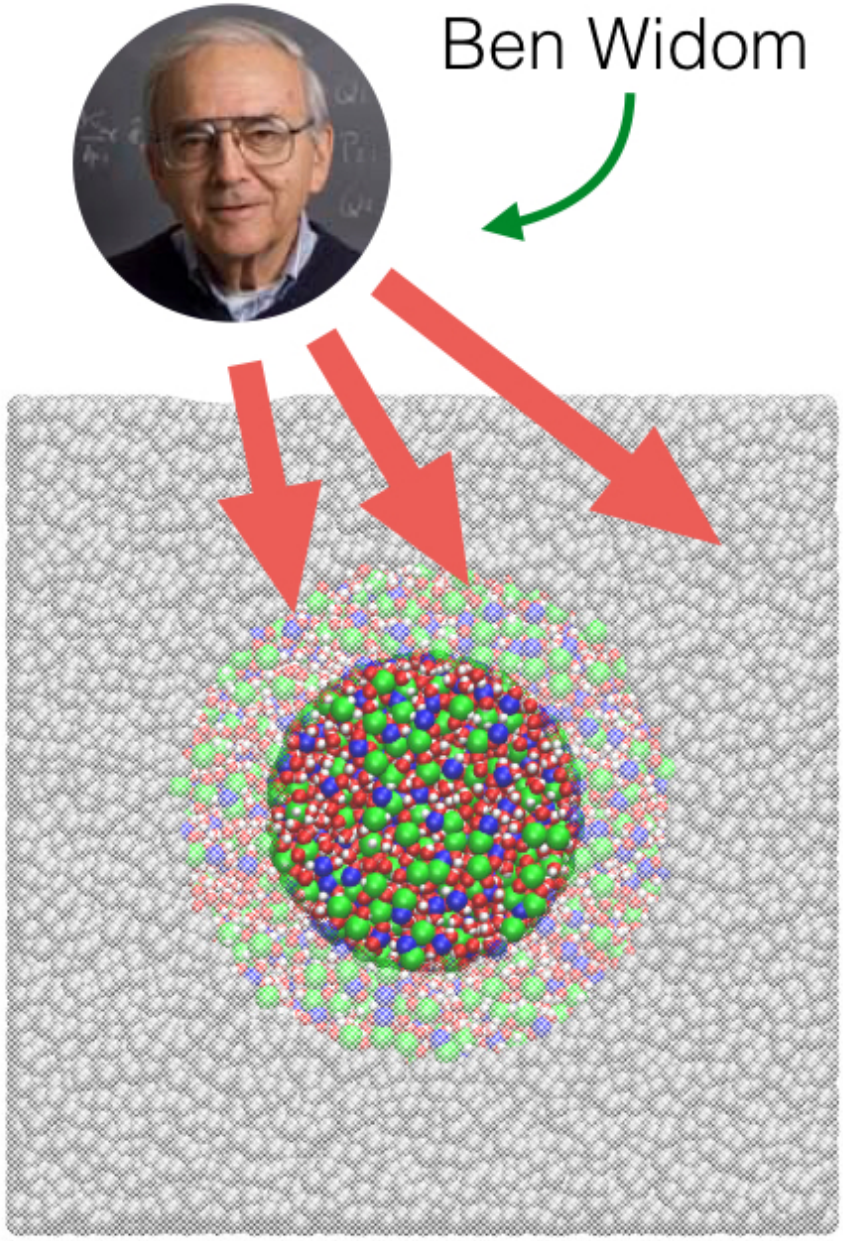

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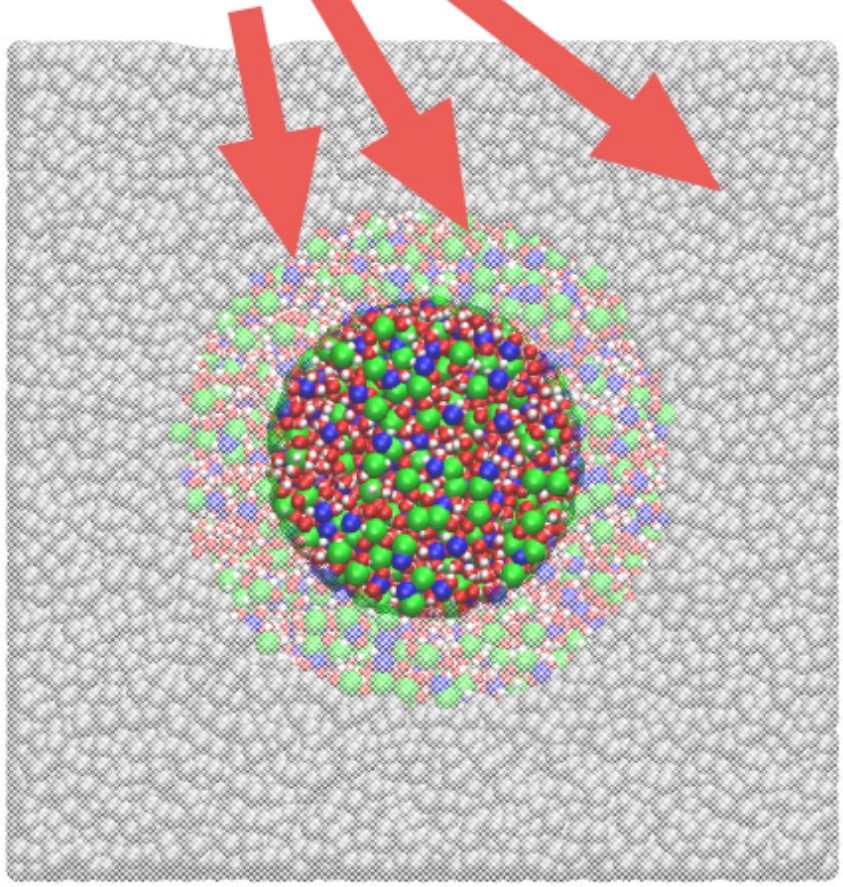


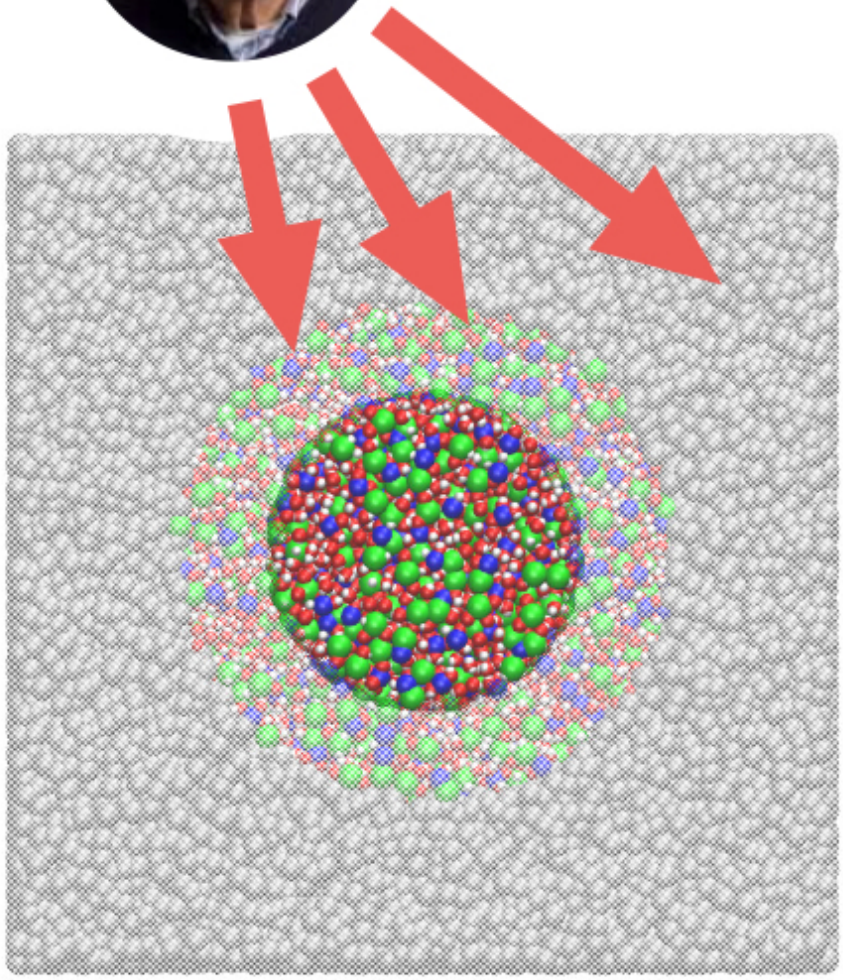
The FEC is the chemical potential difference between high and low resolution model

If the CG model is an ideal gas, the FEC equates the excess chemical potential

M. Heidari, K. Kremer, R. Cortes-Huerto and RP, submitted

Fast calculation of chemical potentials

Ben Widom



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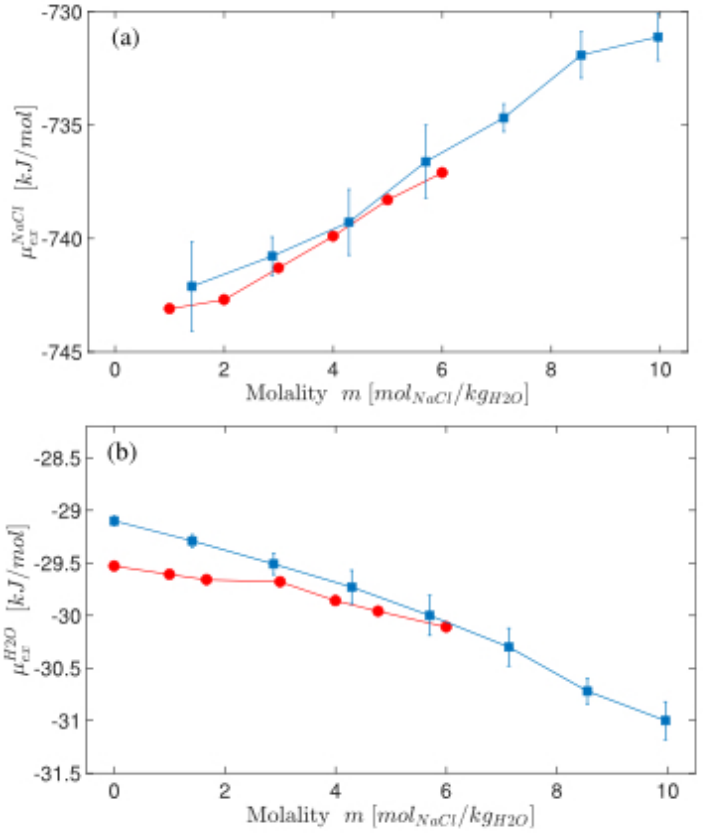

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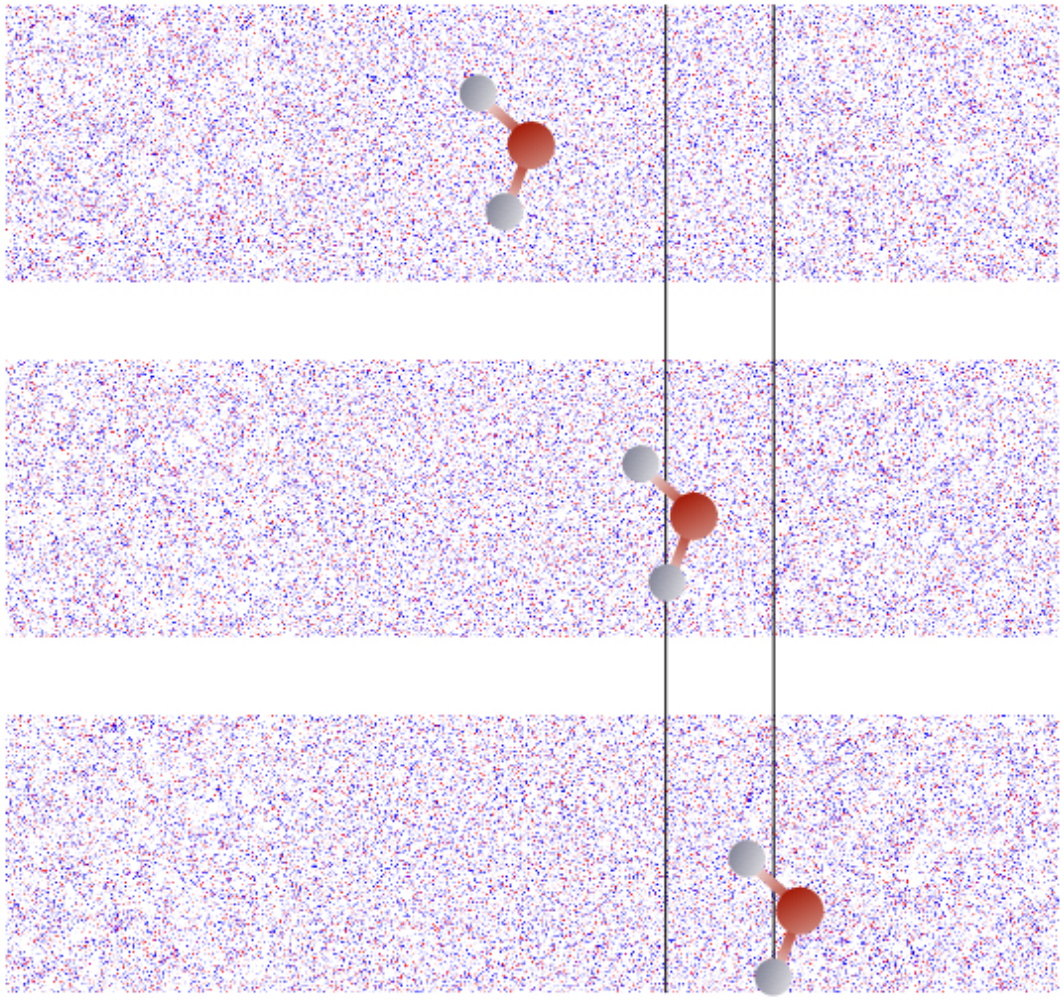
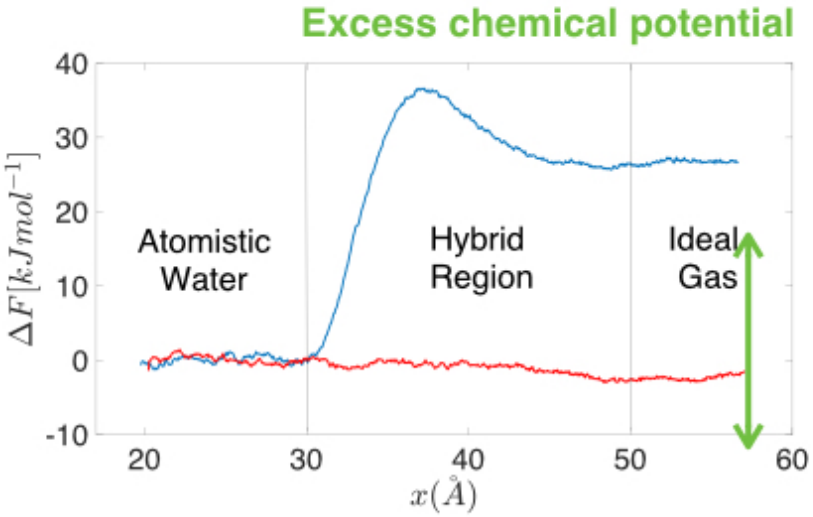
Fast calculation of solvation free energy



Pulling a molecule from the all-atom to the ideal gas region allows us to compute the excess chemical potential.

This approach is simple and effective especially for large molecules, such as fullerenes (ongoing work).



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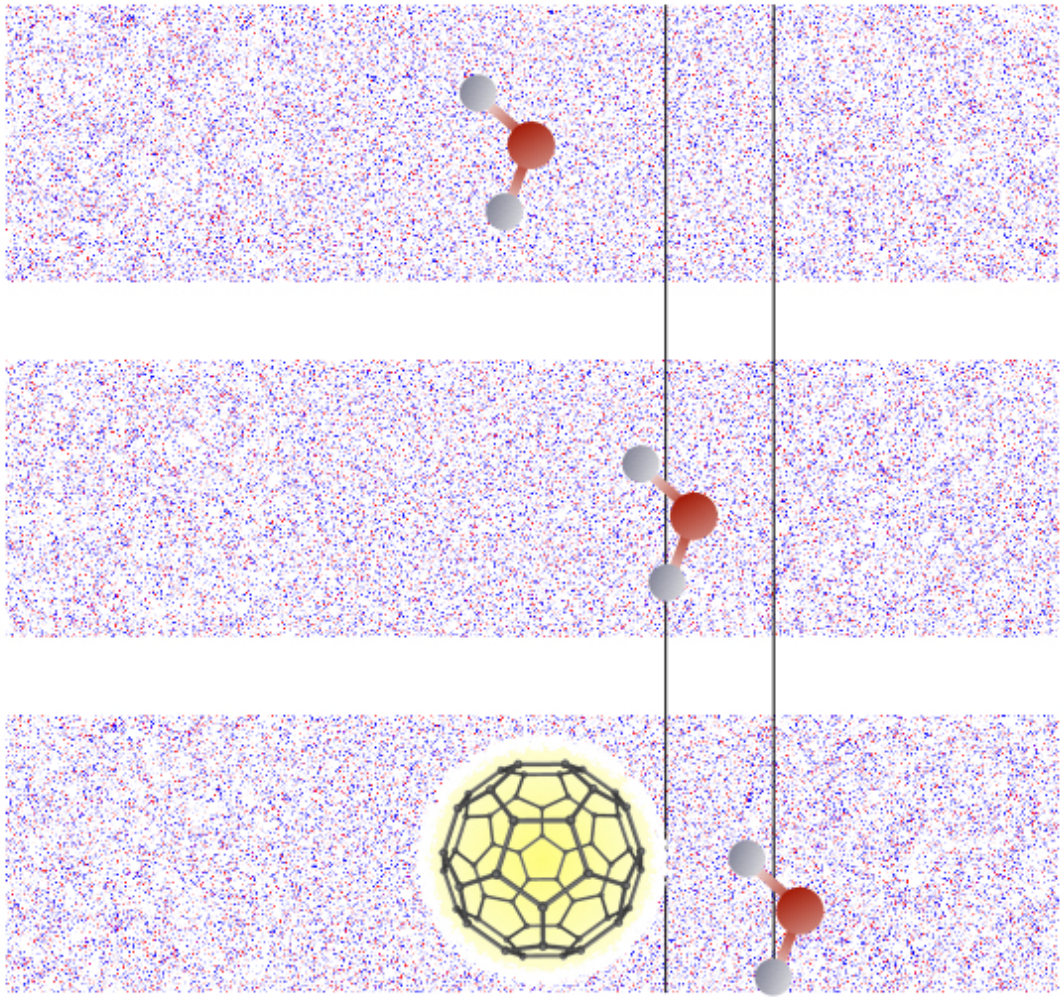

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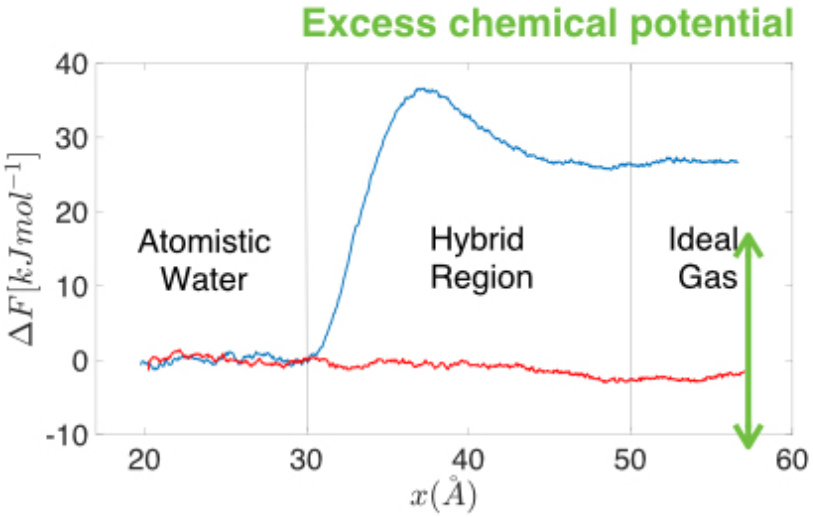
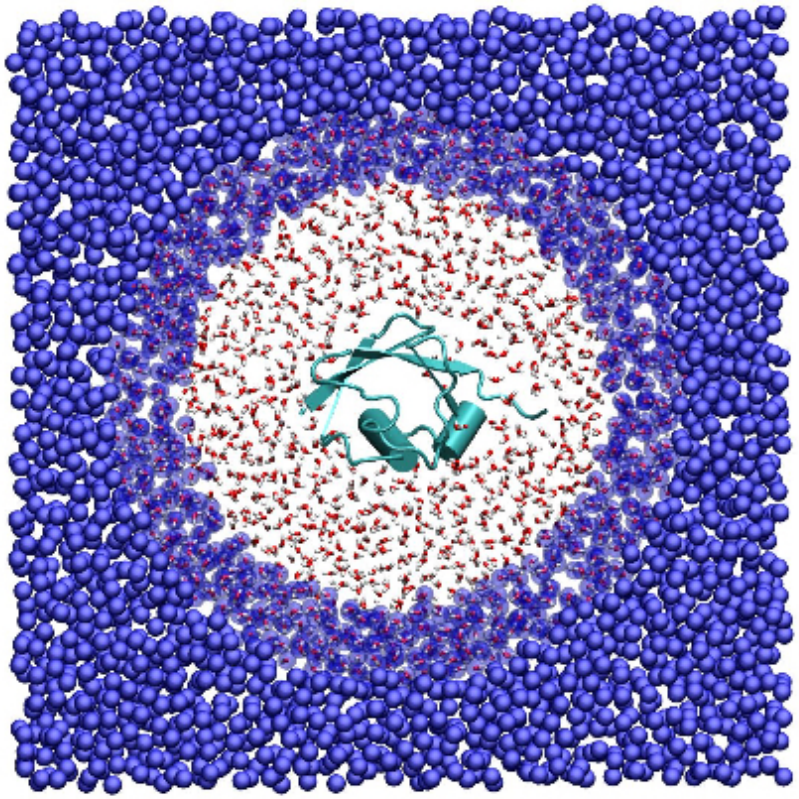
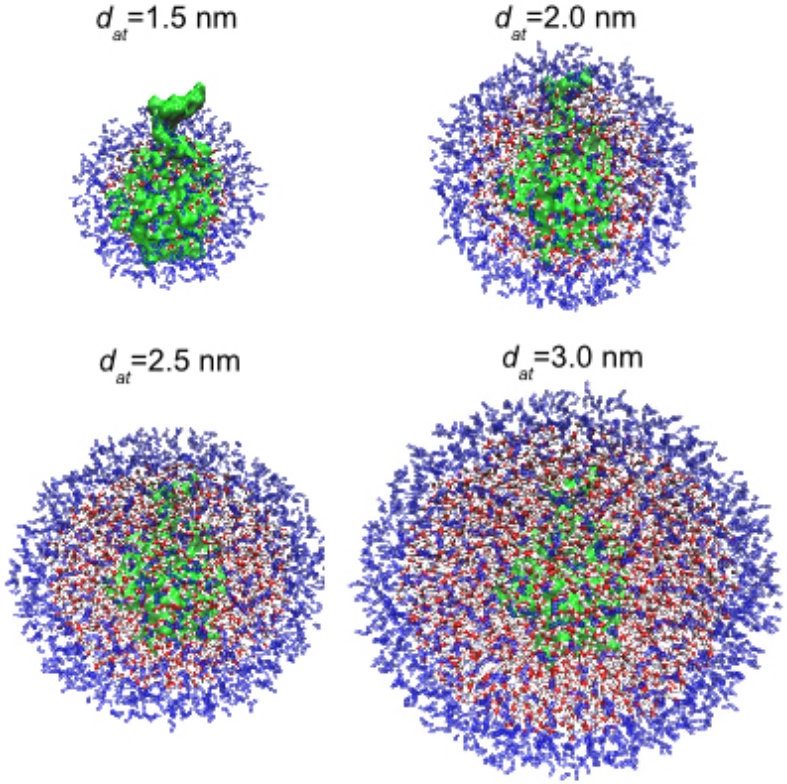


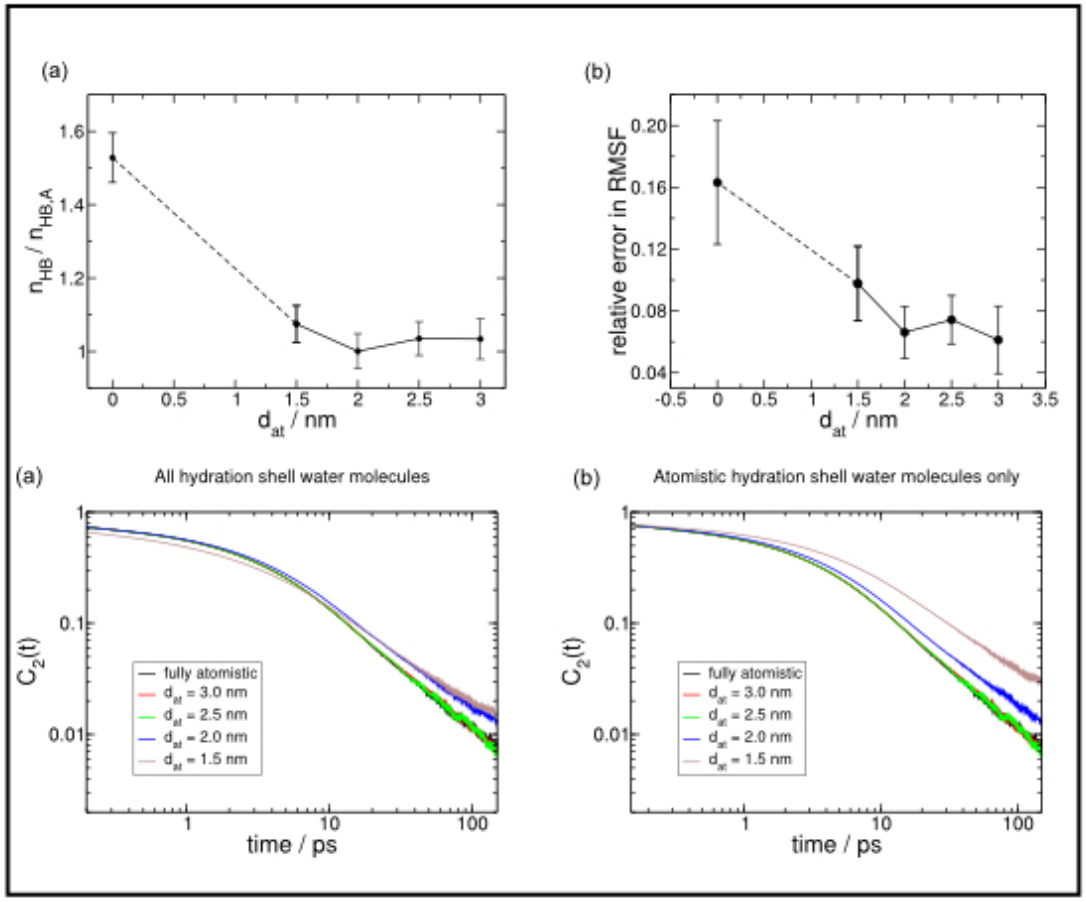
Ubiquitin in dual-res water

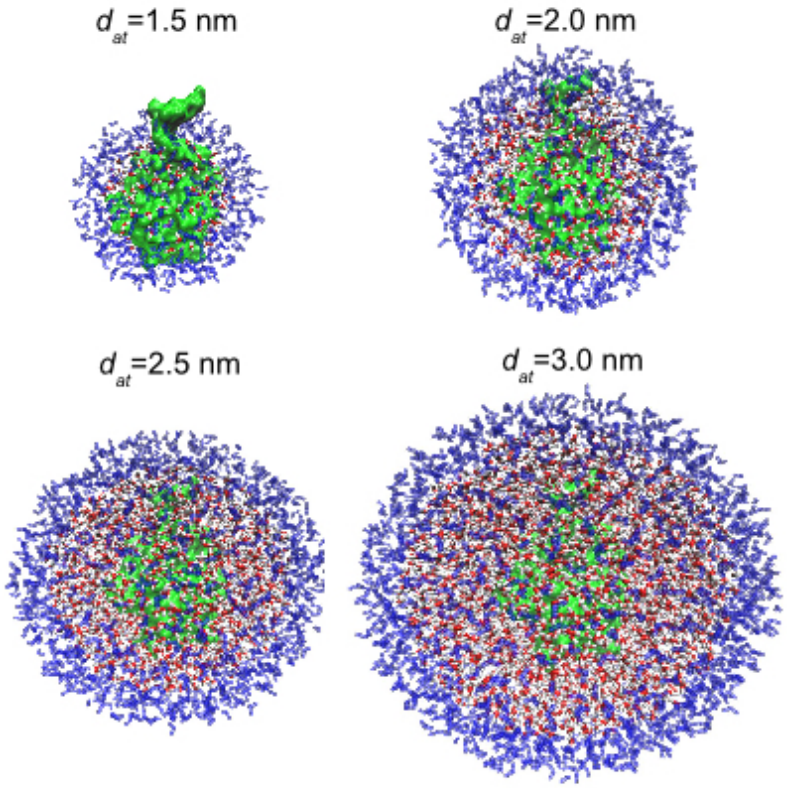




A.C. Fogarty, R.P., K. Kremer, JCP (2015)

Ubiquitin in dual-res water





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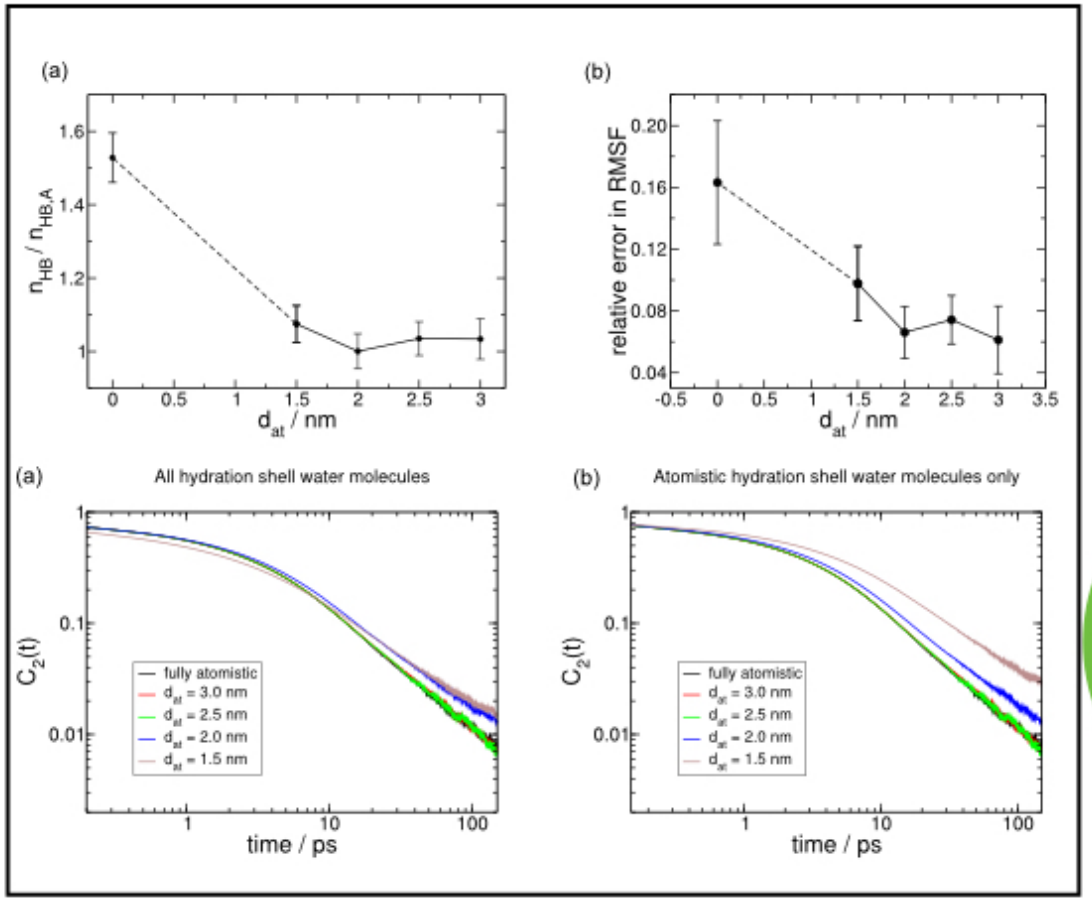

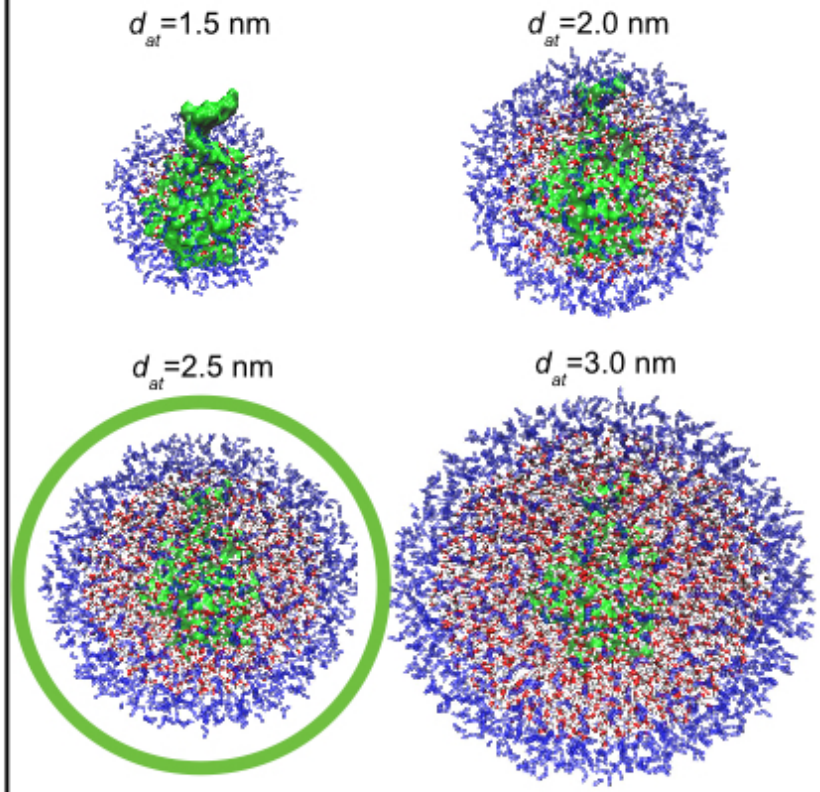

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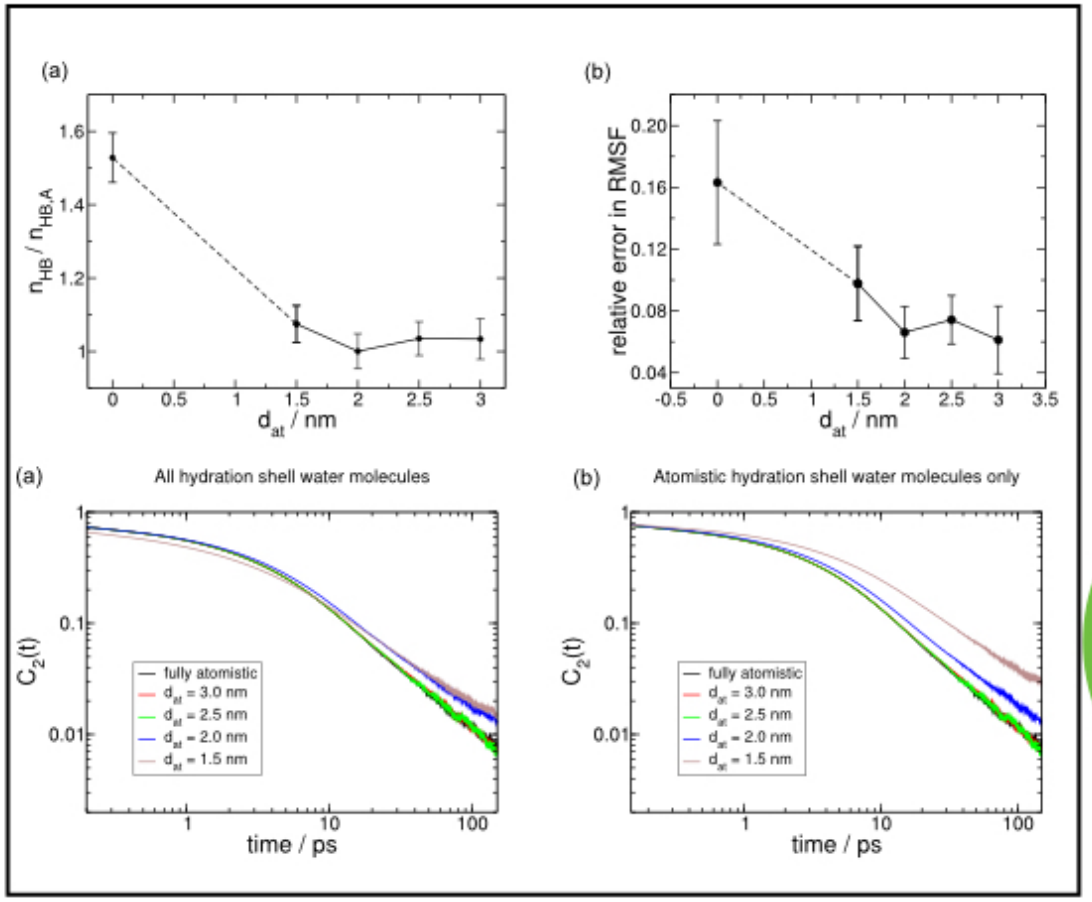
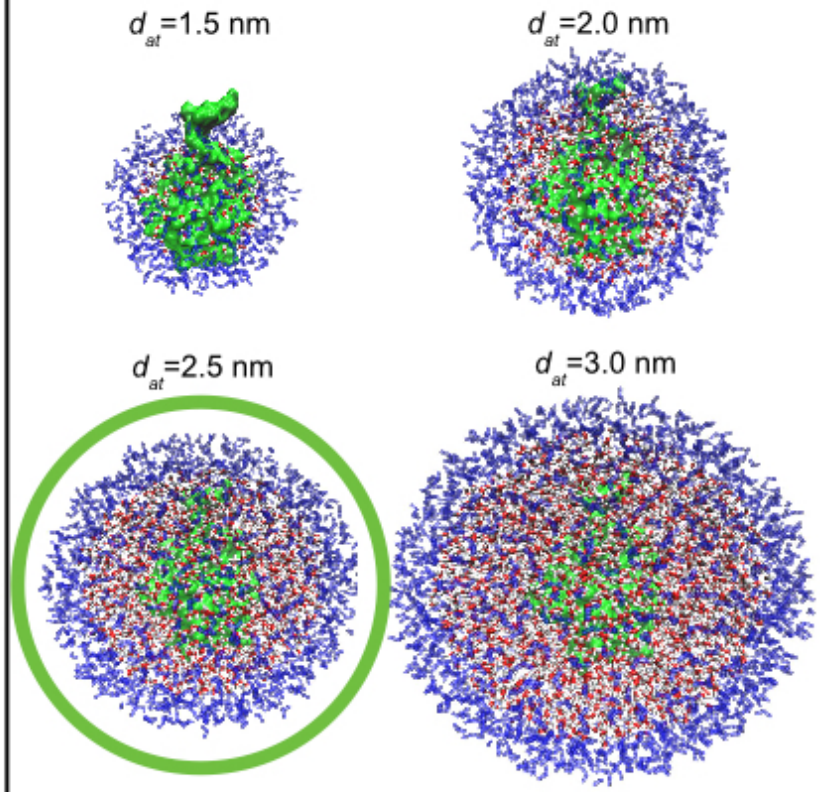
Ubiquitin in dual-res water

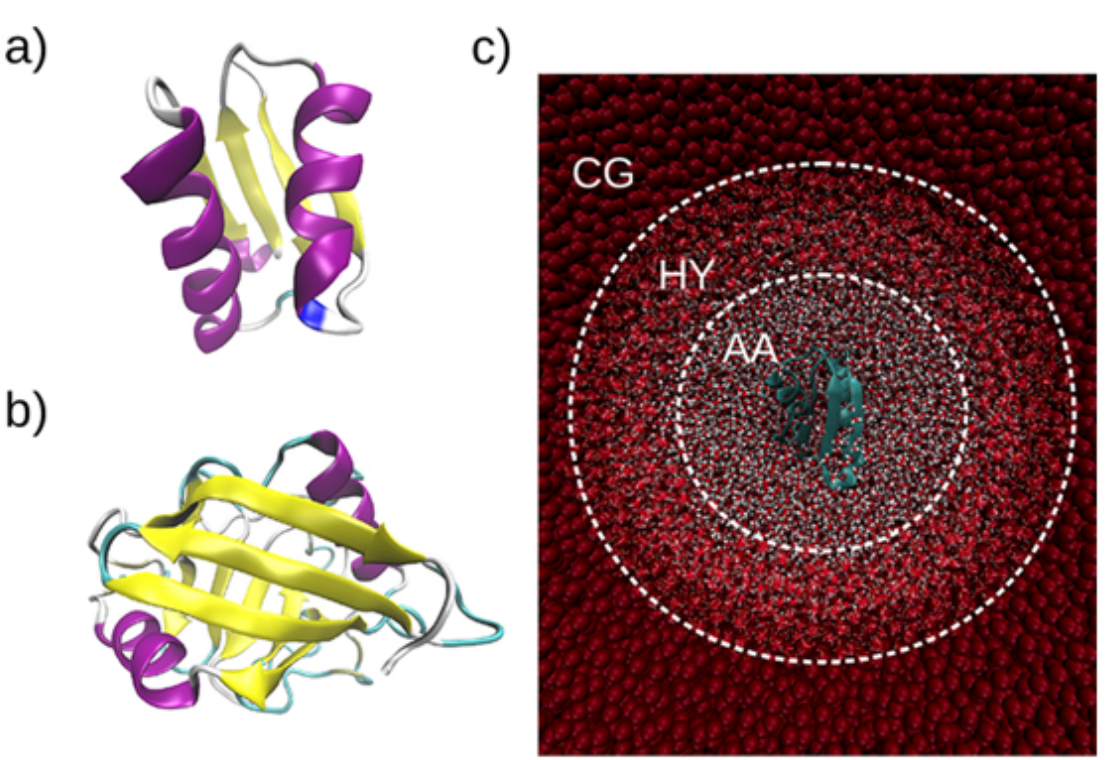


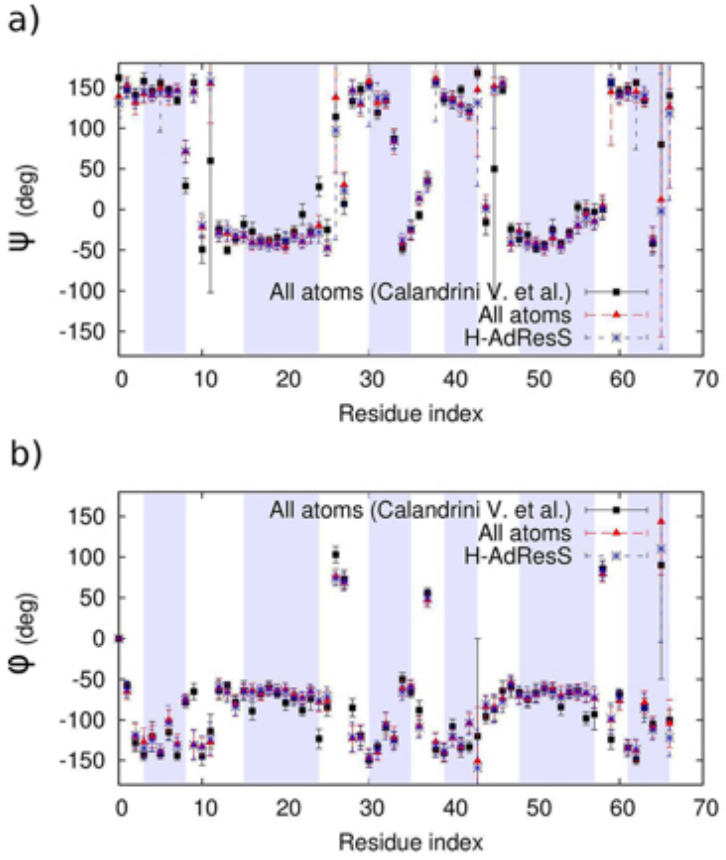


A ~1.3 nm thick water layer is sufficient
to reproduce the reference values of the observables under exam

A.C. Fogarty, R.P., K. Kremer, JCP (2015)

Hamiltonian simulations of human metallochaperone atox1 and the human cyclophilin J in dual-res water



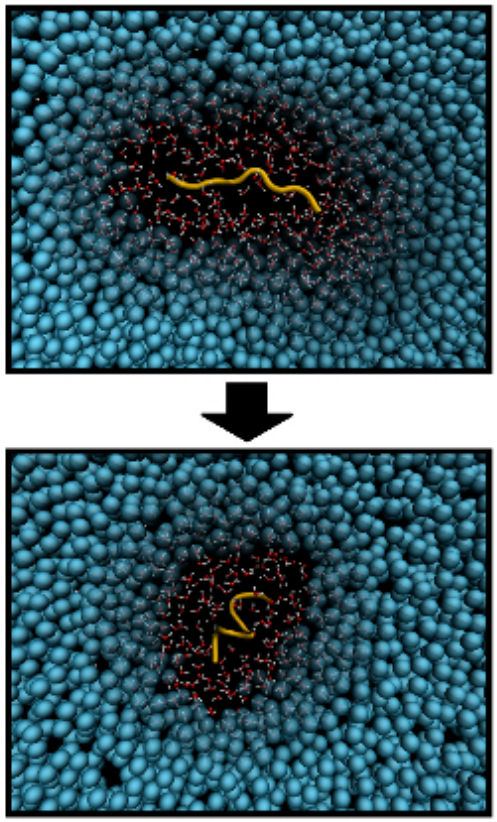


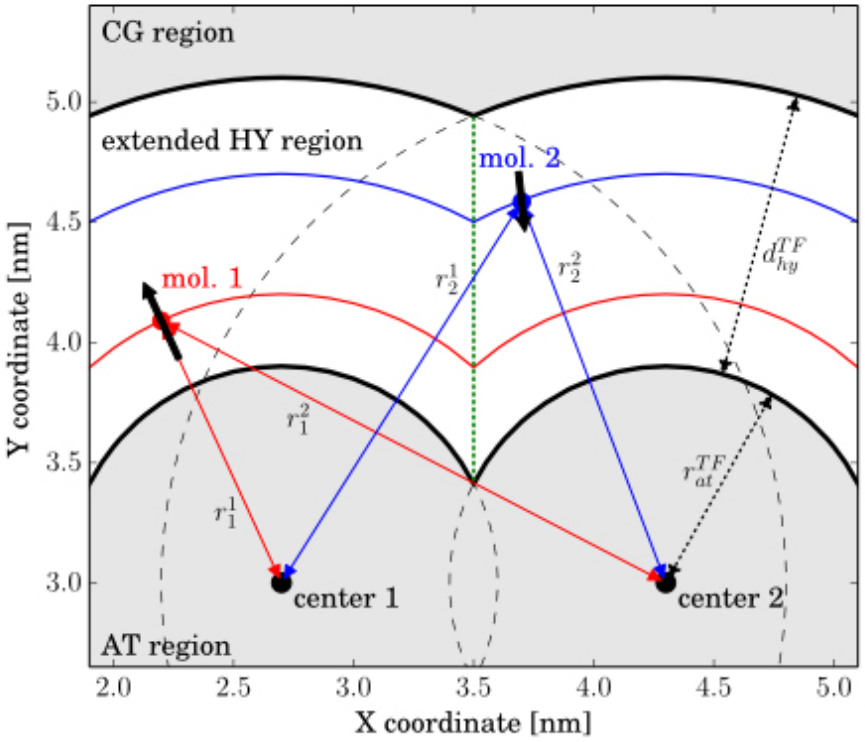
T. Tarenzi, V. Calandrini, R.P., A. Giorgetti, P. Carloni, JCTC (2017)

Adaptive adaptiveness

self-adjusting atomistic region in dual-resolution simulations

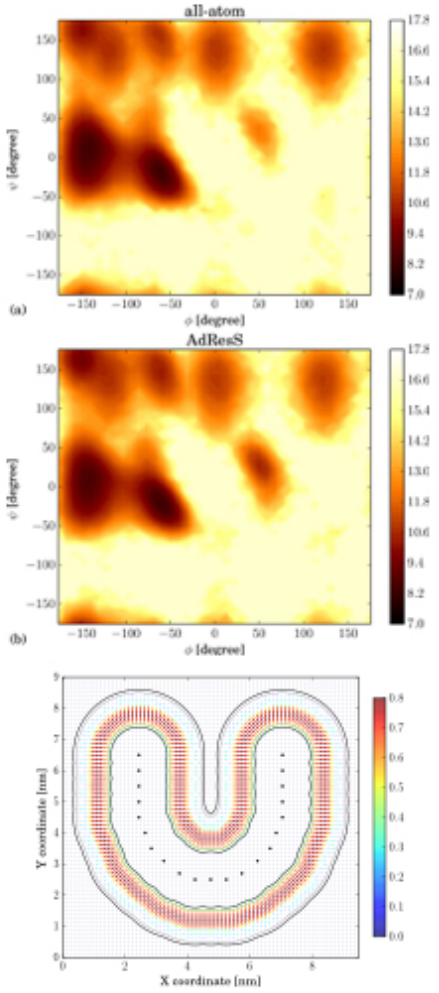
Peptide folding:
the smallest necessary
AT region size is not constant





The full AT region is the union of
several spherical AT subdomains

Structural and dynamical properties
are preserved

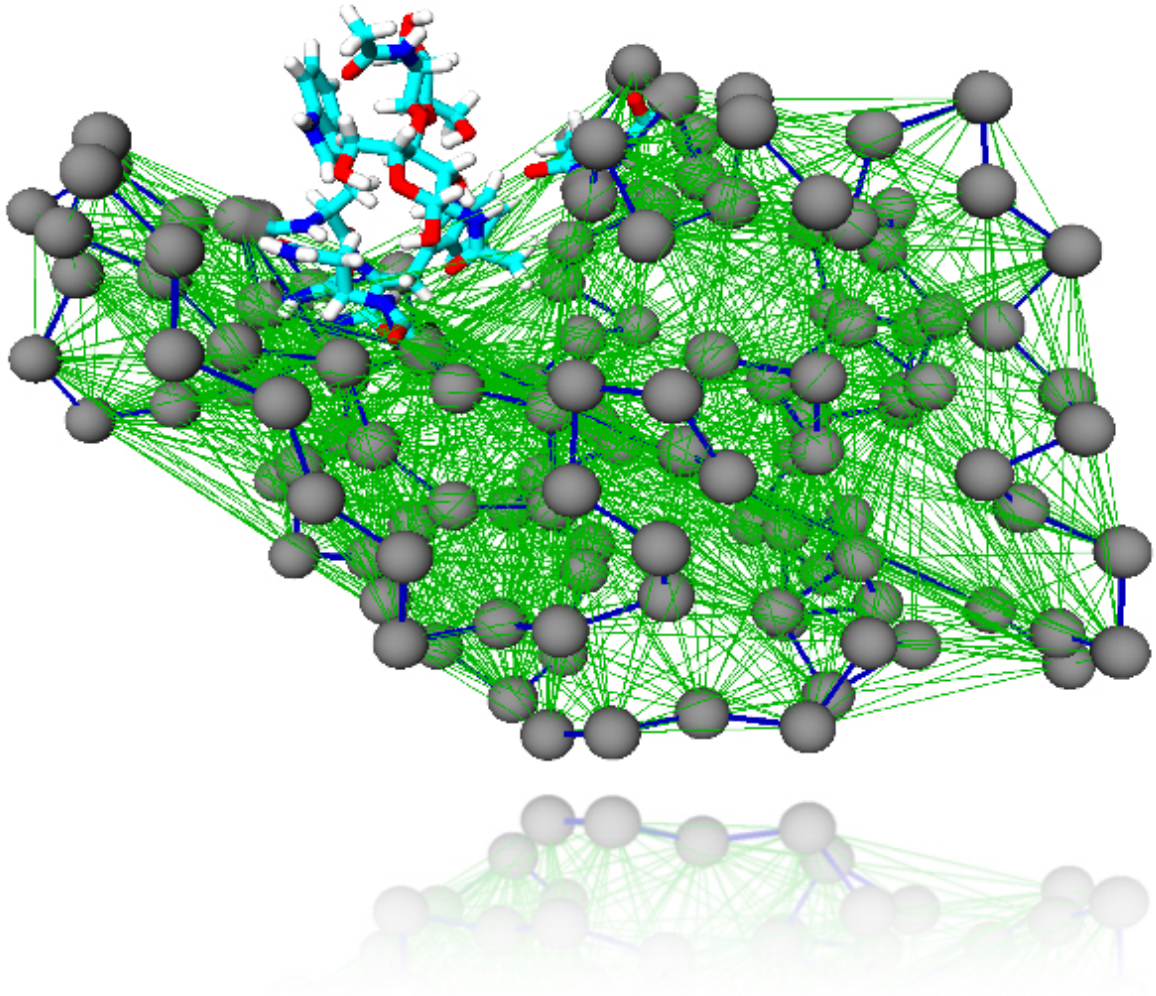


K. Kreis, K. Kremer, RP and A.C. Fogarty, JCTC 12(8) (2016)

Dual-resolution model of lysozyme

Atomistic resolution:
active site, ligand,
neighbouring solvent

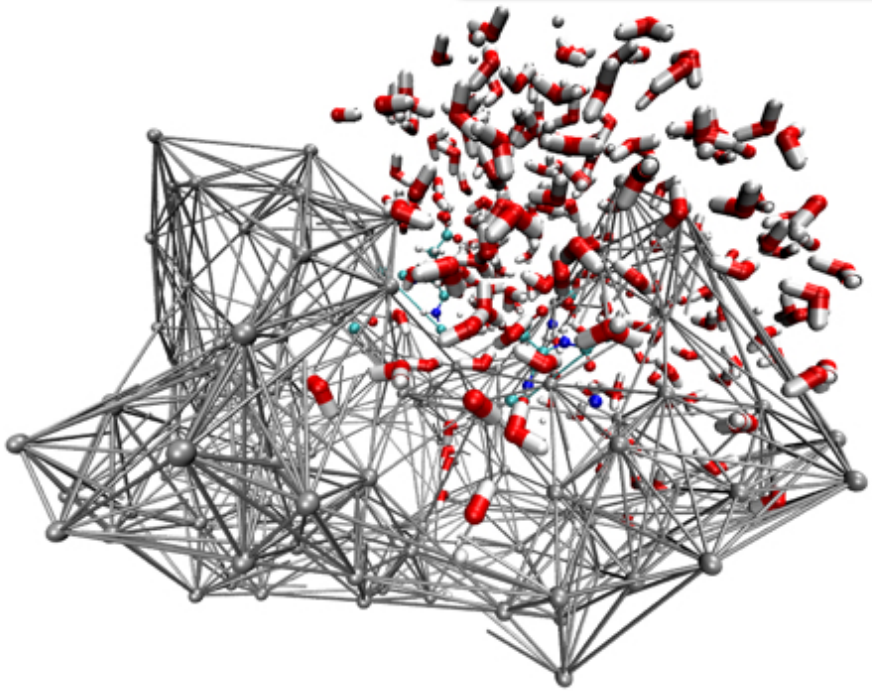
CG resolution:
protein *scaffold* and
rest of the solvent

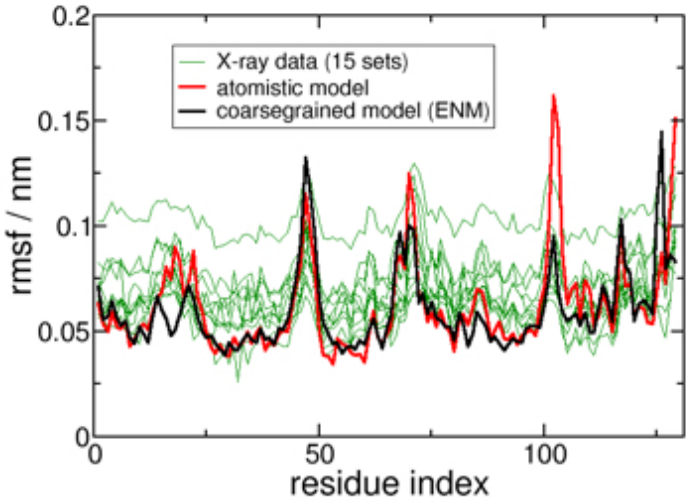


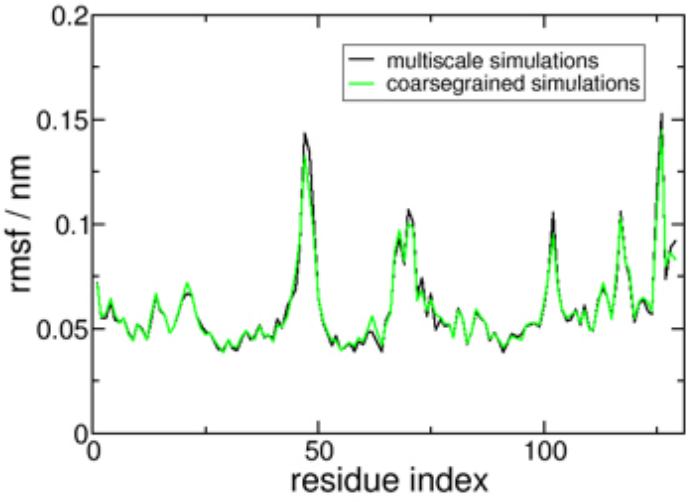
A.C. Fogarty, R.P., K. Kremer, Proteins (2016)

Dual-resolution model of lysozyme

ENM parametrised to reproduce experimental and all-atom MD data



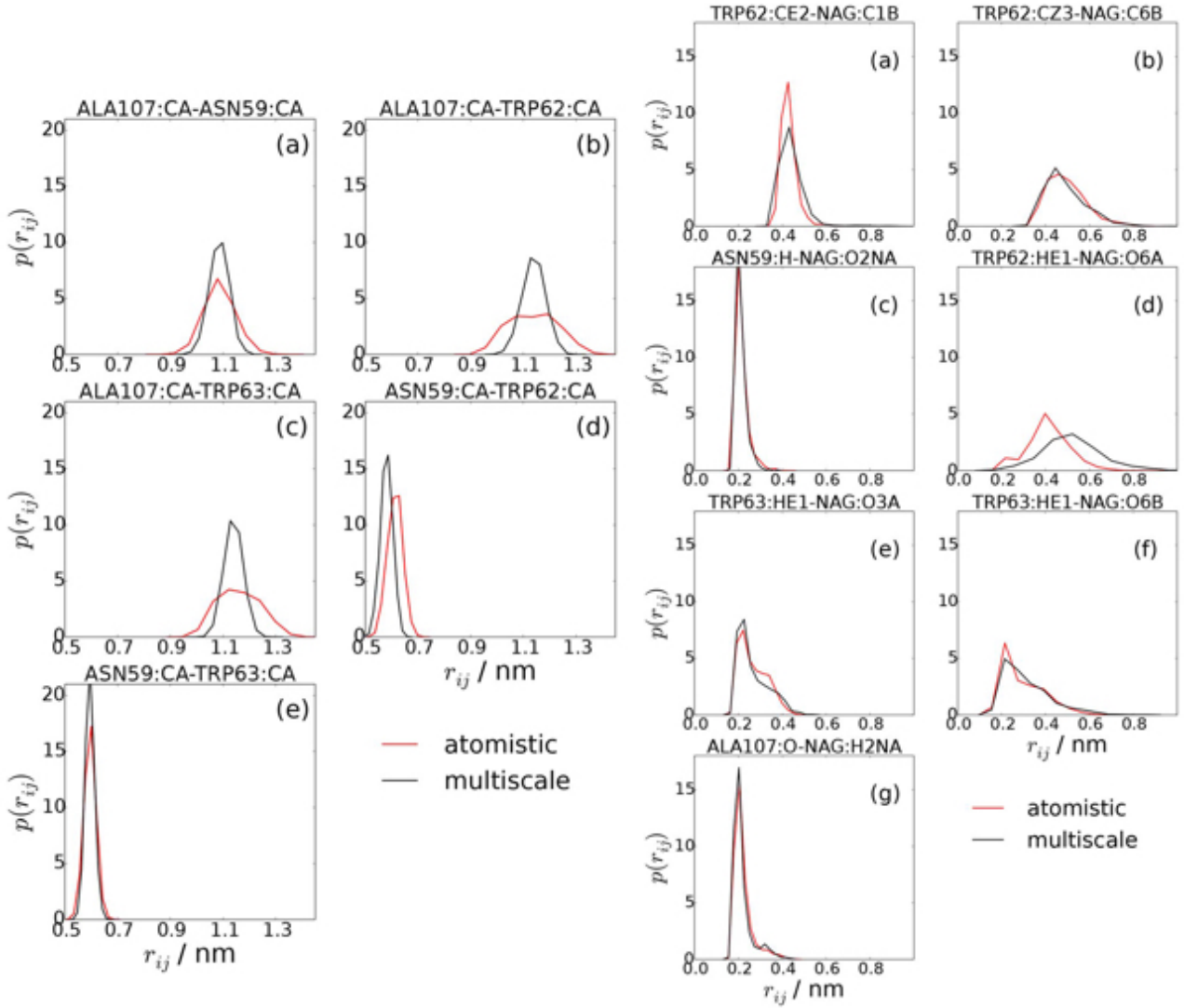




The dual-res system reproduces the global fluctuations of the ENM

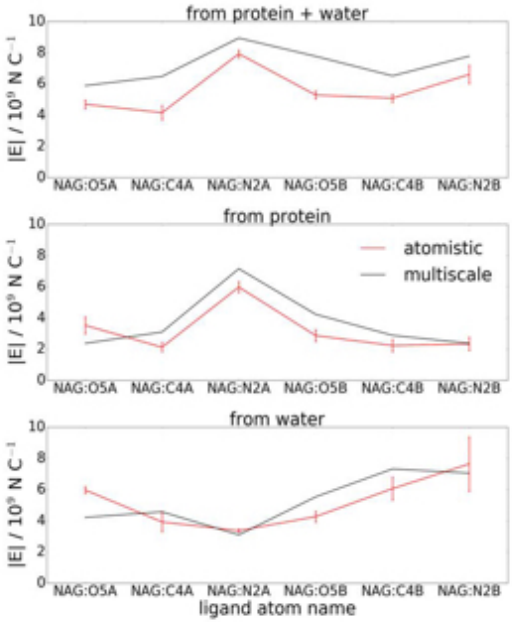
A.C. Fogarty, R.P., K. Kremer, Proteins (2016)

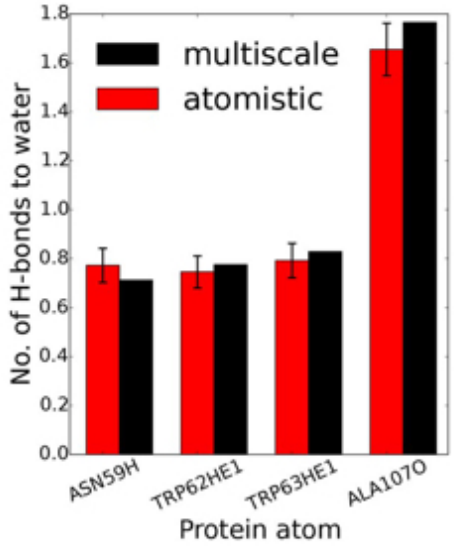
Dual-resolution model of lysozyme



protein-protein distances

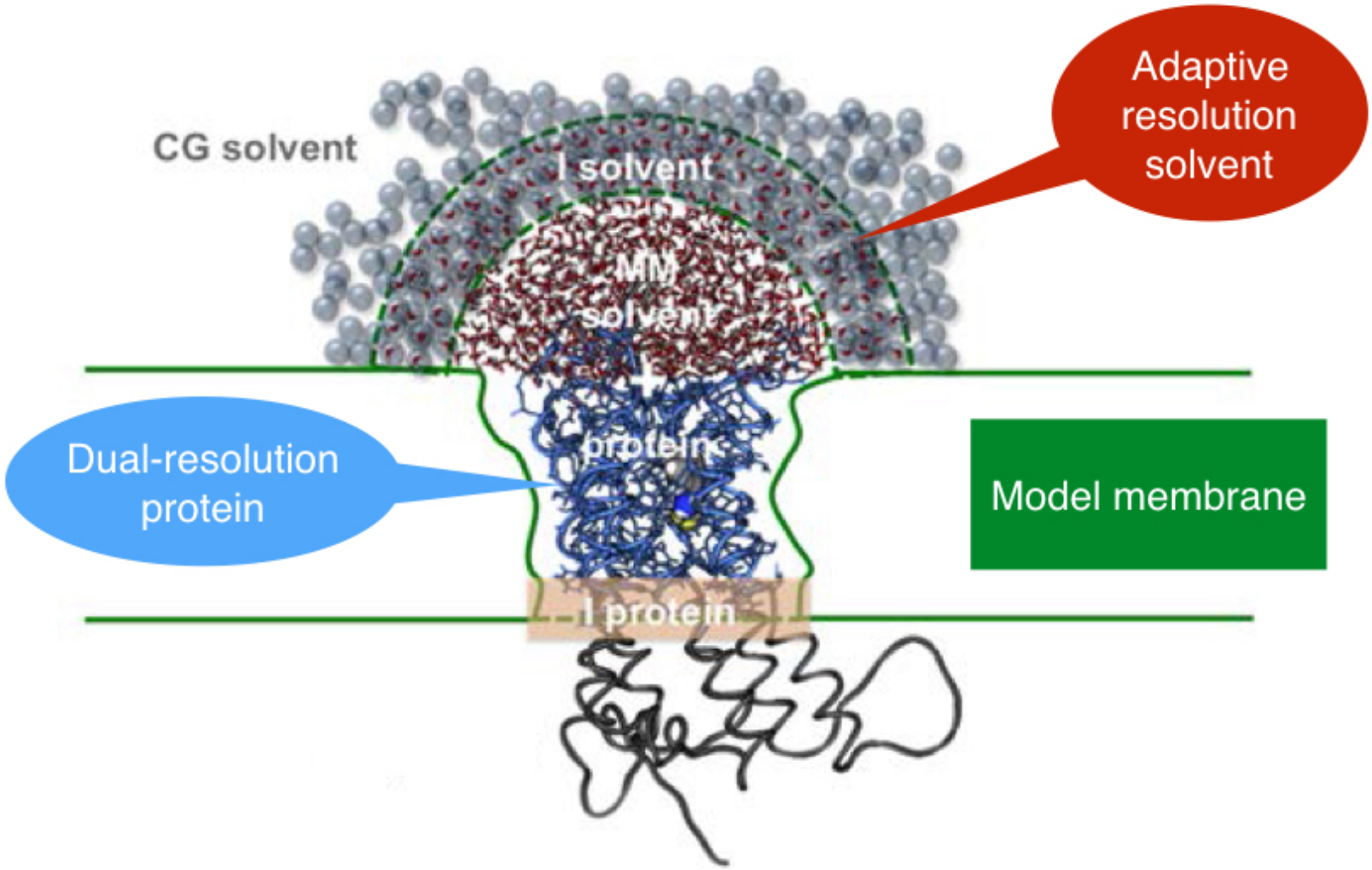
protein-ligand distances





A.C. Fogarty, R.P., K. Kremer, Proteins (2016)

Perspective: large size applications

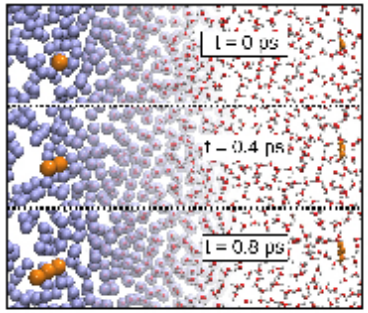


T. Tarenzi, V. Calandrini, R.P., A. Giorgetti, P. Carloni, JCTC 2017

Areas of application of adaptive resolution simulations methods

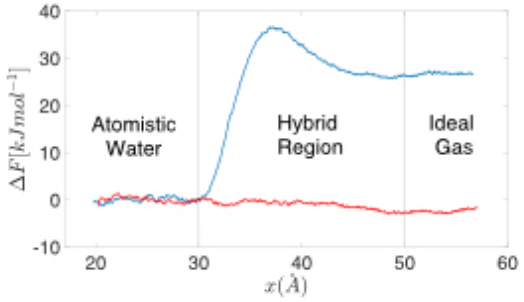
Fundamental Statistical Physics

Adaptive resolution simulation methods to study the stat mech of CG models



K. Kreis, A.C. Fogarty, K. Kremer, RP, EPJ-ST 2015

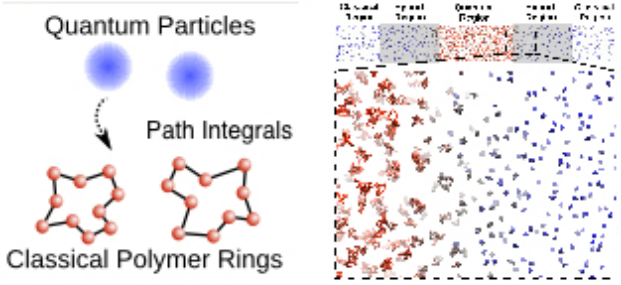
Efficient free energy calculations via adaptive resolution methods



M. Heidari, K. Kremer, R. Cortes Huerto, RP, submitted

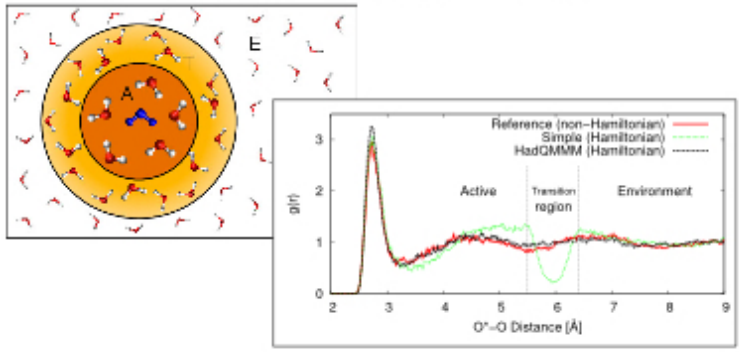
Quantum/Classical coupling

Hybrid quantum/classical models based on adaptive resolution simulation methods



K. Kreis, M. E. Tuckerman, D. Donadio, K. Kremer and RP, JCTC 2016

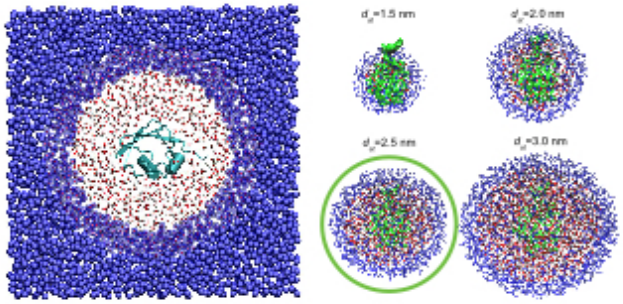
Hamiltonian QM/MM methods based on a many-body extension of H-AdResS



J. Boereboom, RP, D. Donadio, R. Bulo, JCTC 2016

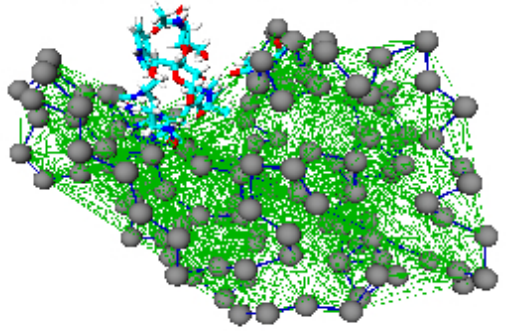
Biomolecule modeling and simulation

Dual-resolution simulation methods for biomolecular systems



A.C. Fogarty, R.P., K. Kremer, JCP 2015

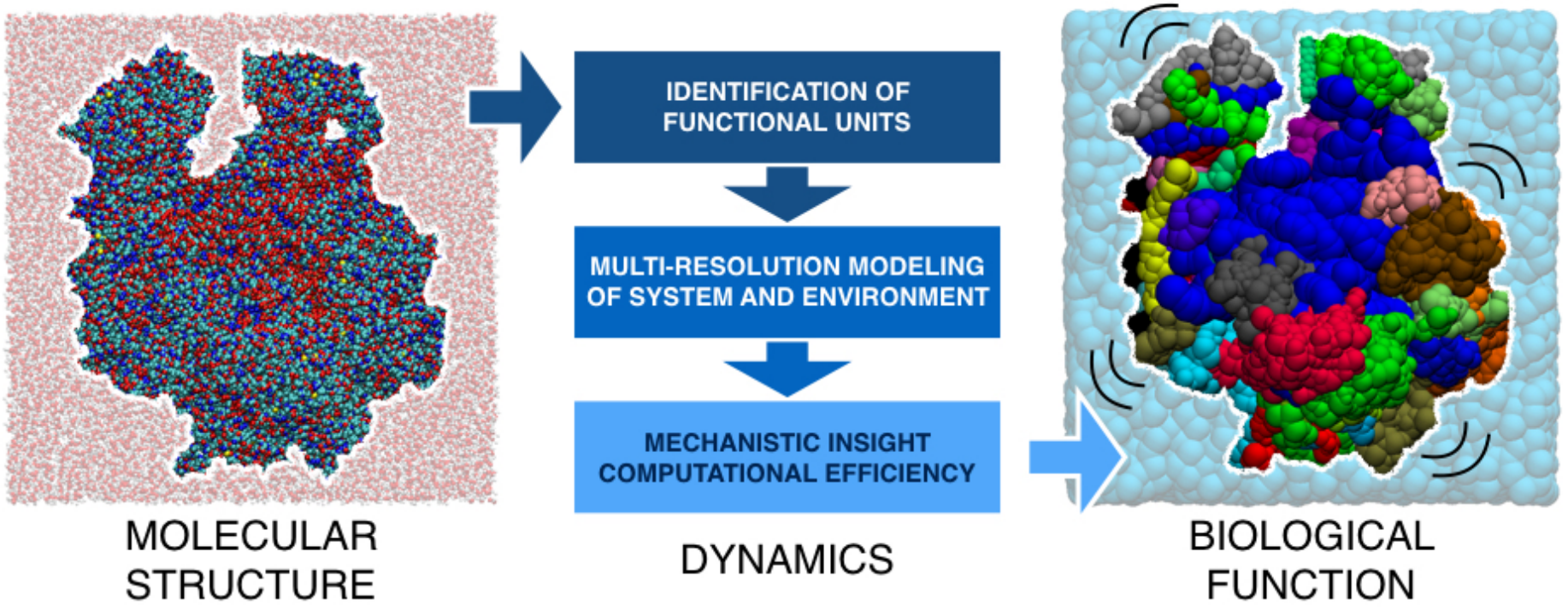
Dual-resolution models of a protein and its aqueous environment



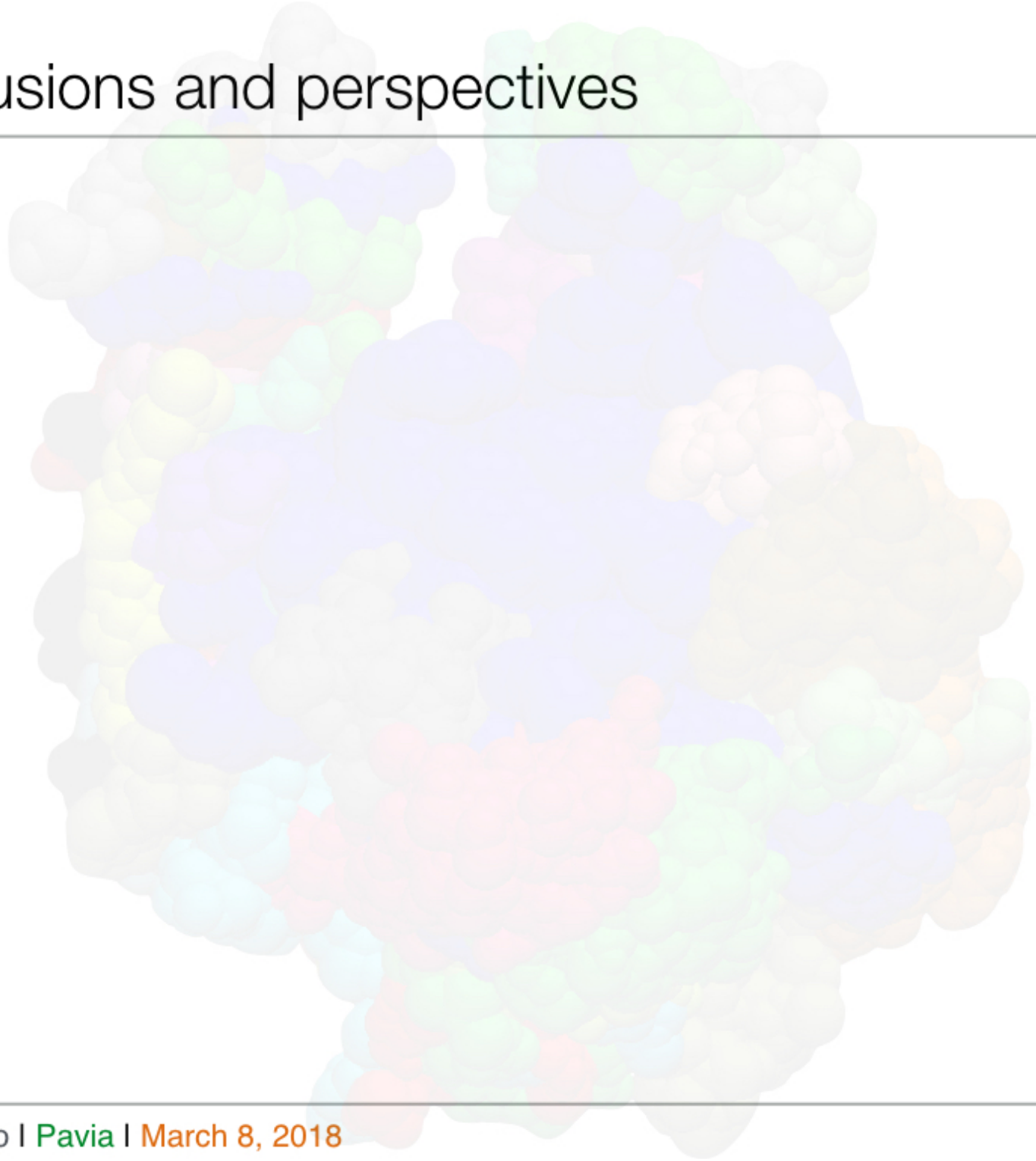
A.C. Fogarty, RP and K. Kremer, Proteins 2016

The big picture

Road map towards the systematic
multi-resolution modelling of large biomolecules



Conclusions and perspectives



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Conclusions and perspectives

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- **Large (supra)molecules pose new challenges** (large size, complex function)
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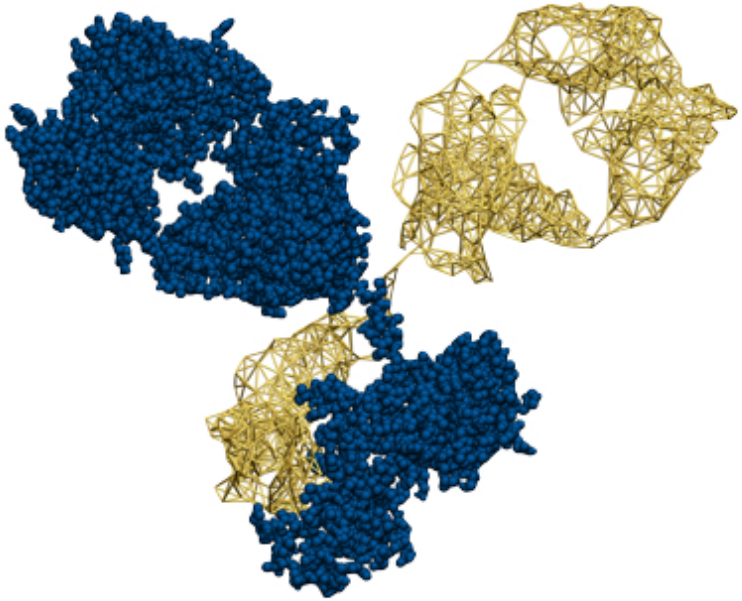
- **Combination of various modelling strategies** for a local system-based modelling

ERC project VARIAMOLS

Variable resolution algorithms for macromolecular simulations



- Start date: January 1st, 2018
- Project goal: develop and apply novel techniques to represent a large biomolecule with models that are at the same time chemically accurate and computationally efficient
- **Open positions available! 2 Phd students + 2 postdocs in 2018 only**
- For info and openings visit: **`sites.google.com/view/variamols`**
- Email: **`variamols@unitn.it`**
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