Multiscale Modeling

Winterschool on
Theoretical Chemistry and Spectroscopy
10-14 December, 2012

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Summary part 1

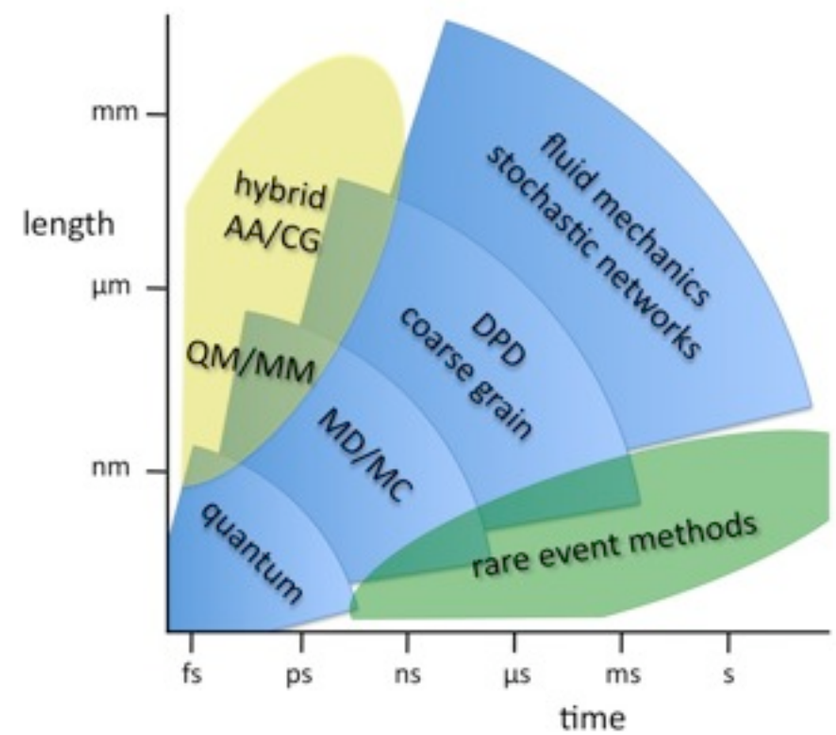
QM/MM

- many QM/MM algorithms and implementations
- electrostatic embedding
- mechanical coupling, link atoms, charge spilling
- polarization of MM environment
- many parameters, not a black box method

QM/QM, density embedding
- spectroscopy
- freeze-thaw cycles

Discreet reaction field
- polarizable MM environment
- self consistent procedure

PCM, COSMO
- implicit solvent model
- only electrostatics
- shape and size of cavity
- low computational cost



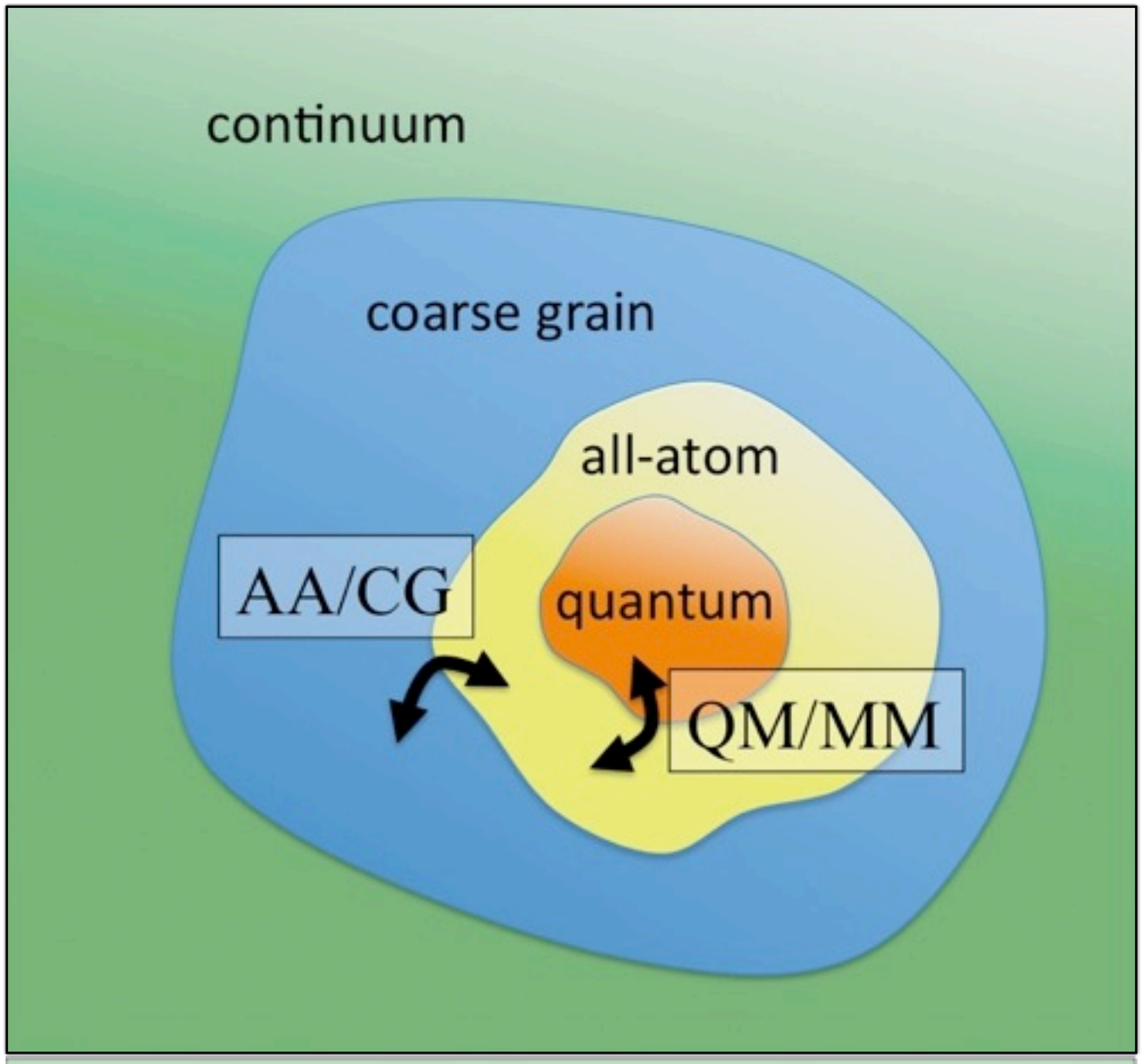
content

- Lecture 1: Density embedding
- Lecture 2: QM/MM
- Lecture 3: Coarse-graining
- Lecture 4: Hybrid multiscale molecular dynamics

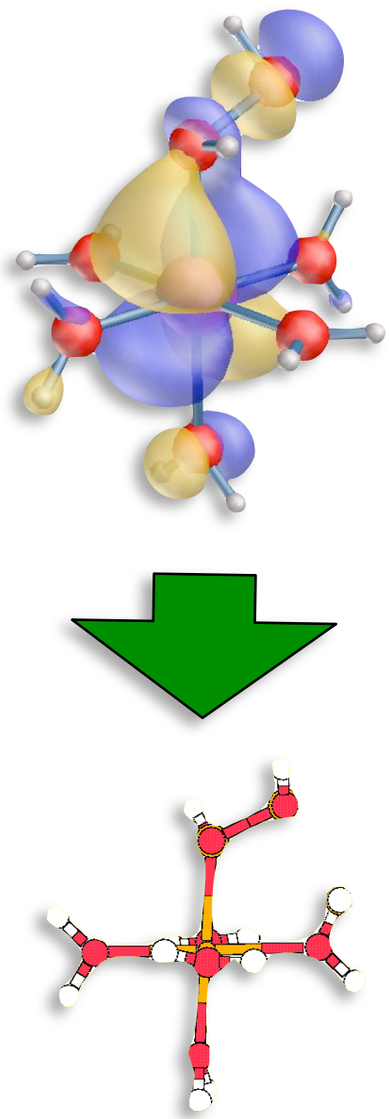
Lecture 3

Coarse graining

Multiscale methods



Coarse-graining

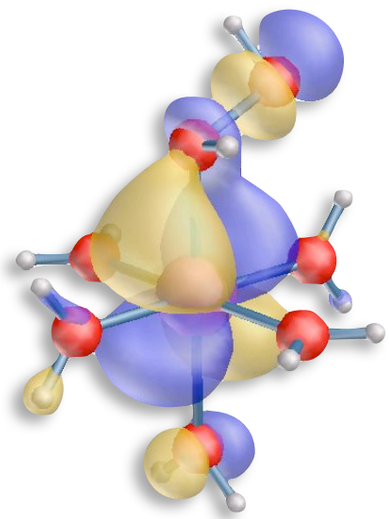


QM ⟶ MM

Integration over electronic degrees of freedom

$$U(R) = -k_B T \ln \int\int\int d\,r\, d\,\dot{r}\, d\dot{R}\, e^{-\beta H(R,\dot{R},r,\dot{r})}$$

Coarse-graining



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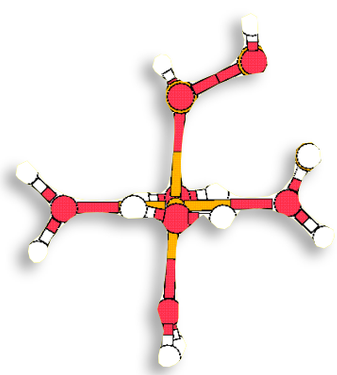
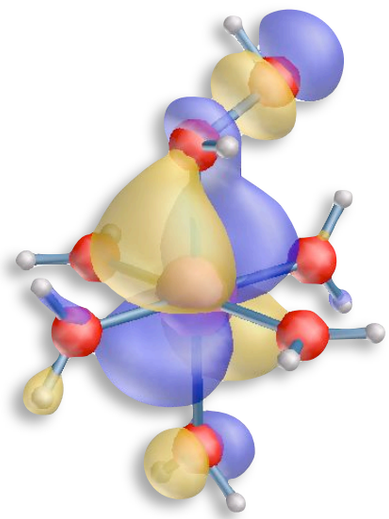


MM ⟶ CG

Integration over non-essential degrees of freedom

$$U(R,V,T) = -k_B T \ln \int d\,r\, e^{-\beta V(R,r)}$$

Coarse-graining



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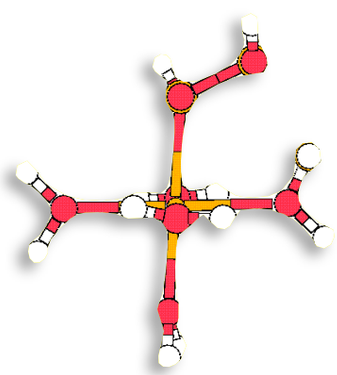


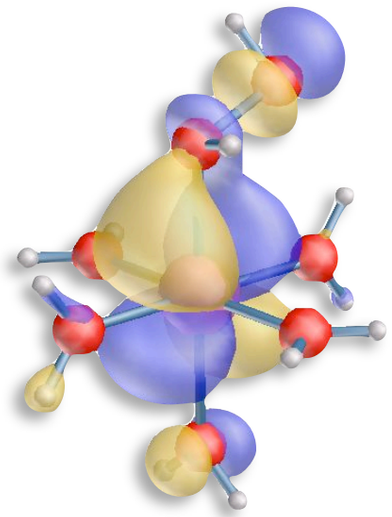
MM ⟶ CG

Integration over non-essential degrees of freedom

$$U(R,V,T) = -k_B T \ln \int d\,r\, e^{-\beta V(R,r)}$$

multi-dimensional free energy surface
metadynamics of collective variables

Coarse-graining



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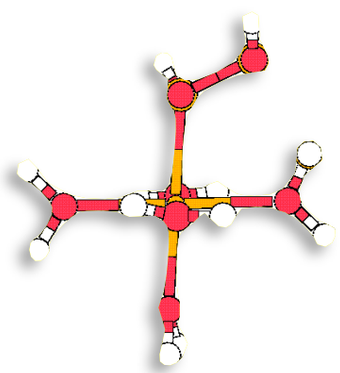


MM ⟶ CG

Integration over non-essential degrees of freedom

$$U(R,V,T) = -k_B T \ln \int d\,r\, e^{-\beta V(R,r)}$$

$$U(R) \approx \sum_{i<j} u(r_i, r_j) = V(R)$$

Methods to coarse-grain

Iterative Boltzmann Inversion

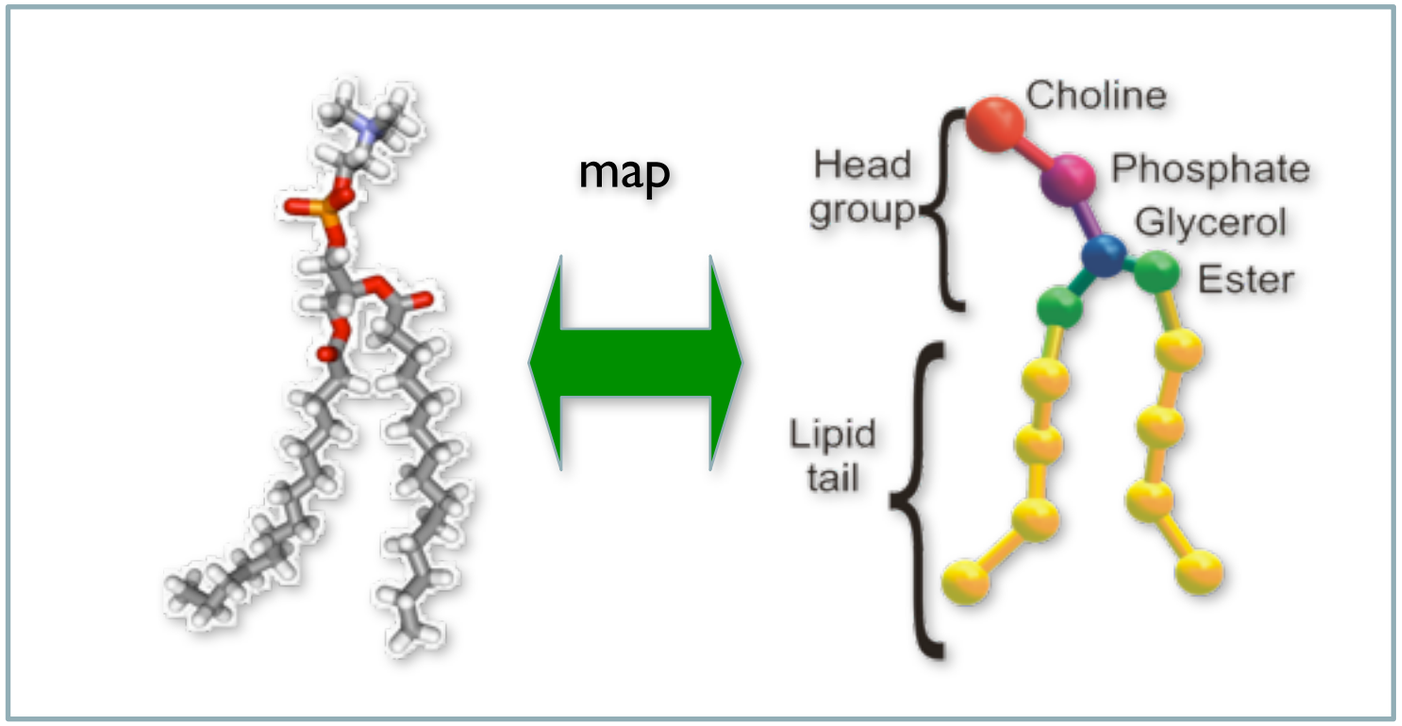
Inverse Monte Carlo

Force matching

Maximum entropy method

Selected experimental and computer target properties

CG to atomistic mapping

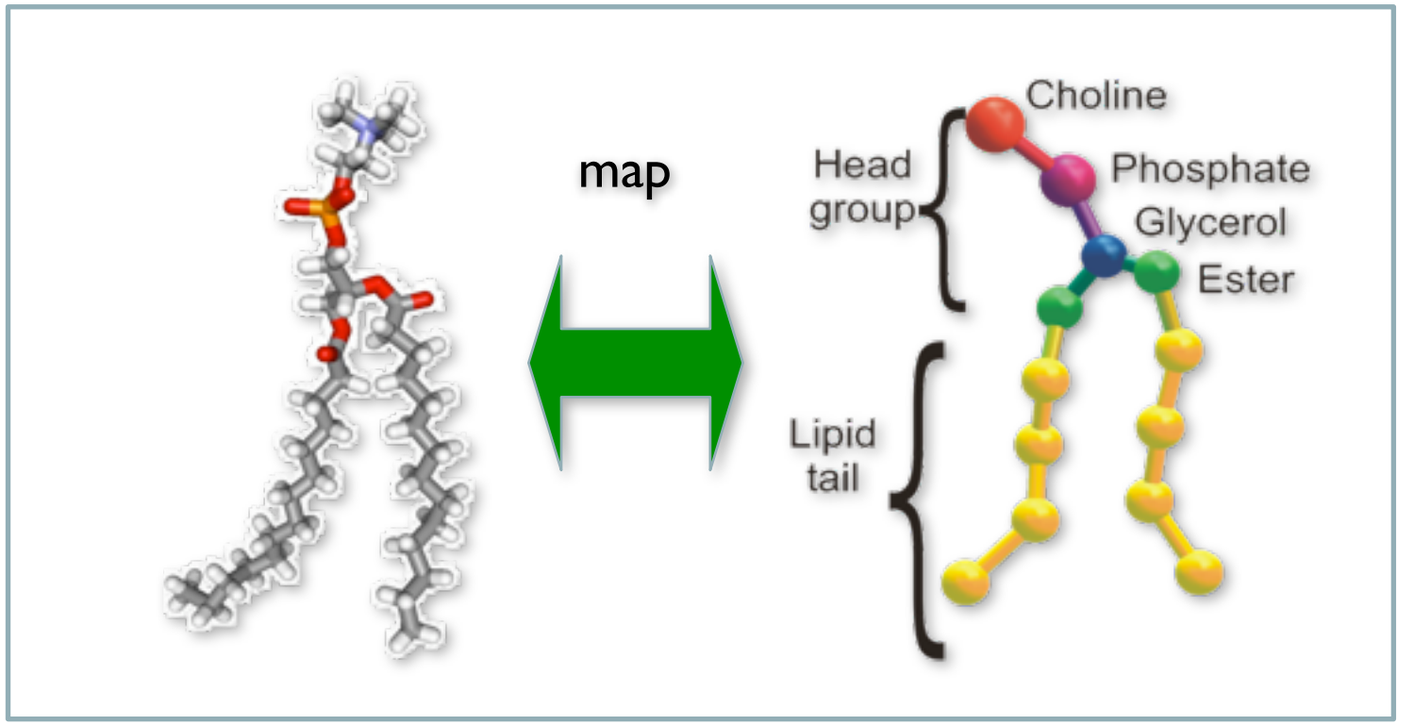


How to choose which degrees of freedom to keep or “integrate out”?

- very problem dependent
- arbitrary, chemical intuition
- or use maximum likelihood or Bayesian information criterion...

- 3-5 orders of magnitude saving in computational cost...

CG to atomistic mapping



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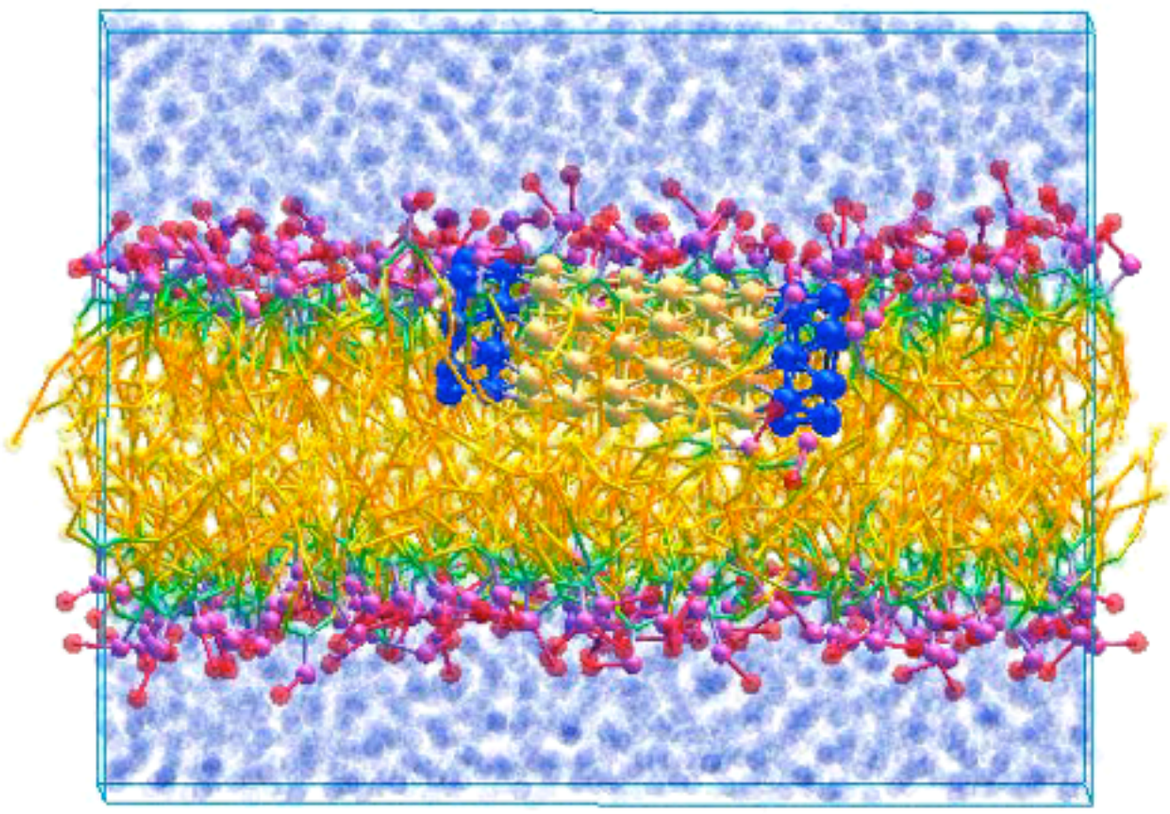


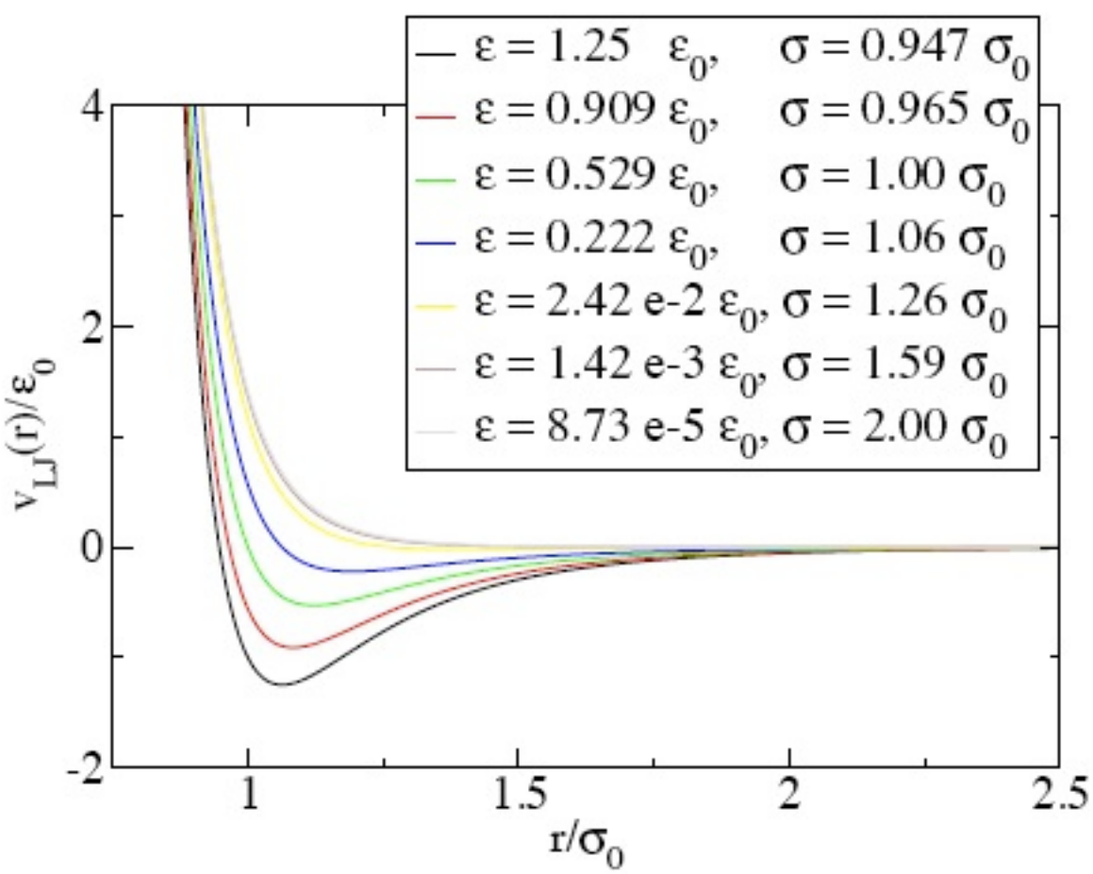
The Henderson theorem

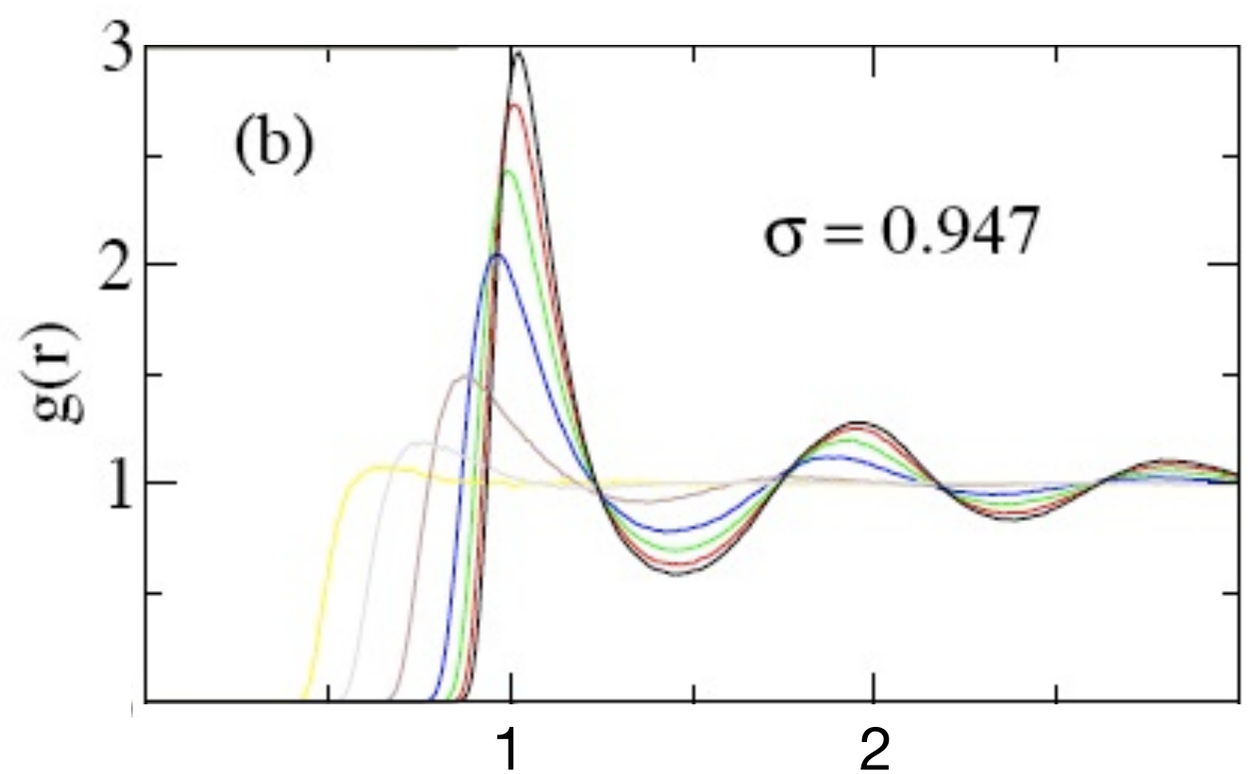
R. L. Henderson [Physics Letters **A49**, 197-198 (1974)]

A (classical or quantum) system described by the Hamiltonian

$$H = \sum_i \frac{p_i^2}{2m} + \frac{1}{2} \sum_{i \neq j} u(|r_i - r_j|)$$

will give rise to a unique pair correlation function (in the canonical ensemble). Henderson's theorem asserts that the reverse is also true: Two systems, which have a Hamiltonian of this form and which feature the same *g(r)* have pair potentials which differ at most by a trivial constant.



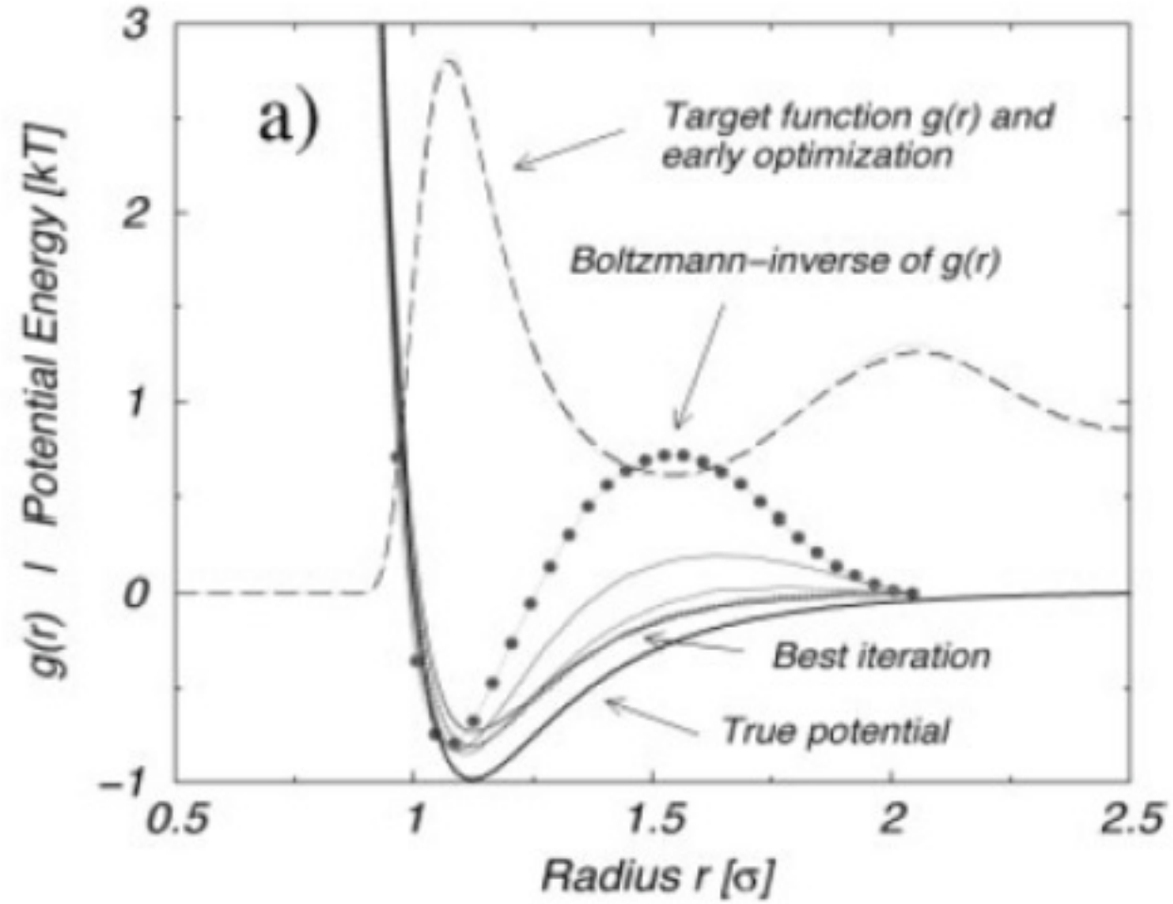


Iterative Boltzmann Inversion

A pair-potential is constructed in an iterative manner

- target is reference probability e.g. radial distribution
- useful for bonded and non-bonded interactions
- update potential until reference probability is matched
- requires a CG simulation for each cycle
- requires smooth function of V, e.g. splines or tabulated
- λ [0, 1] stabilizes optimization

$$V^{n+1} = V^n + \lambda k_B T \ln \frac{P^n}{P_{\mathrm{ref}}}$$



Sometimes the g(r) is used directly to construct a pair-potential. This is not correct.

Inverse Monte Carlo

A pair-potential U is constructed in an iterative manner
- target is histogram of CG property, S^{ref}
- solving set of linear equations, gives improvement ΔU

$$\langle S_\alpha \rangle - S_\alpha^{\mathrm{ref}} = A_{\alpha\gamma} \Delta U_\gamma$$

- Hamilonian can be written as a sum over a grid of pair distances
- S is an estimator of the RDF

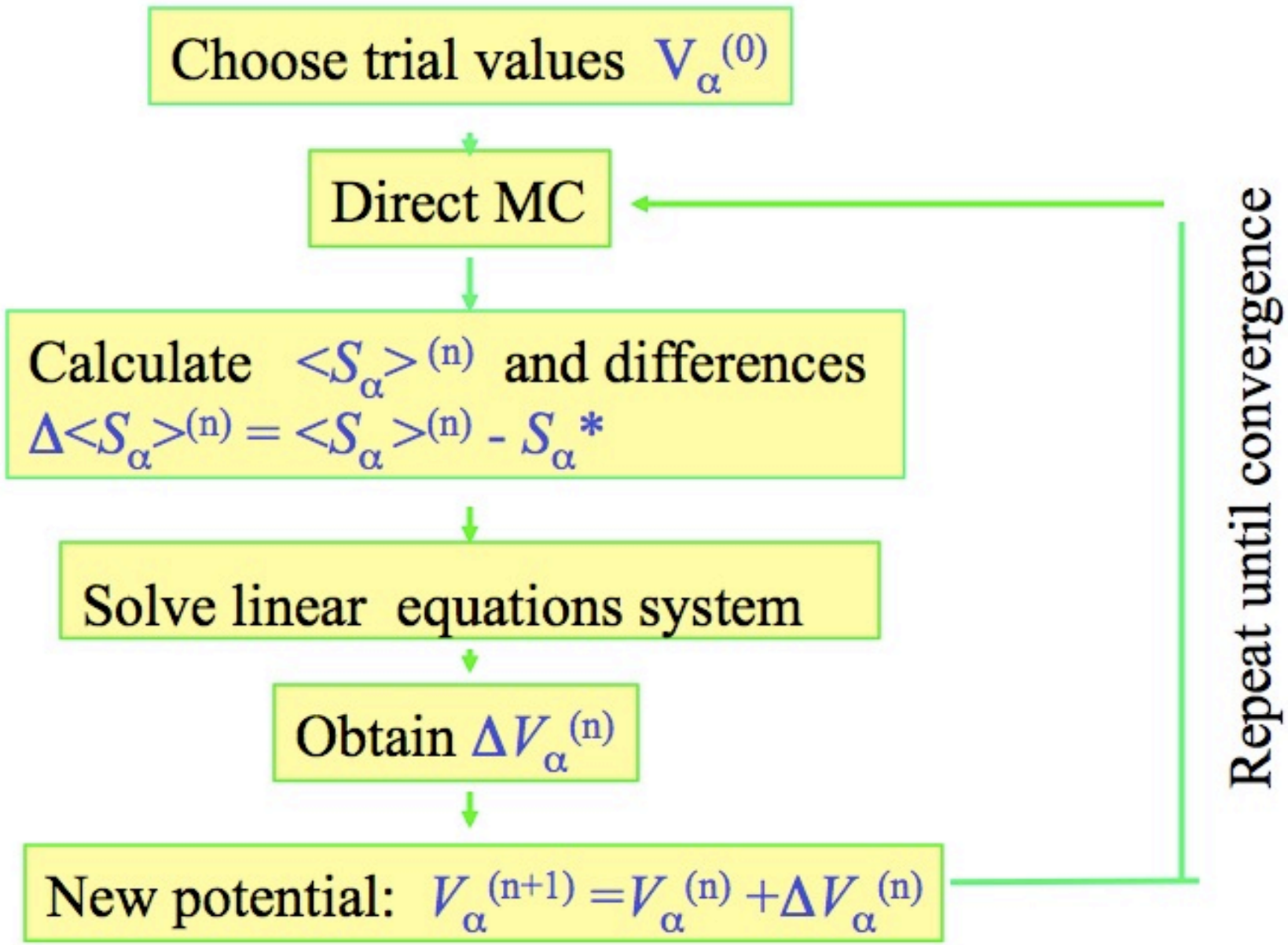
$$H = \sum_{ij} U(r_{ij}) = \sum_\alpha U_\alpha S_\alpha \qquad \langle S_\alpha \rangle = \frac{N(N-1)}{2} \frac{4\pi r_\alpha^2 \Delta r}{V} g(r_\alpha)$$

$$\frac{\partial \langle S_\alpha \rangle}{\partial U_\lambda} = \frac{\partial}{U_\lambda} \left(\frac{\int dq S_\alpha(q) \exp(-\beta \sum_\lambda U_\lambda S_\lambda(q))}{\int dq \exp(-\beta \sum_\lambda U_\lambda S_\lambda(q))} \right)$$

$$A_{\alpha\gamma} = \frac{\partial \langle S_\alpha \rangle}{\partial U_\gamma} = \beta \big(\langle S_\alpha \rangle \langle S_\gamma \rangle - \langle S_\alpha S_\gamma \rangle \big)$$

A Lyubartsev and A Laaksonen. Calculation of effective interaction potentials from radial-distribution functions - a reverse monte-carlo approach. *Phys. Rev. E*, **52**, 3730–3737, (1995)

Inverse Monte Carlo



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Force Matching

Aims to reproduce the potential of mean force
(not aiming to reproduce distribution functions)

- CG forcefield depends on *M* parameters: $g_1, g_2, \ldots g_M$
- calculate reference forces for *L* snapshots

- force on CG bead is constructed from forces on atoms
- mapping coefficients d can be set to c

$$\mathbf{F}_I^{\mathrm{ref}} = \sum_{j \in S_I} \frac{d_{Ii}}{c_{Ii}} \mathbf{f}_j(\mathbf{r}^n)$$

- requires least squares fitting to find optimal parameters
- solve NxL equations

$$\mathbf{F}_{Il}^{\mathrm{CG}}(g_1, \ldots, g_M) = \mathbf{F}_{il}^{\mathrm{ref}}\,,\; I = 1, \ldots, N,\; l = 1, \ldots, L$$

- F is non-linear function of g_i, --> use coefficients for spline or tabulated functions to linearize.

Matching selected properties

Construct CG Forcefield that matches
- experimental properties: density, surface tension, affinities
- atomistic simulation data: RDF, PMF, free energy profiles

Example:
- MARTINI forcefield
- uses solvation free energies and phase partitioning

- requires optimization scheme
- can be better than atomistic forcefields
- limited to target thermodynamic state
- which properties are accurate?

Summary coarse-graining

Transferability

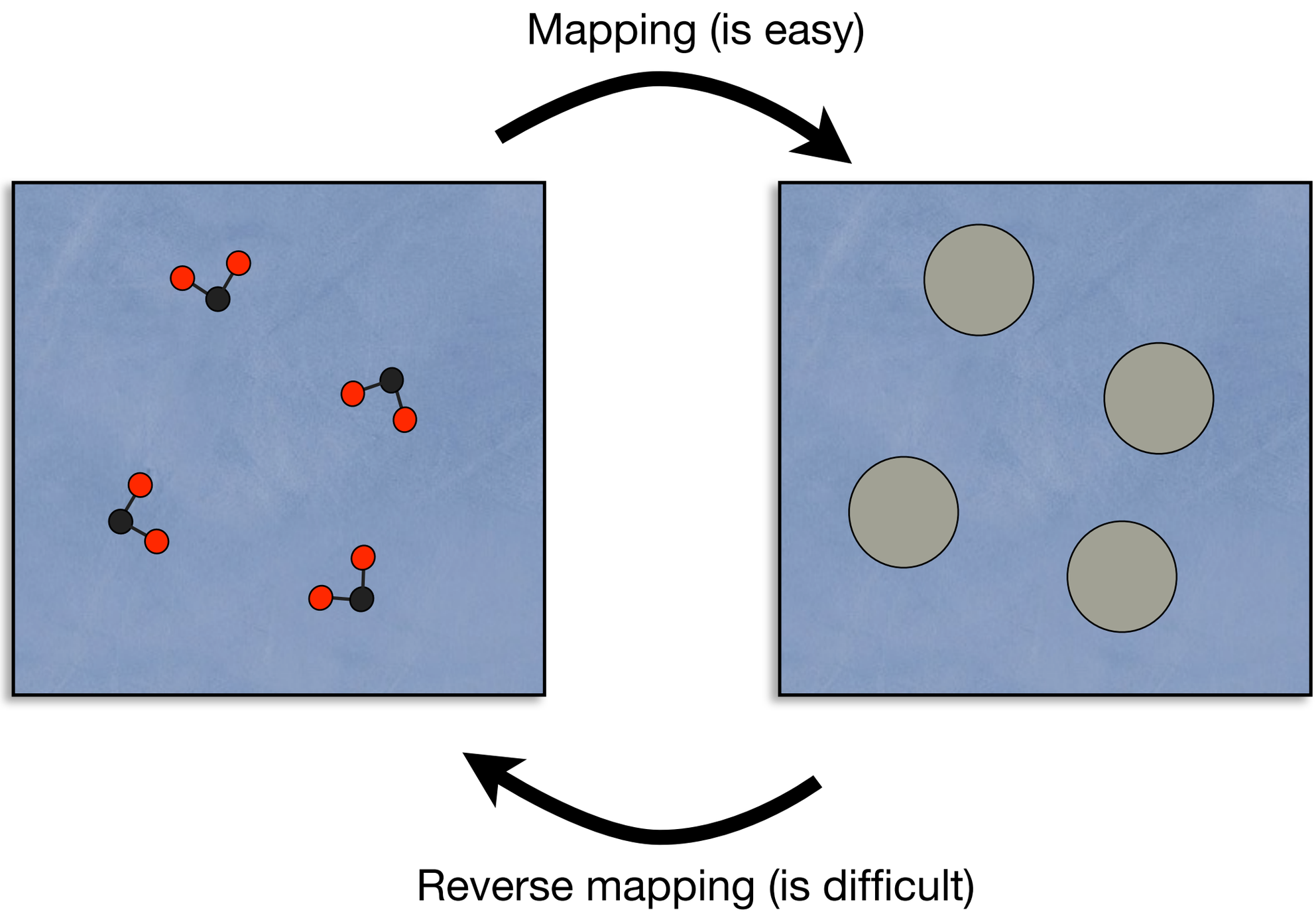
What can you expect from the model?

Dynamical properties?

Lecture 4

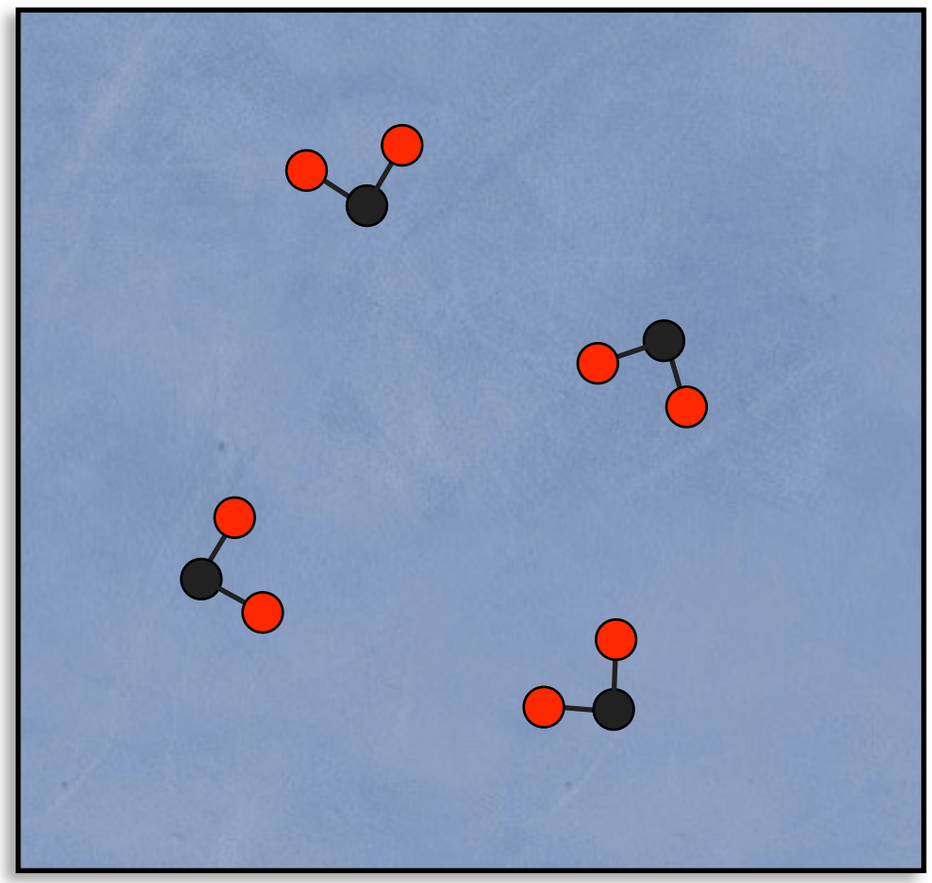
Multscale Molecular Dynamics

Reverse mapping problem



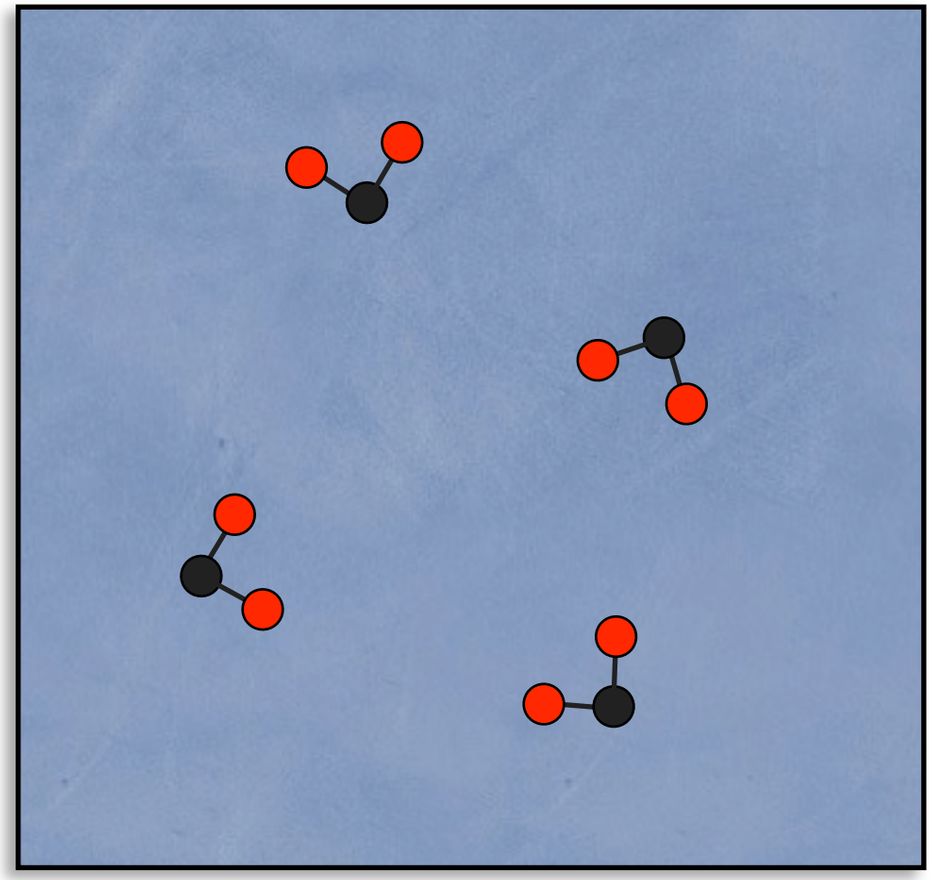
Constructing Hybrid MD

NVE ensemble



$$H = \sum_{i=1}^{n} \frac{p_i^2}{2m_i} + V(r^n)$$

NVT ensemble



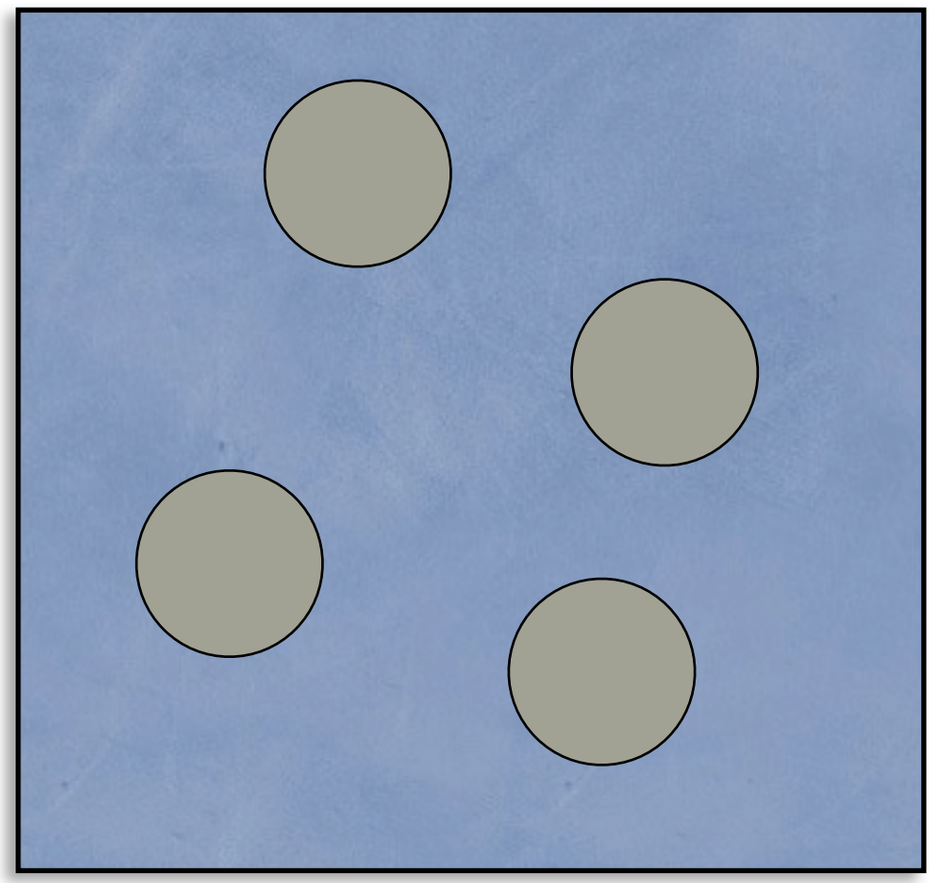
Nosé-Hoover thermostat

- NH thermostat "potential" is a book keeping term
- non-Hamiltonian dynamics

$$E = \sum_{i=1}^{n} \frac{p_i^2}{2m_i} + V(r^n) + \frac{\epsilon^2 Q}{2} + L\frac{\ln s}{\beta}$$

Understanding Molecular Simulation, Frenkel & Smit (chapter 6)

Coarse grained MD

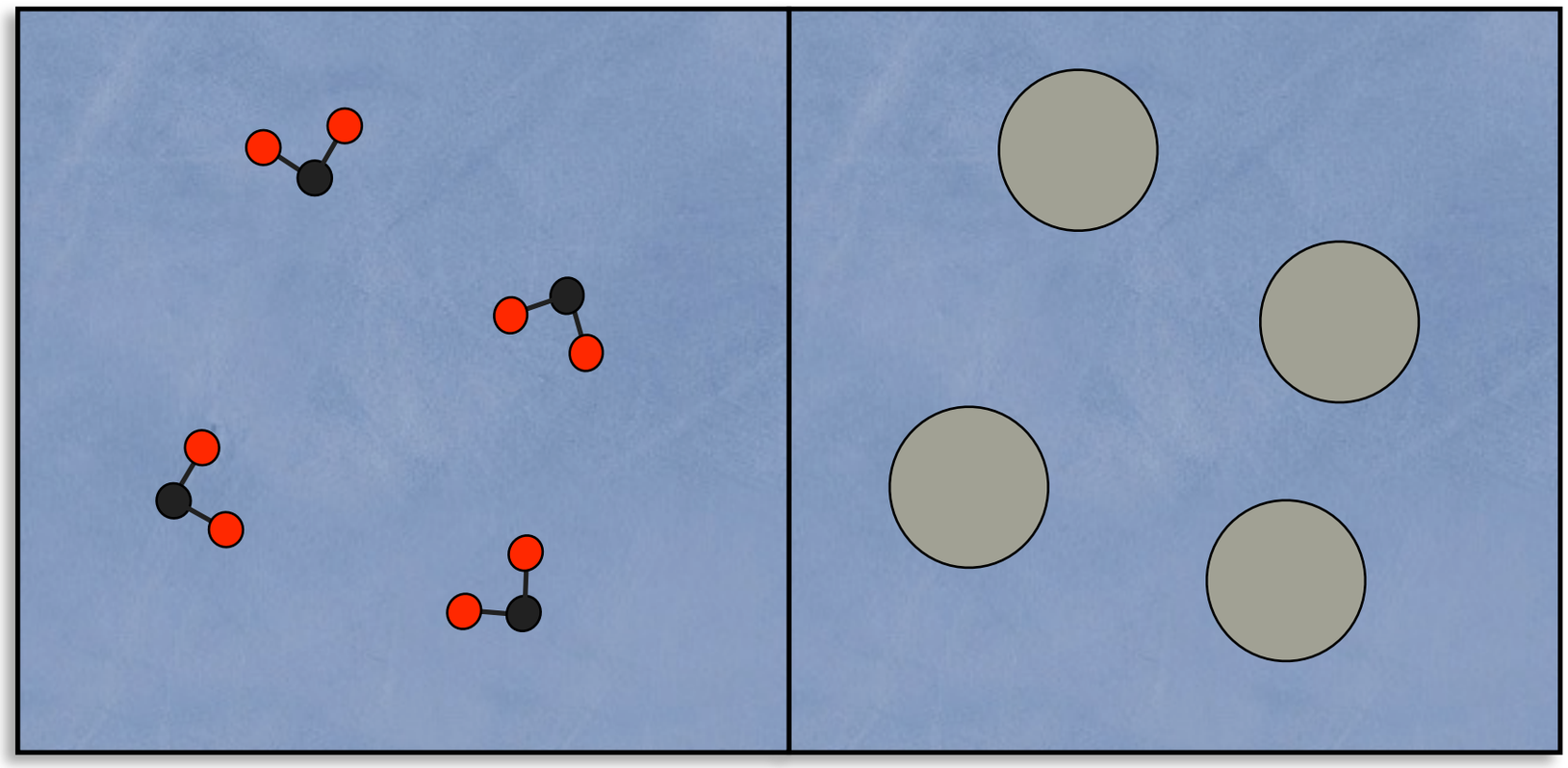


$$E = \sum_{\alpha=1}^{N} \frac{P_\alpha^2}{2M_\alpha} + V(R^N)$$

Constructing Hybrid MD

Atomistic + Coarse grained MD

- non-interacting
- non-adaptive



$$E = \sum_{i=1}^{n} \frac{p_i^2}{2m_i} + V(r^n) + \sum_{\alpha=1}^{N} \frac{P_\alpha^2}{2M_\alpha} + V(R^N)$$

Constructing Hybrid MD

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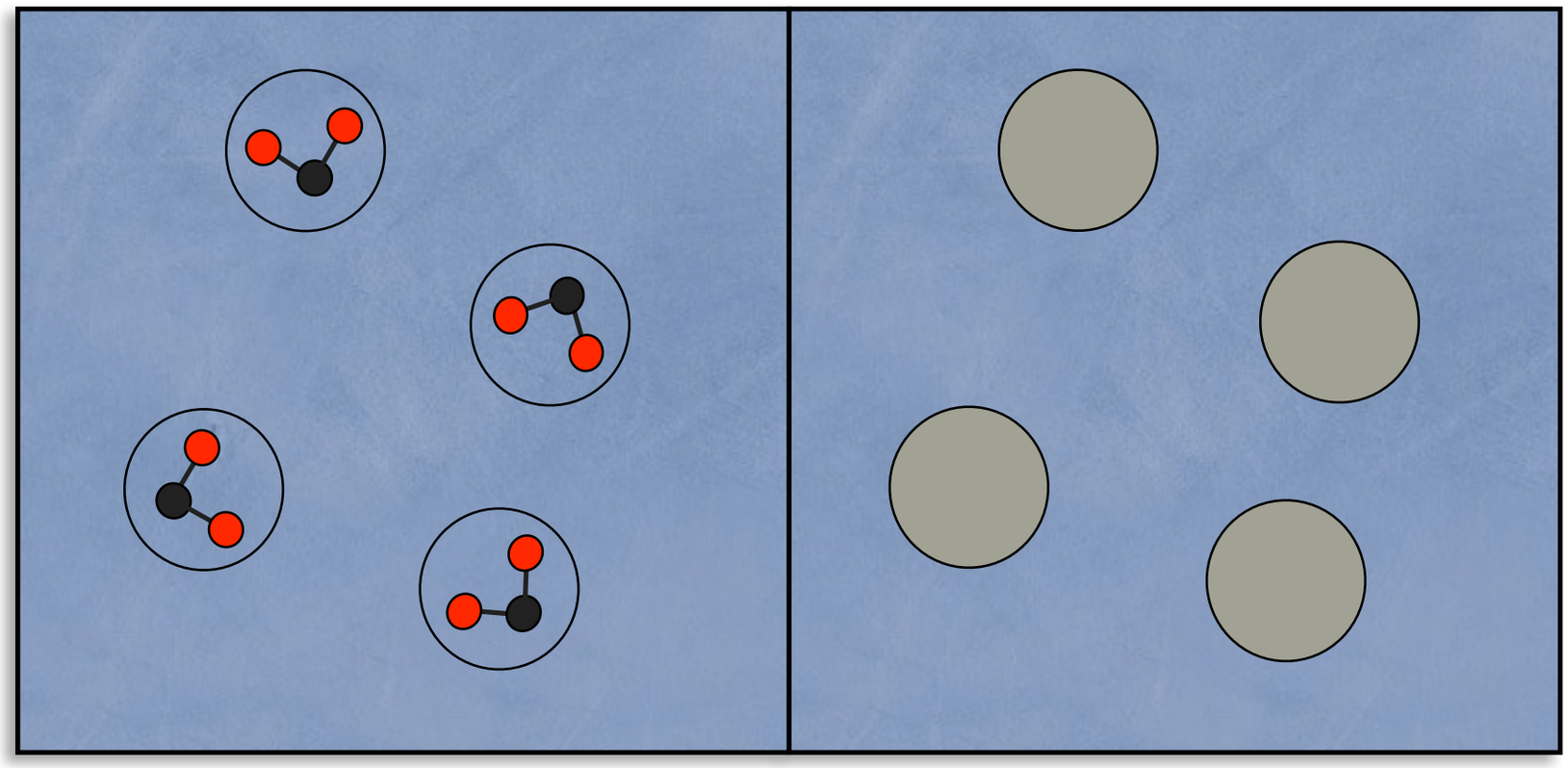


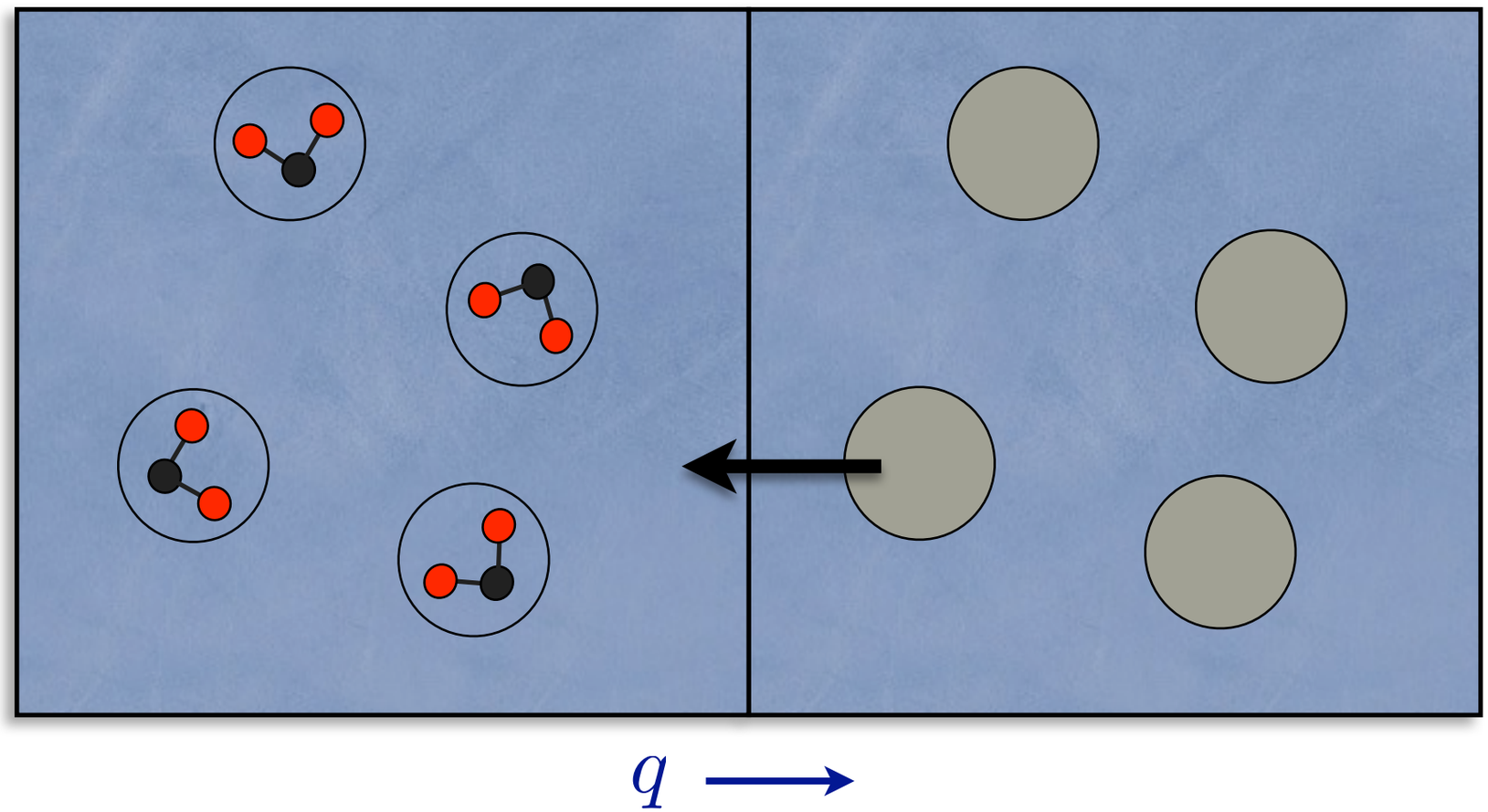
$$E = \sum_{i=1}^{n} \frac{p_i^2}{2m_i} + V(r^n) + \sum_{\alpha=1}^{N} \frac{P_\alpha^2}{2M_\alpha} + V(R^N) + V^{\mathrm{MIX}}(r^n, R^N)$$

$$V_{i\in\alpha} = \sum_j \Phi_{ij}(r_i, r_j) + \frac{m_i}{M_\alpha} \sum_\beta^N \Phi_{\alpha,\beta}(R_\alpha, R_\beta)$$

Constructing Hybrid MD

- order parameter
- book keeping
- smooth transition

$s(q < q^\dagger) = 0$ $\qquad q^\dagger \qquad$ $s(q > q^\dagger) = 1$



$$\lambda_{\alpha\beta} = \max(s(q_\alpha), s(q_\beta))$$

$$\begin{aligned} V &= V(r^n) + V(R^N) + V^{\mathrm{MIX}} \\ &= \sum_{\alpha,\beta} \left(\lambda \Phi^{\mathrm{CG}}_{\alpha\beta} + (1-\lambda) \sum_{\substack{i\in\alpha \\ j\in\beta}} \Phi^{\mathrm{A}}_{ij} \right) + \sum_{\alpha} \sum_{ij\in\alpha} \Phi^{\mathrm{A}}_{ij} \end{aligned}$$

Constructing Hybrid MD

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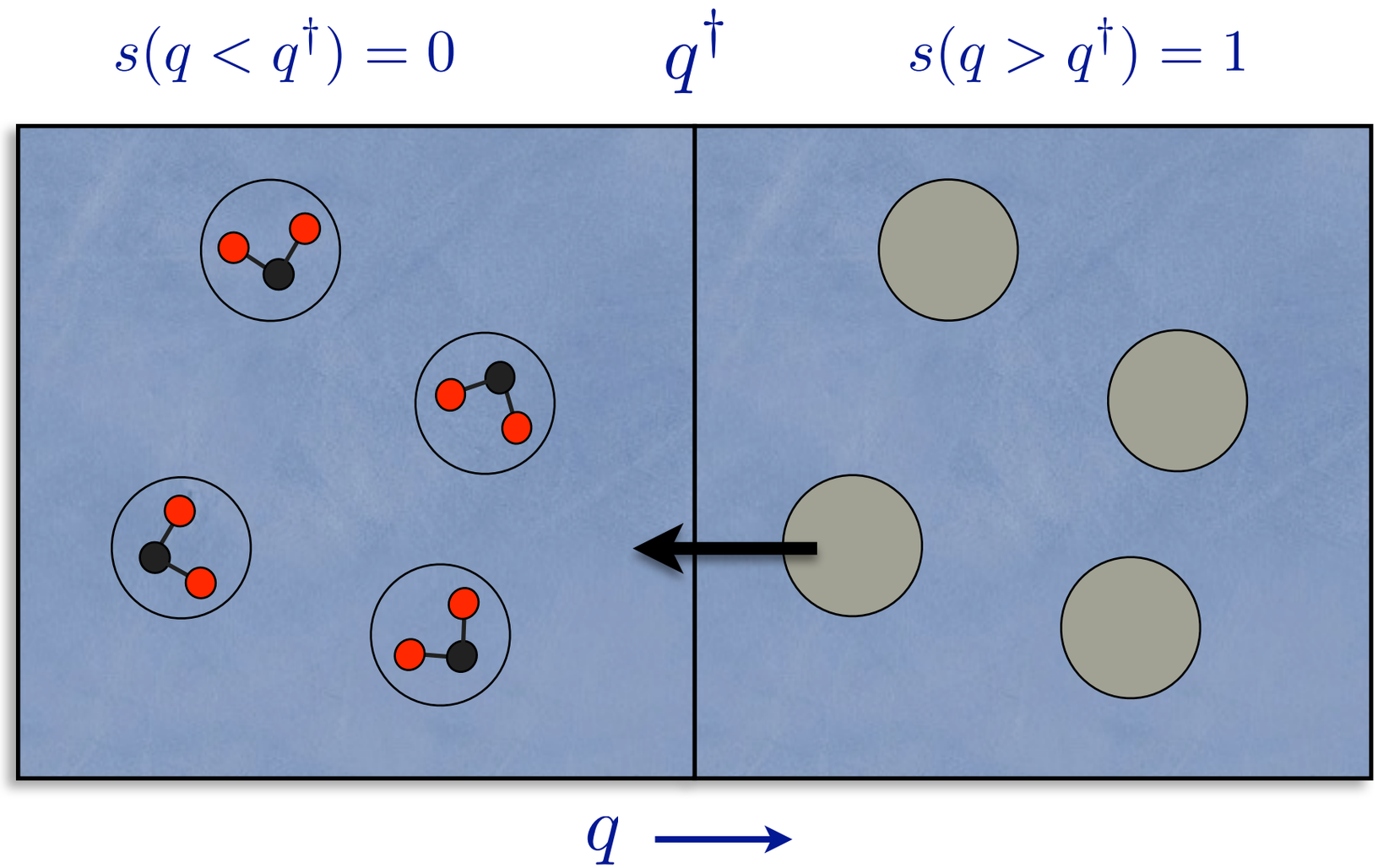

$$V = \sum_{\alpha,\beta}\left(\lambda\Phi^{\mathrm{CG}}_{\alpha\beta} + (1-\lambda)\sum_{\substack{i\in\alpha\\ j\in\beta}}\Phi^{\mathrm{A}}_{ij}\right) + \sum_{\alpha}\sum_{ij\in\alpha}\Phi^{\mathrm{A}}_{ij} - \Delta U(q^\dagger)$$

$$\Delta U_\alpha(q^\dagger) = \Delta\lambda\sum_{\beta}\left(\Phi^{\mathrm{CG}^\dagger}_{\alpha\beta} - \sum_{\substack{i\in\alpha\\ j\in\beta}}\Phi^{\mathrm{A}^\dagger}_{ij}\right)$$

Constructing Hybrid MD

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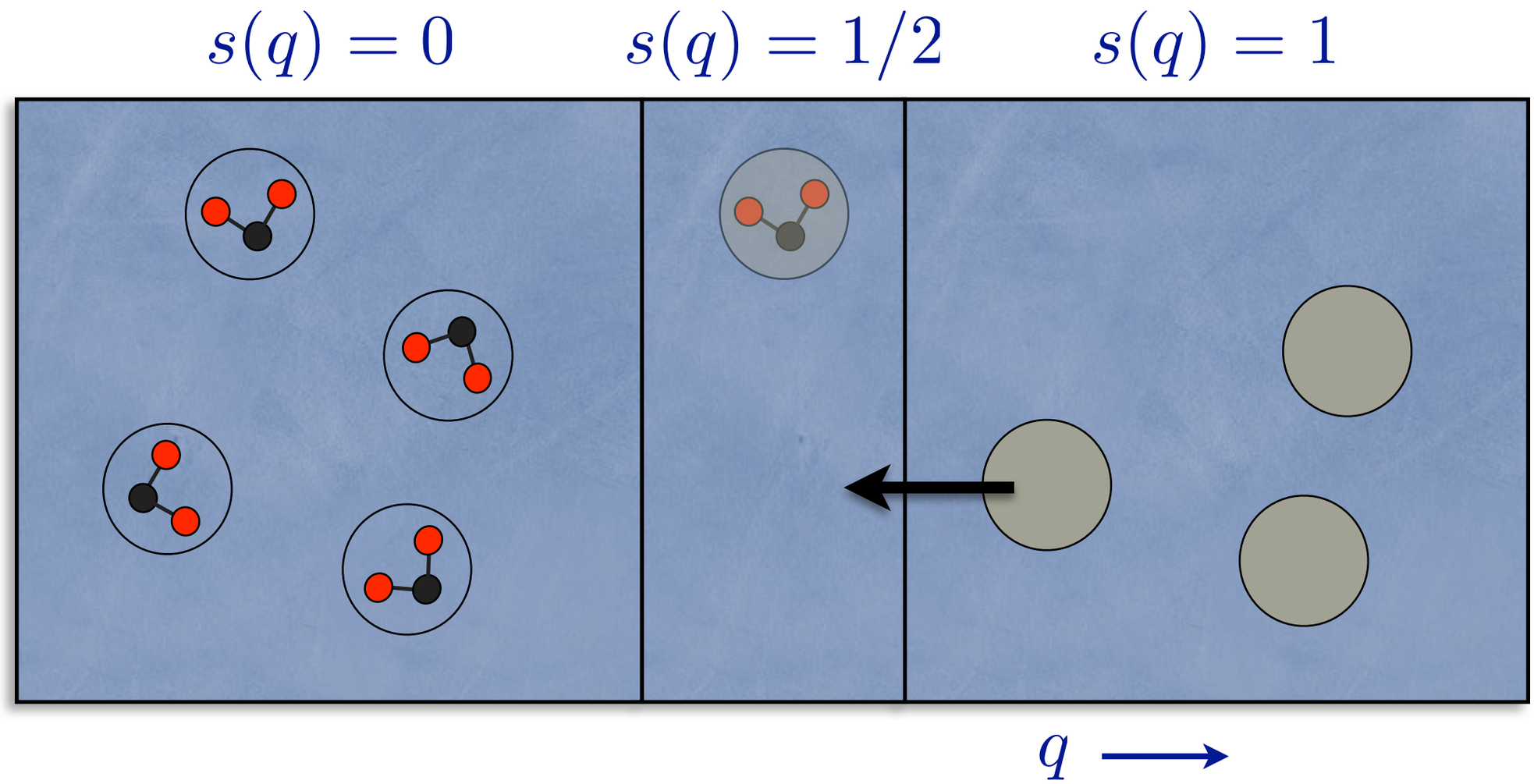

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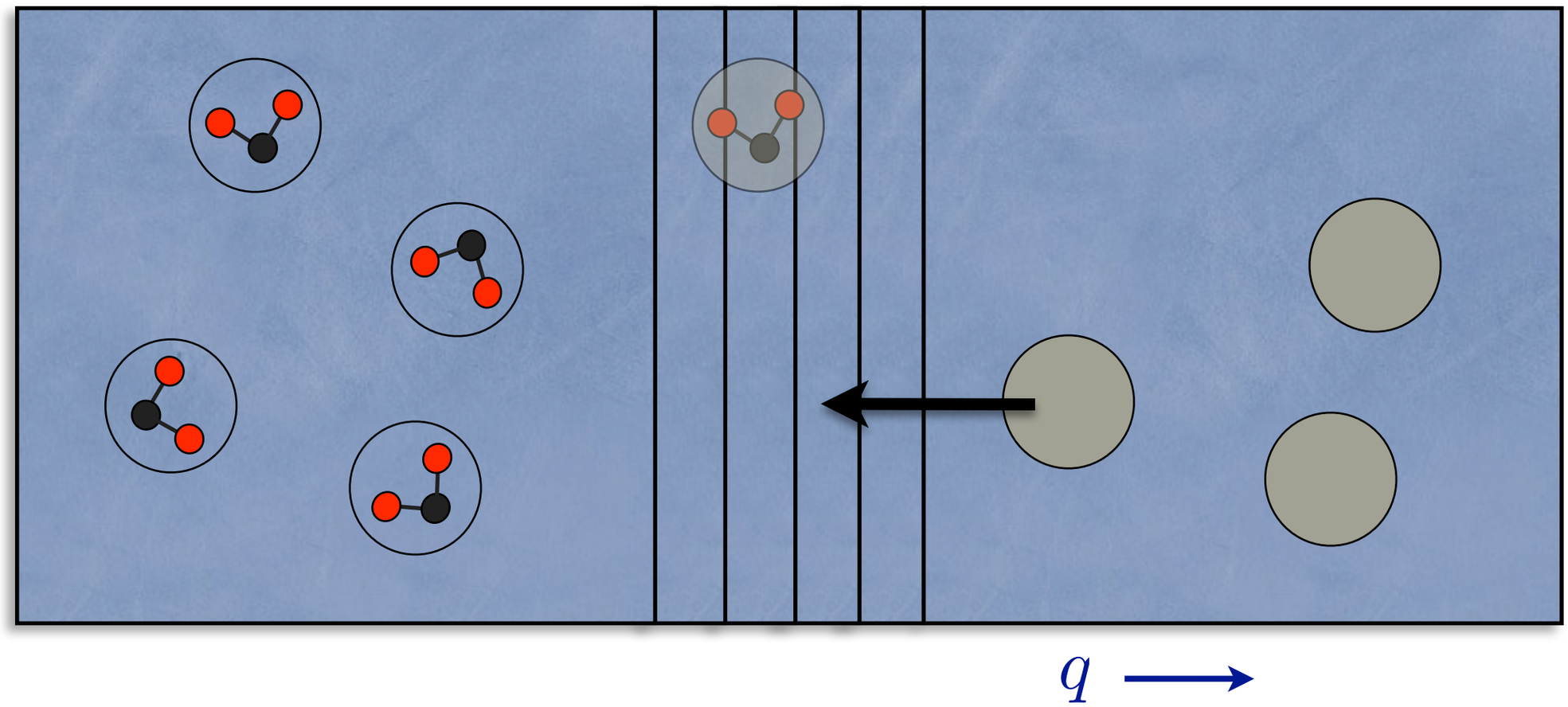
Constructing Hybrid MD

- order parameter
- book keeping
- smooth transition

$$s(q) = 0 \qquad S = \frac{1}{N}, \frac{2}{N} \cdots \frac{N-1}{N} \qquad s(q) = 1$$



$$\Delta U_\alpha(q^\dagger) \quad = \quad \sum_{q_1}^{q_2} \Delta\lambda \sum_\beta \left(\Phi_{\alpha\beta}^{\mathrm{CG}^\dagger} - \sum_{\substack{i\in\alpha \\ j\in\beta}} \Phi_{ij}^{\mathrm{A}^\dagger} \right)$$

Constructing Hybrid MD

- order parameter
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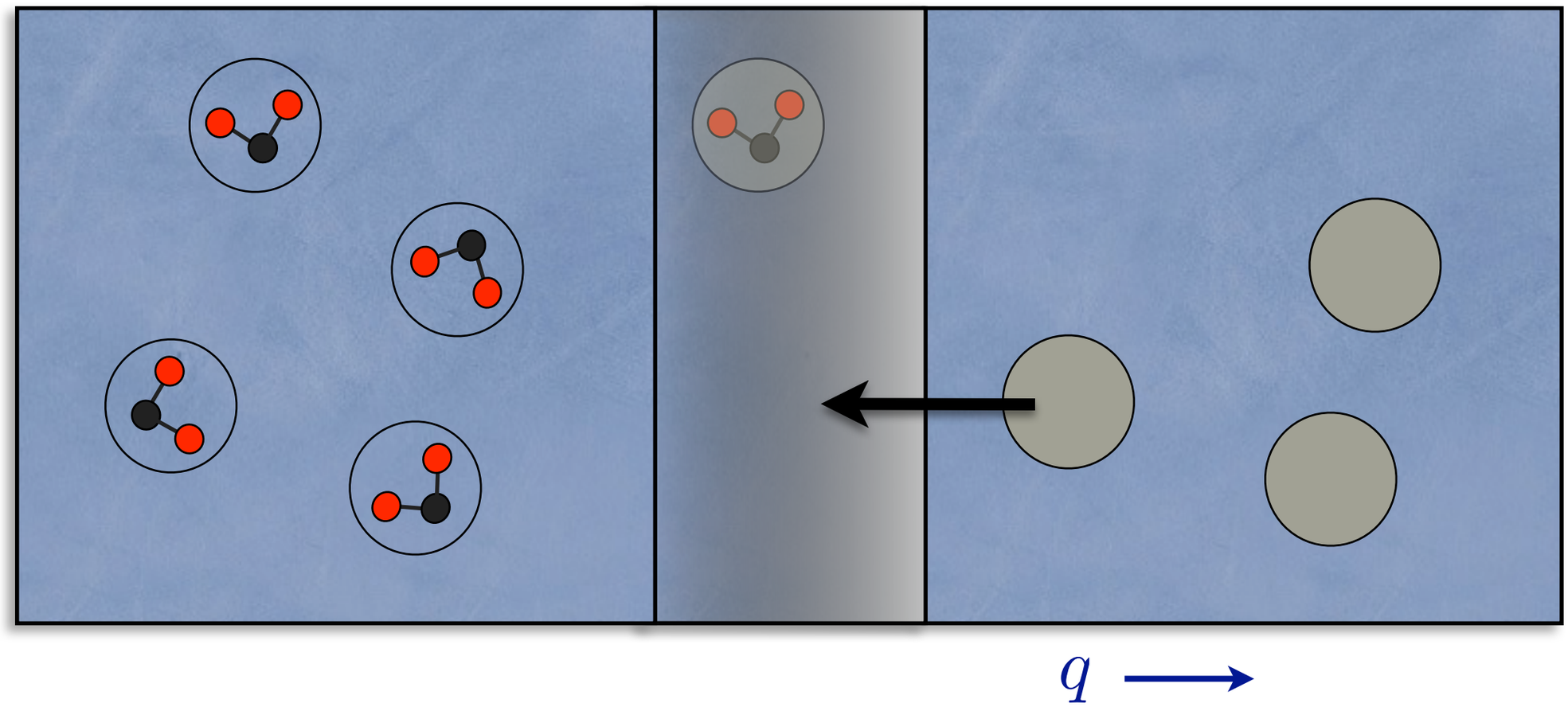
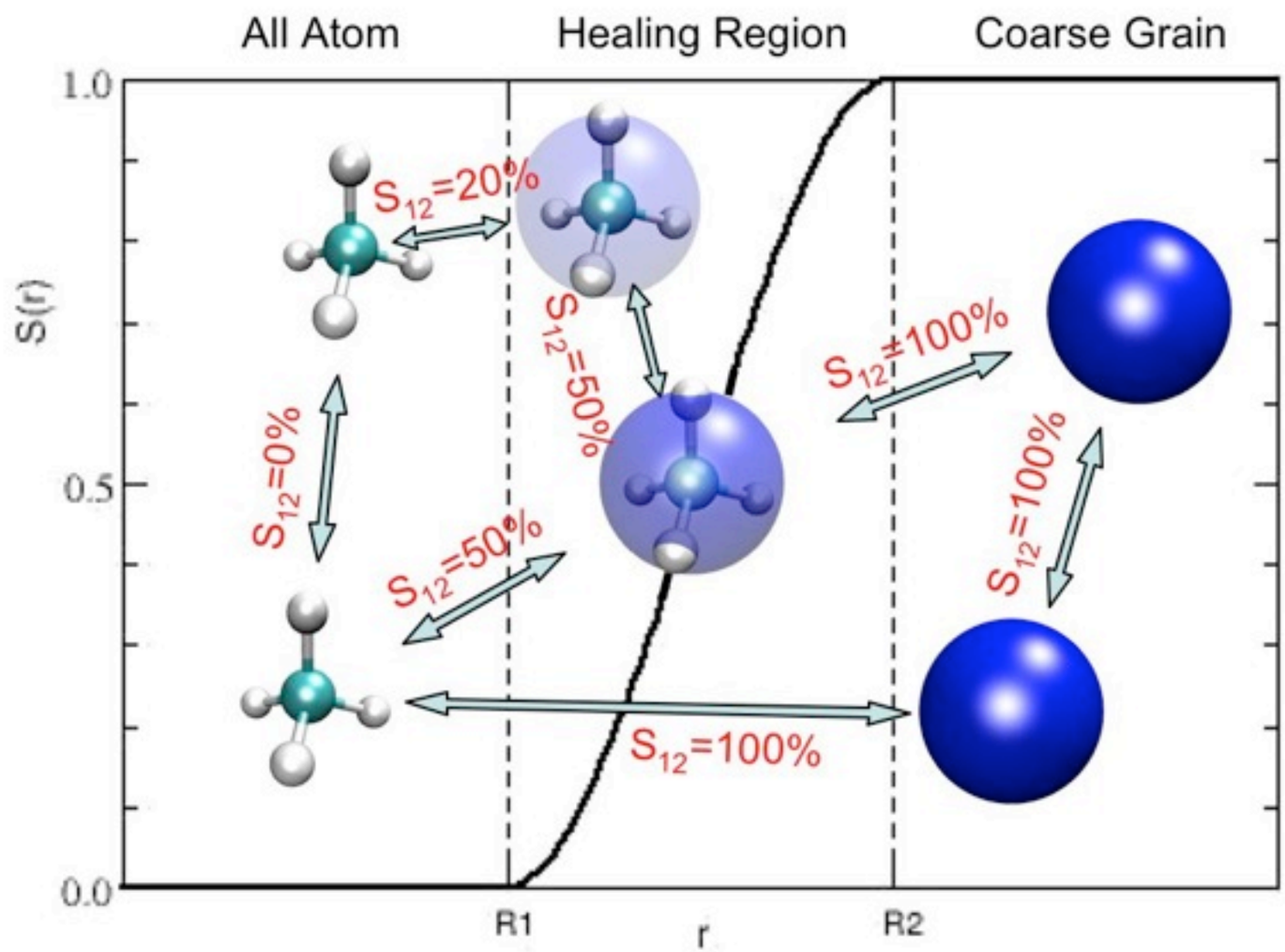


$$\Delta U_\alpha(q^\dagger) = \lim_{N\to\infty} \sum_{q_1}^{q_2} \Delta\lambda \sum_\beta \left(\Phi_{\alpha\beta}^{\mathrm{CG}^\dagger} - \sum_{\substack{i\in\alpha \\ j\in\beta}} \Phi_{ij}^{\mathrm{A}^\dagger} \right)$$

$$= \int_{q1}^{q2} \frac{d\lambda}{dq} \sum_\beta \left(\Phi_{\alpha\beta}^{\mathrm{CG}^\dagger} - \sum_{\substack{i\in\alpha \\ j\in\beta}} \Phi_{ij}^{\mathrm{A}^\dagger} \right) dq'$$

Switching Function



$$S(r) = (r - R_{AA})^2 * (3R_{CG} - R_{AA} - 2r)/(R_{CG} - R_{AA})^3$$

$$\lambda_{\alpha\beta} \quad = \quad \max(s(r_\alpha), s(r_\beta))$$

Conserved Quantity

Energy function, E = K +V

$$V_\alpha = \sum_\beta \left(\lambda \Phi^{\mathrm{CG}}_{\alpha\beta} + (1-\lambda) \sum_{\substack{i\in\alpha \\ j\in\beta}} \Phi^{\mathrm{A}}_{ij} \right) + \sum_{ij\in\alpha} \Phi^{\mathrm{A}}_{ij} - \sum_\beta \Delta U_\alpha(q)$$

$$\Delta U_\alpha(q) = \int_{q1}^{q2} \frac{d\lambda}{dq} \left(\Phi^{\mathrm{CG}}_{\alpha\beta} - \sum_{\substack{i\in\alpha \\ j\in\beta}} \Phi^{\mathrm{A}}_{ij} \right) dq'$$

Forces

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Forces

$$\begin{aligned} f_\alpha &= -\frac{\partial V}{\partial r_\alpha} \\ &= -\lambda \frac{\partial \Phi^{\mathrm{CG}}_{\alpha\beta}}{\partial r_\alpha} - \frac{d\lambda}{dr_\alpha} \Phi^{\mathrm{CG}}_{\alpha\beta} - \sum_{\substack{i\in\alpha \\ j\in\beta}} (1-\lambda) \frac{\partial \Phi^{\mathrm{A}}_{ij}}{\partial r_\alpha} + \sum_{\substack{i\in\alpha \\ j\in\beta}} \frac{d\lambda}{dr_\alpha} \Phi^{\mathrm{A}}_{ij} + \frac{\partial \Delta U_\alpha}{\partial r_\alpha} \end{aligned}$$

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Forces

$$f_\alpha = -\frac{\partial V}{\partial r_\alpha}$$

$$= -\lambda \frac{\partial \Phi^{\mathrm{CG}}_{\alpha\beta}}{\partial r_\alpha} - \frac{d\lambda}{dr_\alpha} \Phi^{\mathrm{CG}}_{\alpha\beta} - \sum_{\substack{i\in\alpha \\ j\in\beta}} (1-\lambda) \frac{\partial \Phi^{\mathrm{A}}_{ij}}{\partial r_\alpha} + \sum_{\substack{i\in\alpha \\ j\in\beta}} \frac{d\lambda}{dr_\alpha} \Phi^{\mathrm{A}}_{ij} + \frac{\partial \Delta U_\alpha}{\partial r_\alpha}$$

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Energy function, E = K +V

$$V_\alpha = \sum_\beta \left(\lambda \Phi^{\mathrm{CG}}_{\alpha\beta} + (1-\lambda) \sum_{\substack{i\in\alpha \\ j\in\beta}} \Phi^{\mathrm{A}}_{ij} \right) + \sum_{ij\in\alpha} \Phi^{\mathrm{A}}_{ij} - \sum_\beta \Delta U_\alpha(q)$$

$$\Delta U_\alpha(q) = \int_{q1}^{q2} \frac{d\lambda}{dq} \left(\Phi^{\mathrm{CG}}_{\alpha\beta} - \sum_{\substack{i\in\alpha \\ j\in\beta}} \Phi^{\mathrm{A}}_{ij} \right) dq'$$

Forces

$$f_\alpha = -\frac{\partial V}{\partial r_\alpha}$$

$$= -\lambda \frac{\partial \Phi^{\mathrm{CG}}_{\alpha\beta}}{\partial r_\alpha} - \frac{d\lambda}{dr_\alpha} \Phi^{\mathrm{CG}}_{\alpha\beta} - \sum_{\substack{i\in\alpha \\ j\in\beta}} (1-\lambda) \frac{\partial \Phi^{\mathrm{A}}_{ij}}{\partial r_\alpha} + \sum_{\substack{i\in\alpha \\ j\in\beta}} \frac{d\lambda}{dr_\alpha} \Phi^{\mathrm{A}}_{ij} + \frac{\partial \Delta U_\alpha}{\partial r_\alpha}$$

Conserved Quantity

Energy function, E = K +V

$$V_\alpha = \sum_\beta \left(\lambda \Phi^{\mathrm{CG}}_{\alpha\beta} + (1-\lambda) \sum_{\substack{i\in\alpha \\ j\in\beta}} \Phi^{\mathrm{A}}_{ij} \right) + \sum_{ij\in\alpha} \Phi^{\mathrm{A}}_{ij} - \sum_\beta \Delta U_\alpha(q)$$

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$$\frac{d\lambda}{dr_\alpha} = \frac{d\lambda}{dq}$$

Conserved Quantity

Energy function, E = K +V

$$V_\alpha = \sum_\beta \left(\lambda \Phi^{\mathrm{CG}}_{\alpha\beta} + (1-\lambda) \sum_{\substack{i\in\alpha \\ j\in\beta}} \Phi^{\mathrm{A}}_{ij} \right) + \sum_{ij\in\alpha} \Phi^{\mathrm{A}}_{ij} - \sum_\beta \Delta U_\alpha(q)$$

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Forces

$$f_\alpha = -\frac{\partial V}{\partial r_\alpha}$$

$$= -\lambda \frac{\partial \Phi^{\mathrm{CG}}_{\alpha\beta}}{\partial r_\alpha} - \frac{d\lambda}{dq} \Phi^{\mathrm{CG}}_{\alpha\beta} - \sum_{\substack{i\in\alpha \\ j\in\beta}} (1-\lambda) \frac{\partial \Phi^{\mathrm{A}}_{ij}}{\partial r_\alpha} + \sum_{\substack{i\in\alpha \\ j\in\beta}} \frac{d\lambda}{dq} \Phi^{\mathrm{A}}_{ij} + \frac{\partial \Delta U_\alpha}{\partial r_\alpha}$$

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Forces

$$f_\alpha = -\frac{\partial V}{\partial r_\alpha}$$

$$= -\lambda \frac{\partial \Phi^{\mathrm{CG}}_{\alpha\beta}}{\partial r_\alpha} - \frac{d\lambda}{dq} \Phi^{\mathrm{CG}}_{\alpha\beta} - \sum_{\substack{i\in\alpha \\ j\in\beta}} (1-\lambda) \frac{\partial \Phi^{\mathrm{A}}_{ij}}{\partial r_\alpha} + \sum_{\substack{i\in\alpha \\ j\in\beta}} \frac{d\lambda}{dq} \Phi^{\mathrm{A}}_{ij} + \frac{\partial \Delta U_\alpha}{\partial r_\alpha}$$

$$\frac{\partial \Delta U_\alpha}{\partial r_\alpha} = \frac{\partial \Delta U_\alpha}{\partial q} = \frac{d\lambda}{dq} \Phi^{\mathrm{CG}}_{\alpha\beta} - \sum_{\substack{i\in\alpha \\ j\in\beta}} \frac{d\lambda}{dq} \Phi^{\mathrm{A}}_{ij}$$

Conserved Quantity

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$$V_\alpha = \sum_\beta \left(\lambda \Phi^{\mathrm{CG}}_{\alpha\beta} + (1-\lambda) \sum_{\substack{i\in\alpha \\ j\in\beta}} \Phi^{\mathrm{A}}_{ij} \right) + \sum_{ij\in\alpha} \Phi^{\mathrm{A}}_{ij} - \sum_\beta \Delta U_\alpha(q)$$

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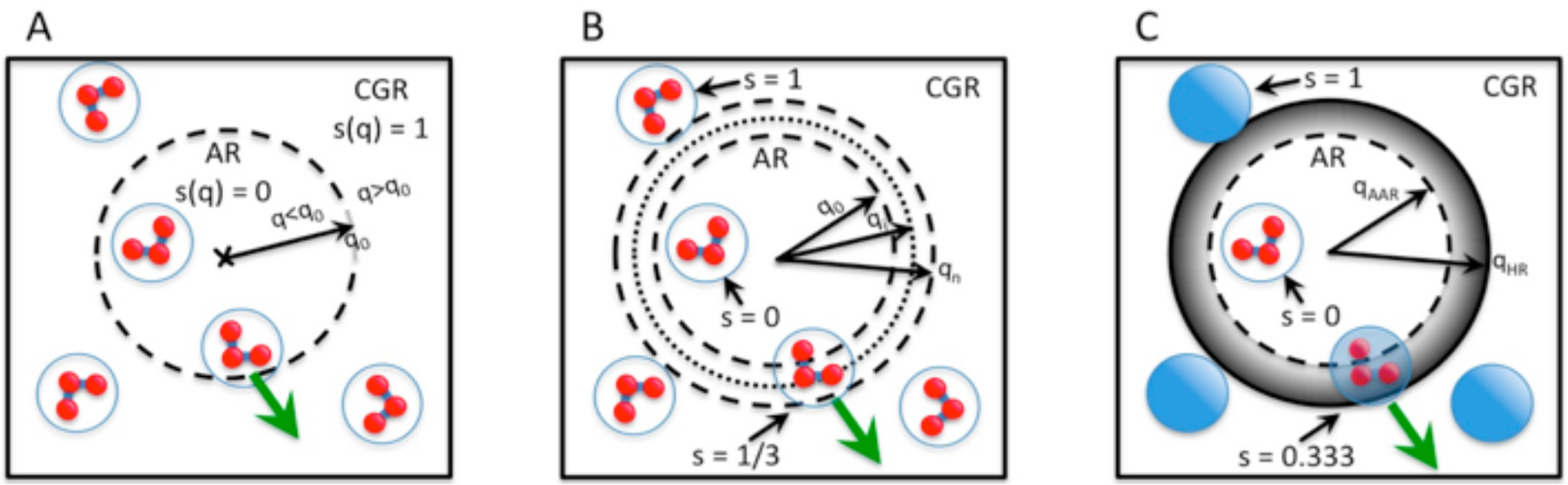
Forces

$$f_\alpha = -\frac{\partial V}{\partial r_\alpha} = -\lambda \frac{\partial \Phi^{\mathrm{CG}}_{\alpha\beta}}{\partial r_\alpha} - \sum_{\substack{i\in\alpha \\ j\in\beta}} (1-\lambda) \frac{\partial \Phi^{\mathrm{A}}_{ij}}{\partial r_\alpha}$$

Healing region

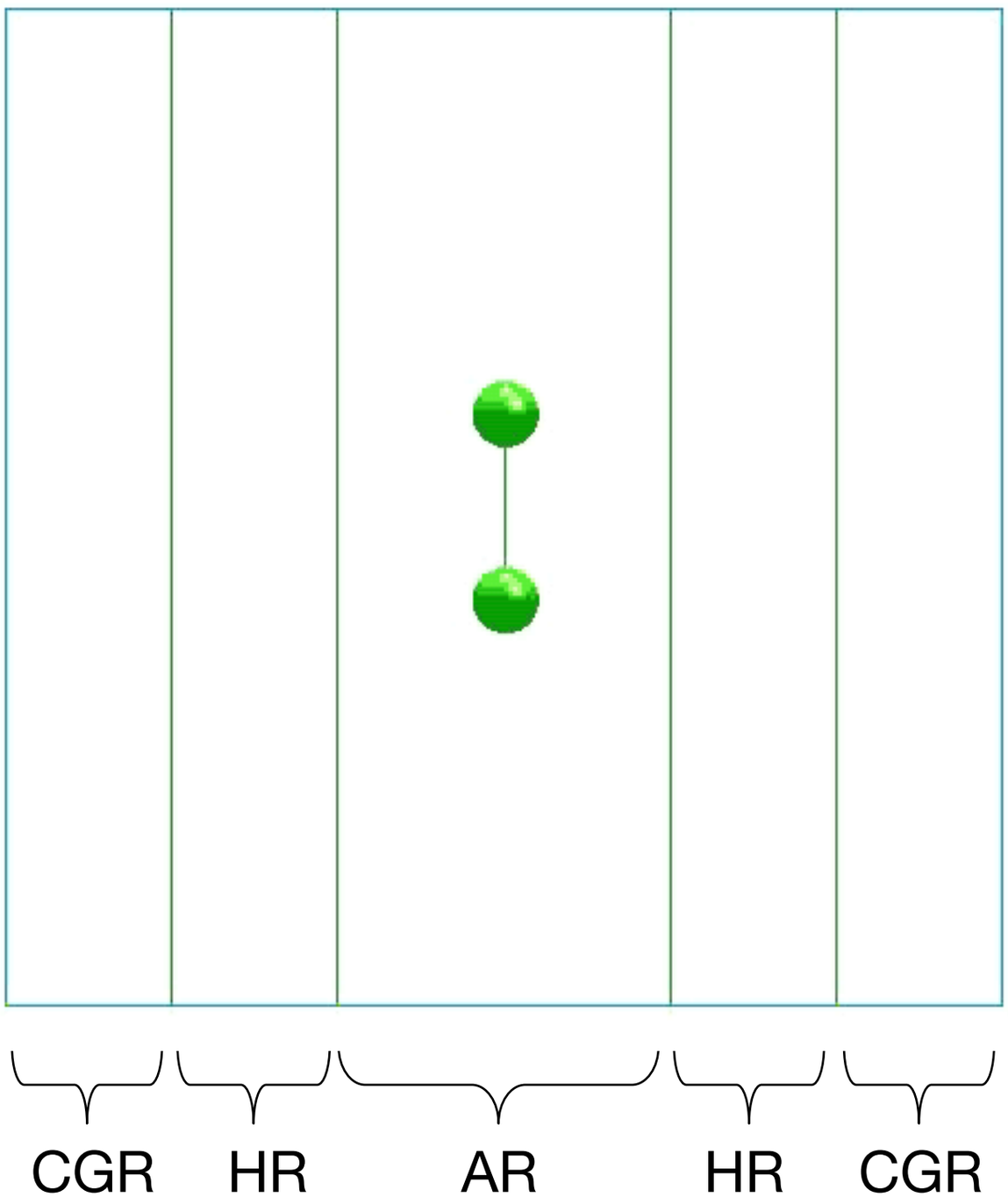


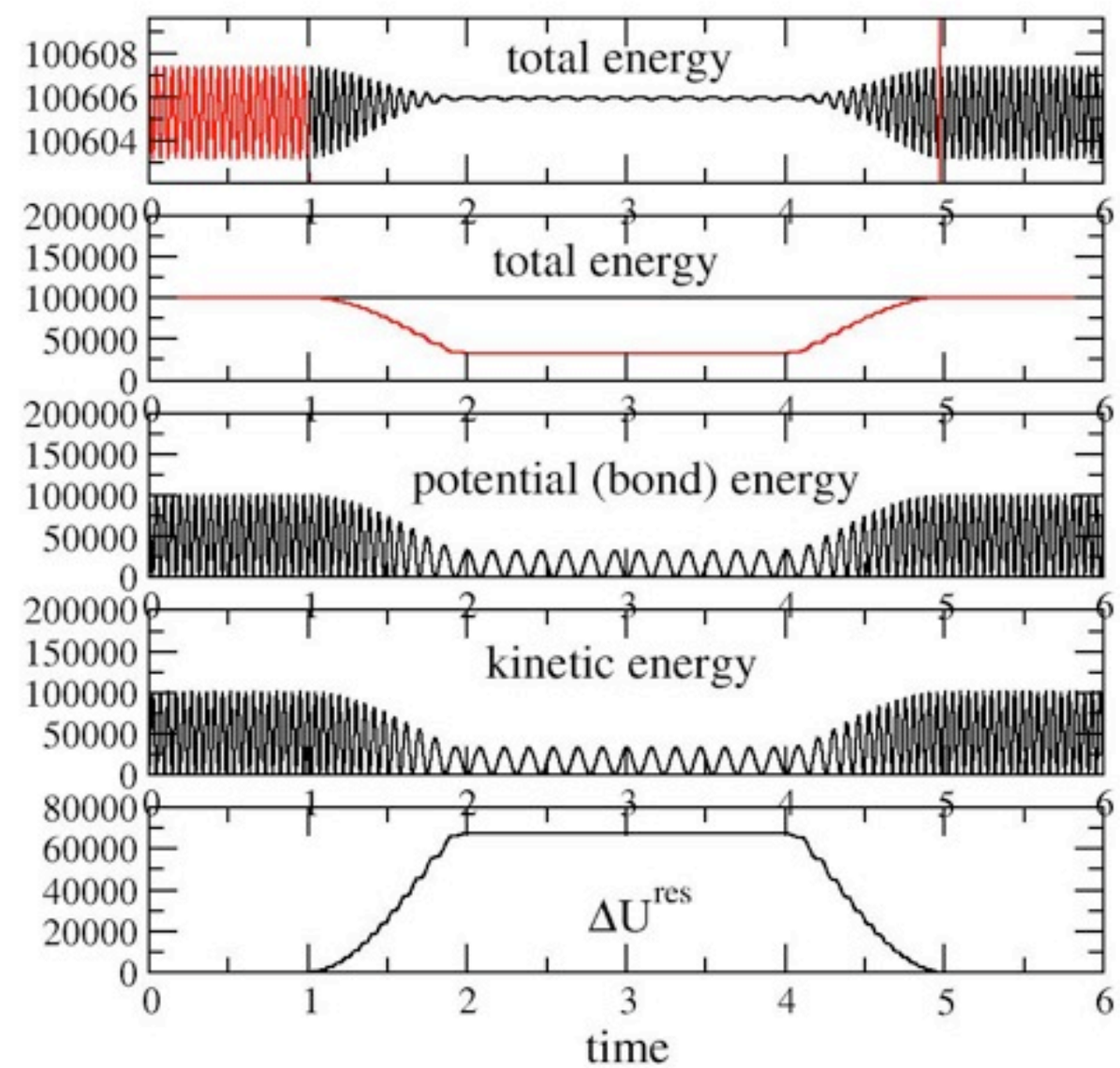
Coupled atomistic and coarse-grain regions

- *adaptive resolution*
- *smooth forces*
- *equilibration of AA degrees of freedom*
- *equilibration generates heat, which requires thermostating*
- *conserved total momentum*
- *conserved auxiliary total energy*

Simple Example

Switching a harmonic bond interaction by a factor 10

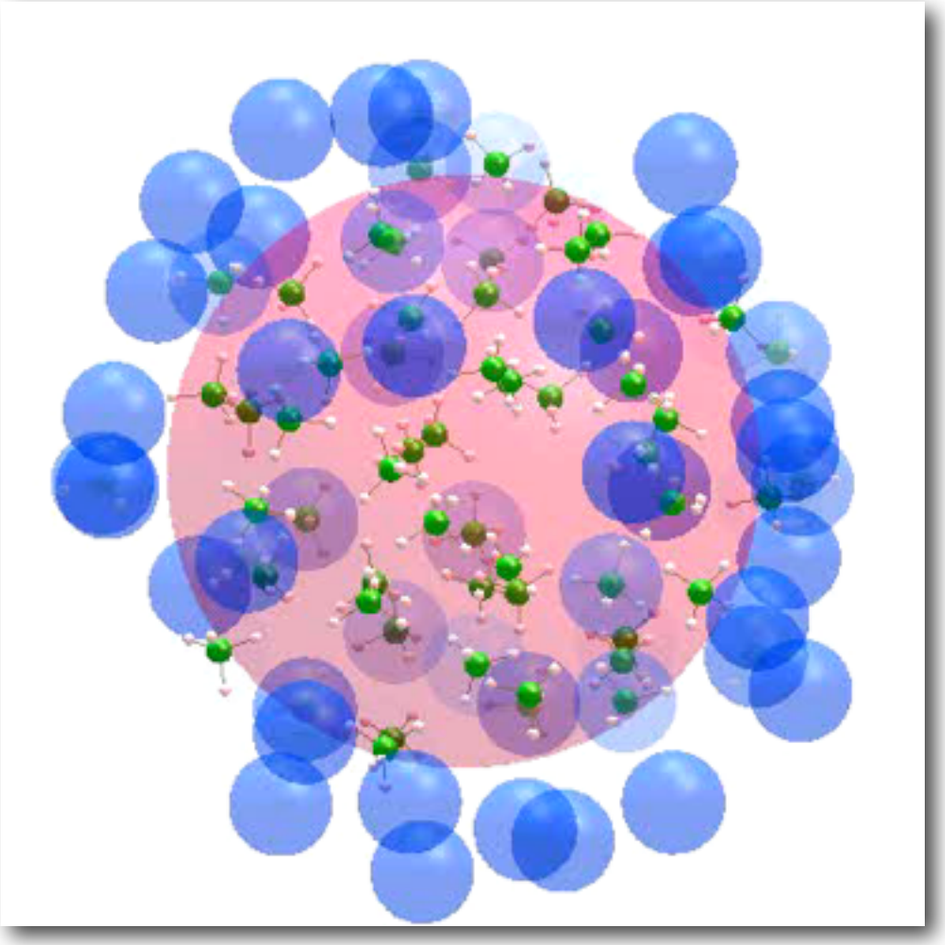




Hybrid Molecular Dynamics

Hybrid atomistic/coarse grained MD: 8000 methane molecules

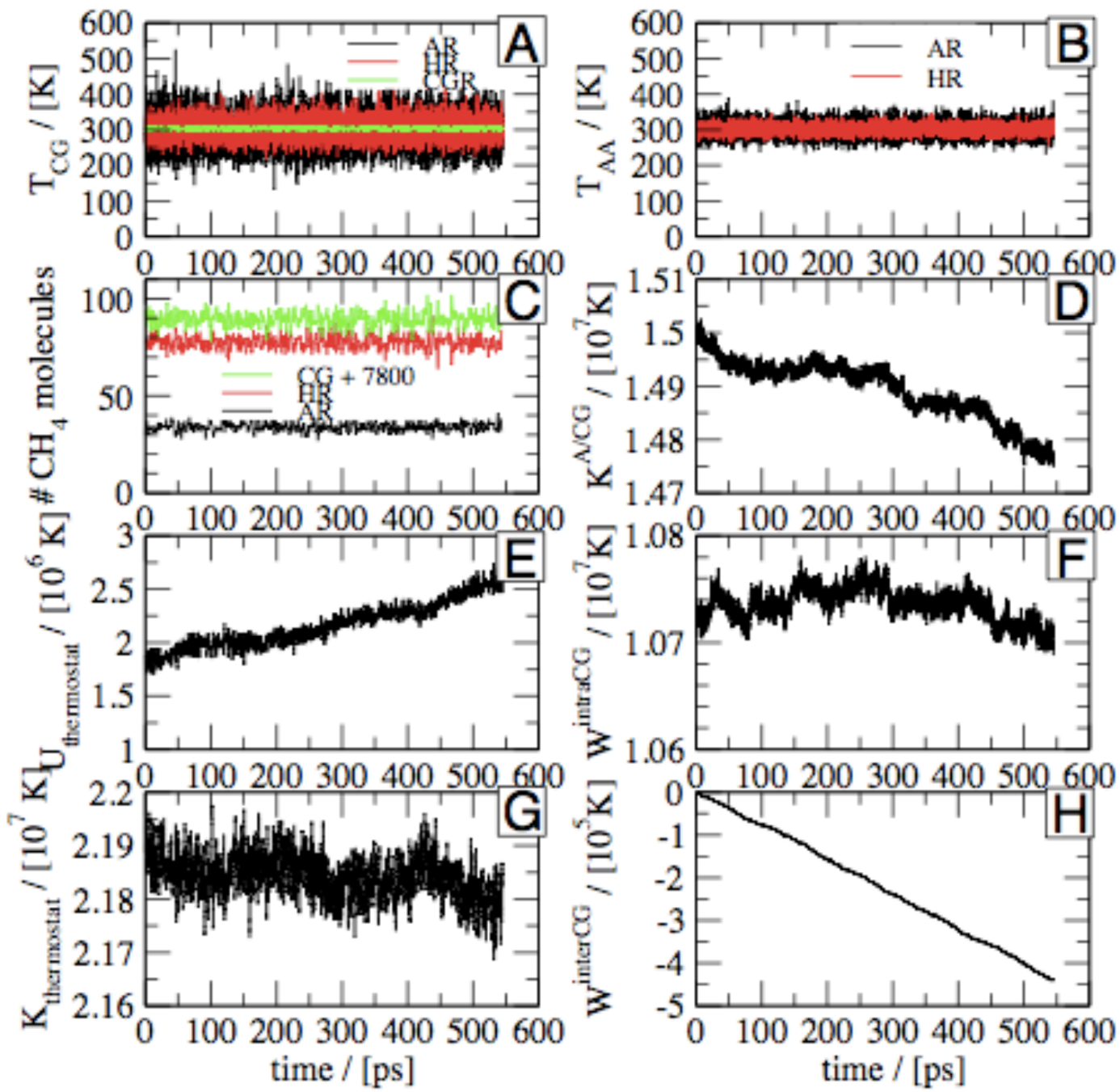
Spherical AA-region, R=8A (+ 4A)
ca. 34 AA/78 HR/7889 CG molecules



B. Ensing, S. O. Nielsen, P. B. Moore, M. L. Klein and M. Parrinello
J. Chem. Theor. Comp. 3 1100-1105 (2007)

Hybrid Molecular Dynamics

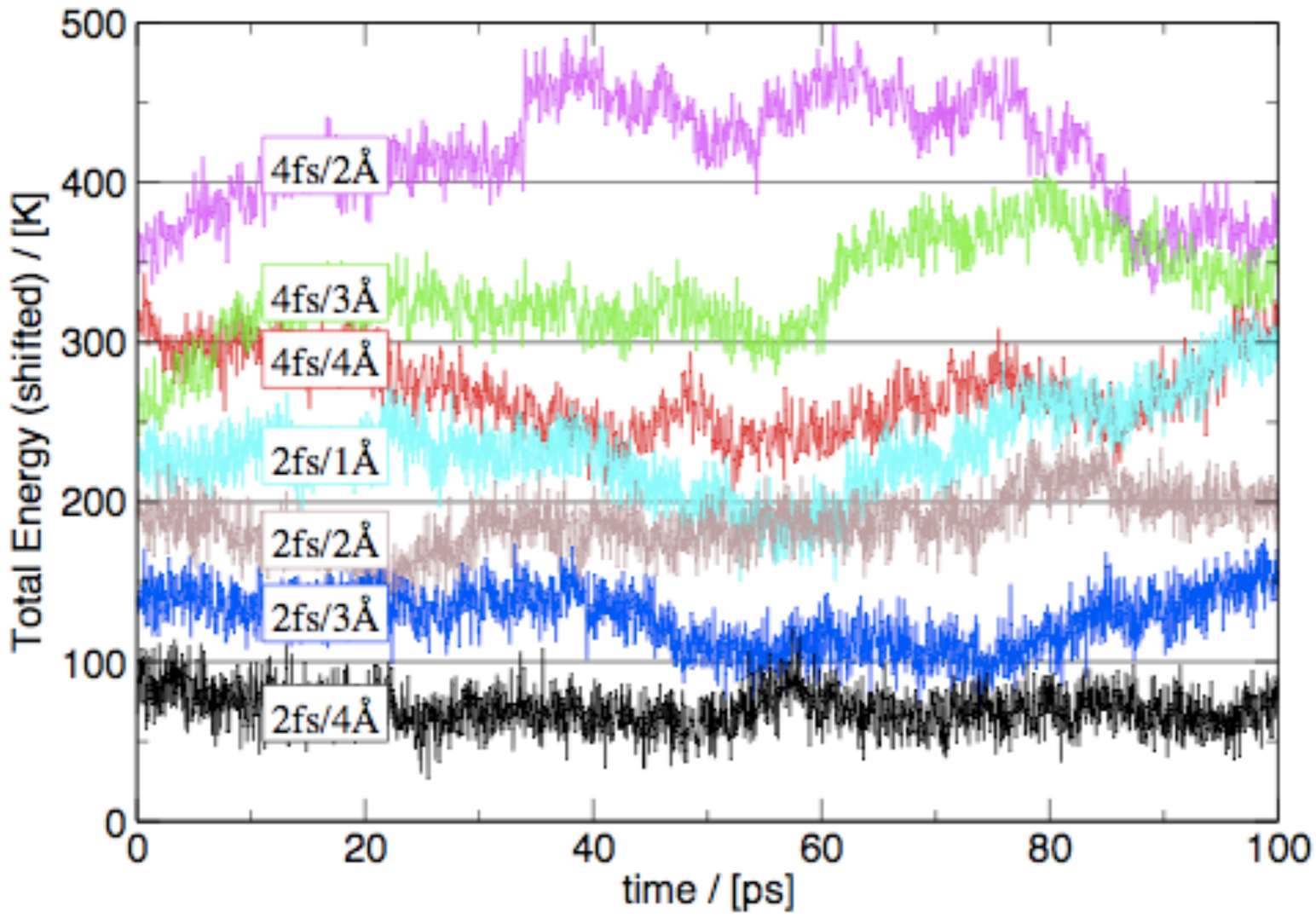
Hybrid atomistic/coarse grained MD: 8000 methane molecules



Hybrid Molecular Dynamics

Hybrid atomistic/coarse grained MD: 8000 methane molecules

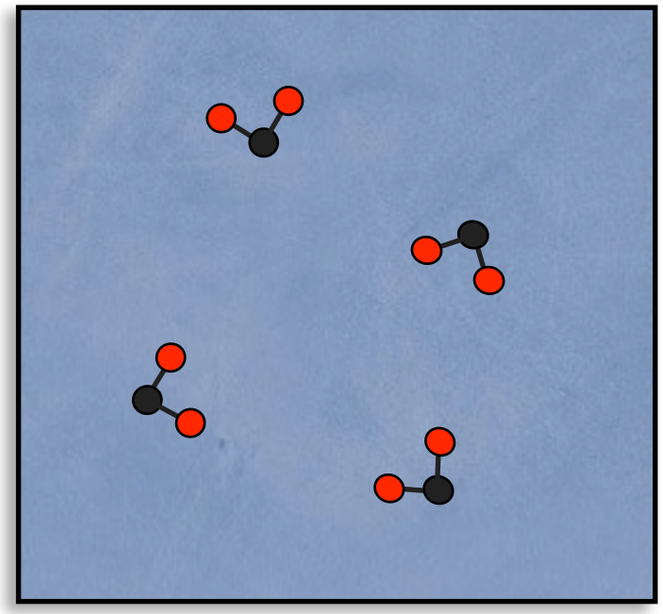
Total Energy



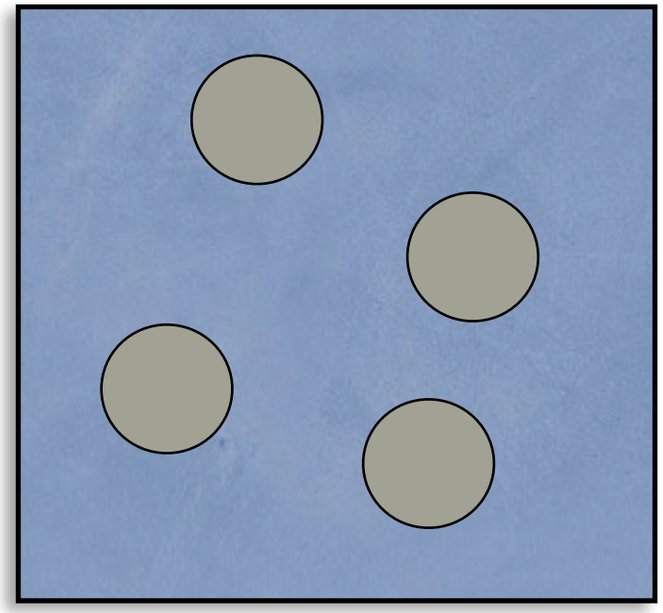
B. Ensing, S. O. Nielsen, P. B. Moore, M. L. Klein and M. Parrinello
J. Chem. Theor. Comp. 3 1100-1105 (2007)

Switching resolution

Atoms

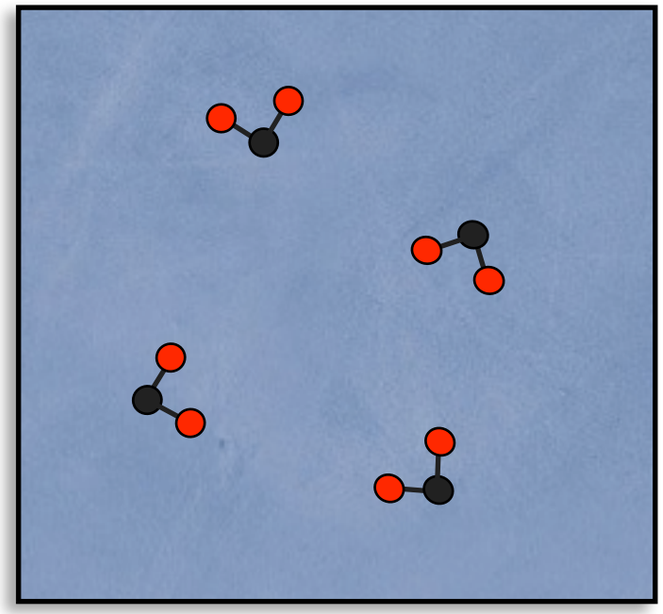


Coarse grain “blobs”



Switching resolution

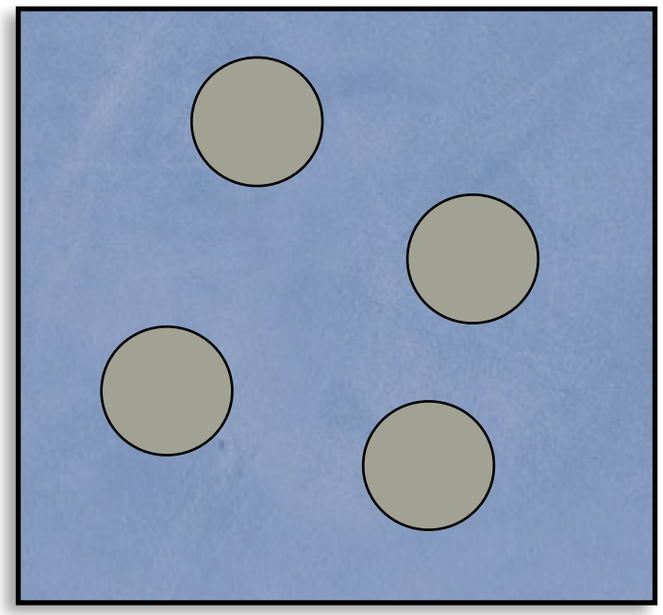
Atoms



Forward mapping
Zoom out
Fast forward

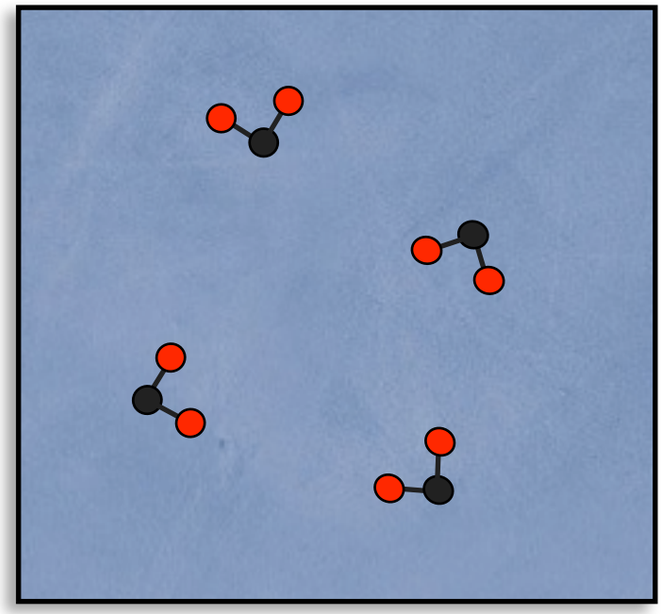
Easy

Coarse grain “blobs”



Switching resolution

Atoms



Atoms

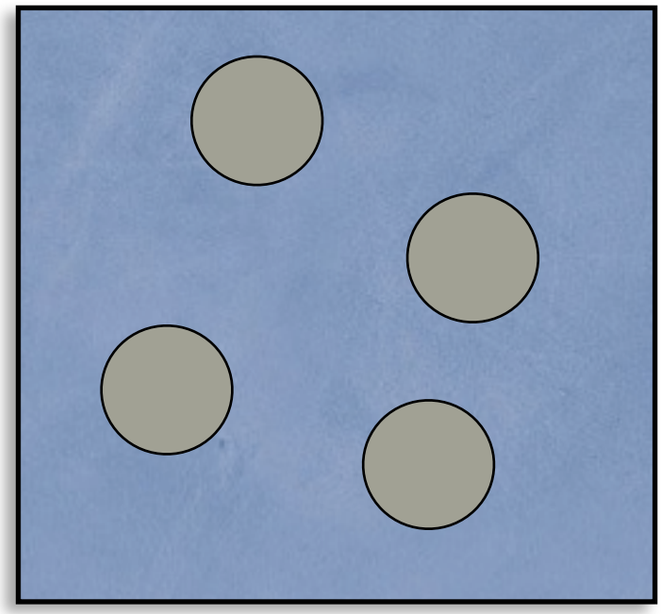
Forward mapping
Zoom out
Fast forward

Easy

Reverse mapping
Zoom in
Slow motion

Difficult

Coarse grain “blobs”



Coarse grain “blobs”

Rigid body rotation

- Frozen atomic library function
- Match centers of mass

- The body frame can only rotate: SO(3) operations
- reduced energy function

- Verlet algorithm by P. Krysl and L. Endres

- remove CG-CG bond distance from inter-CG interactions

S. O. Nielsen, B. Ensing, P. B. Moore and M. L. Klein. Book chapter in:
"Advances in Hierarchical and Multi-Scale Simulations of Materials"
(publisher: Taylor and Francis; editors: Sanat Mohanty and Richard B. Ross).

Reverse Mapping

Rigid body rotation

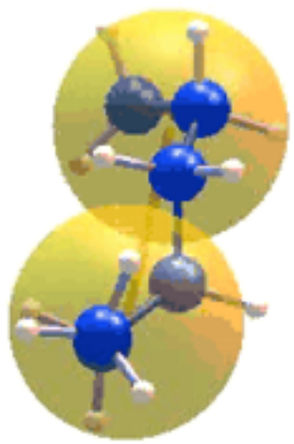
- Frozen atomic library function
- Match centers of mass

- The body frame can only rotate: SO(3) operations
- reduced energy function

- Verlet algorithm by P. Krysl and L. Endres

- remove CG-CG bond distance from inter-CG interactions

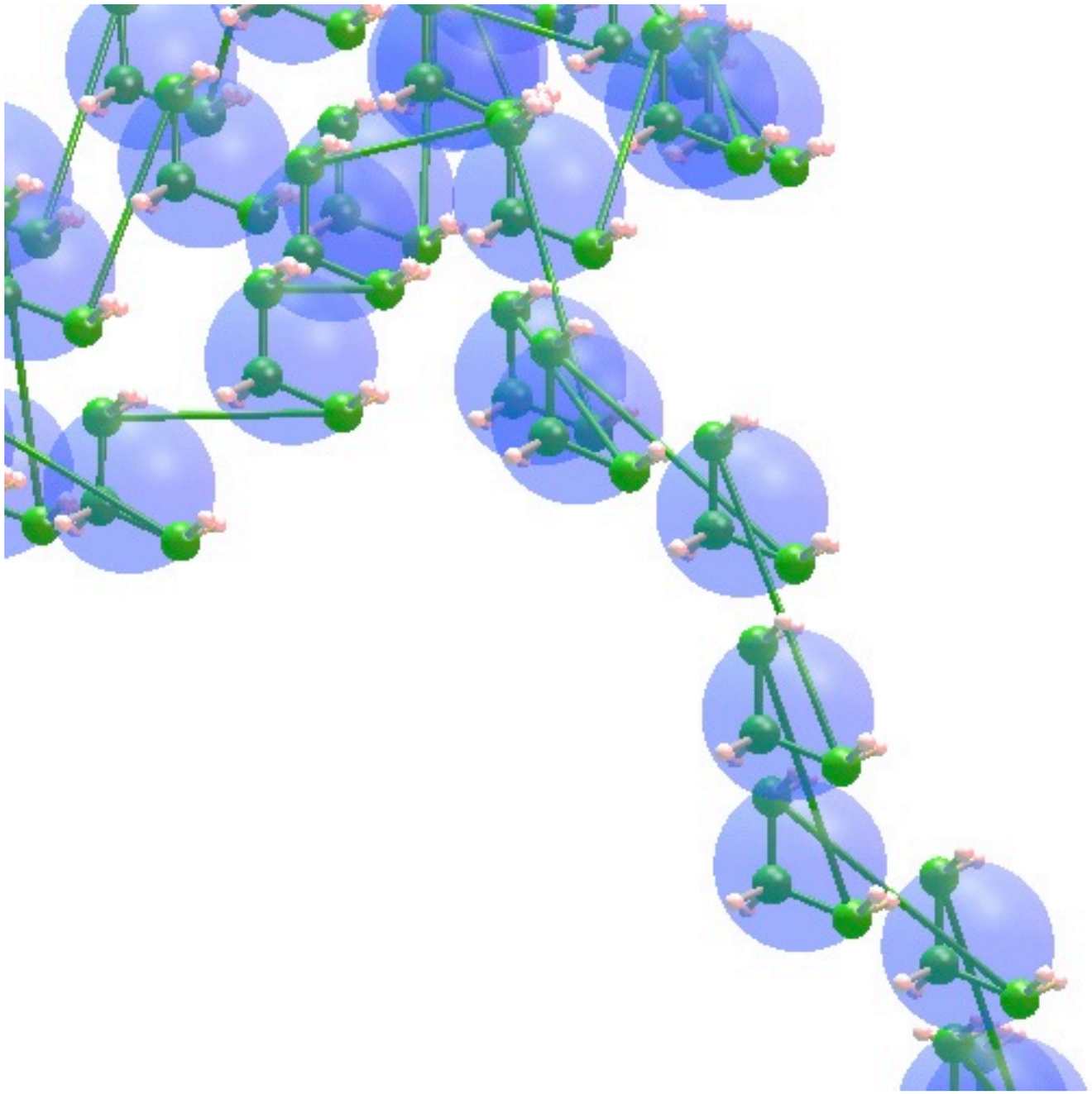
$$
\begin{aligned}
\omega_{i+\frac{1}{2}} &= \omega_i + \frac{\Delta t}{2}\alpha_i \\
R_{i+1} &= \exp\left[\Delta t \omega_{i+\frac{1}{2}} + \frac{\Delta t^2}{2}\alpha_i\right] R_i \\
T &= f \times r_{i+1} \\
I_{\alpha\beta} &= \sum_i m_i(\delta_{\alpha\beta} r_i^2 - r_i^\alpha r_i^\beta) \\
\alpha_{i+1} &= I^{-1}(T - \omega_{i+1} \times I_{i+1}\omega_{i+1}) \\
\omega_{i+1} &= \omega_{i+\frac{1}{2}} + \frac{\Delta t}{2}\alpha_{i+1}
\end{aligned}
$$



S. O. Nielsen, B. Ensing, P. B. Moore and M. L. Klein. Book chapter in: "Advances in Hierarchical and Multi-Scale Simulations of Materials" (publisher: Taylor and Francis; editors: Sanat Mohanty and Richard B. Ross).

Reverse Mapping

Poly ethylene chain (50 blobs - 150 CH2)



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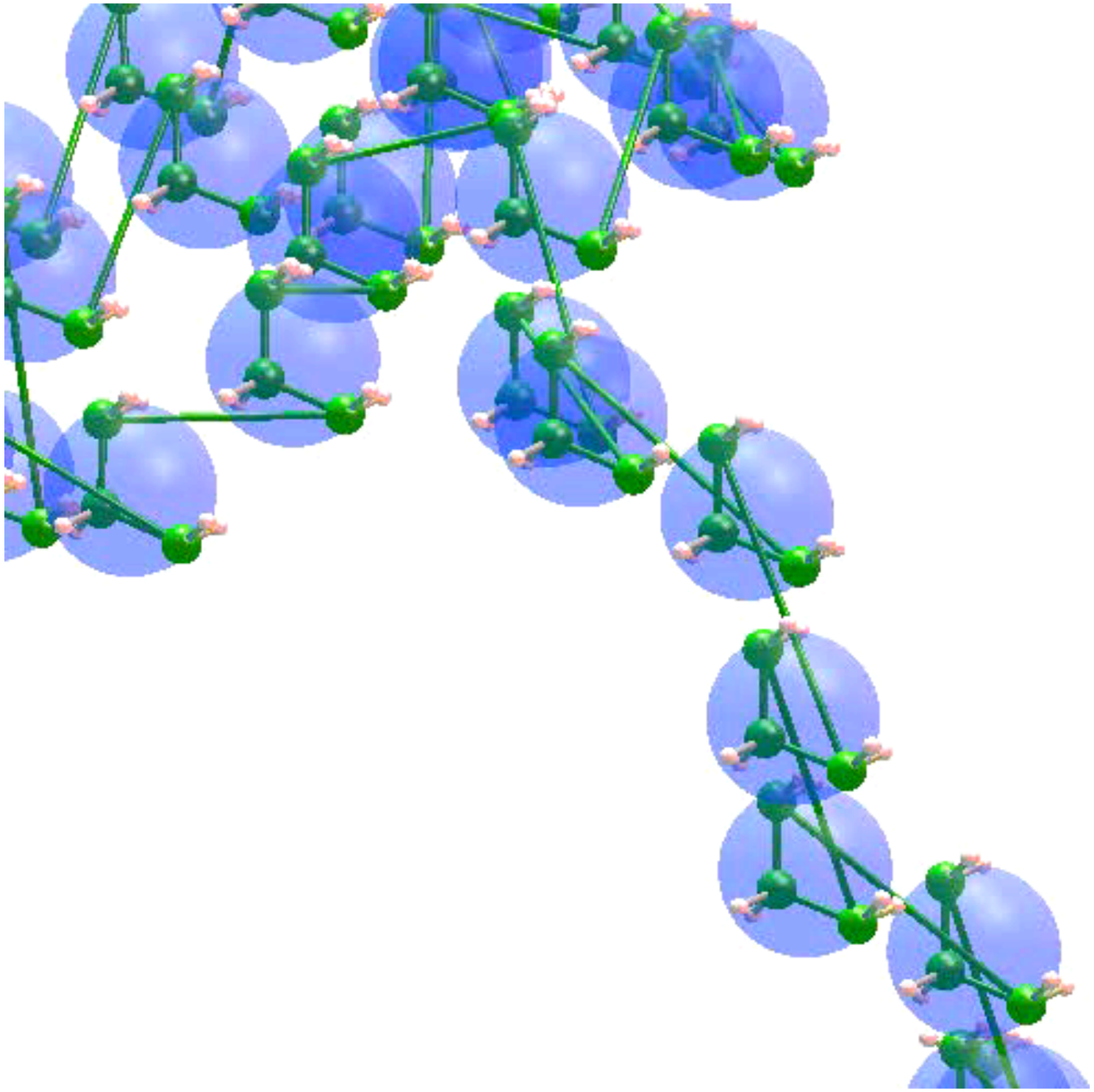
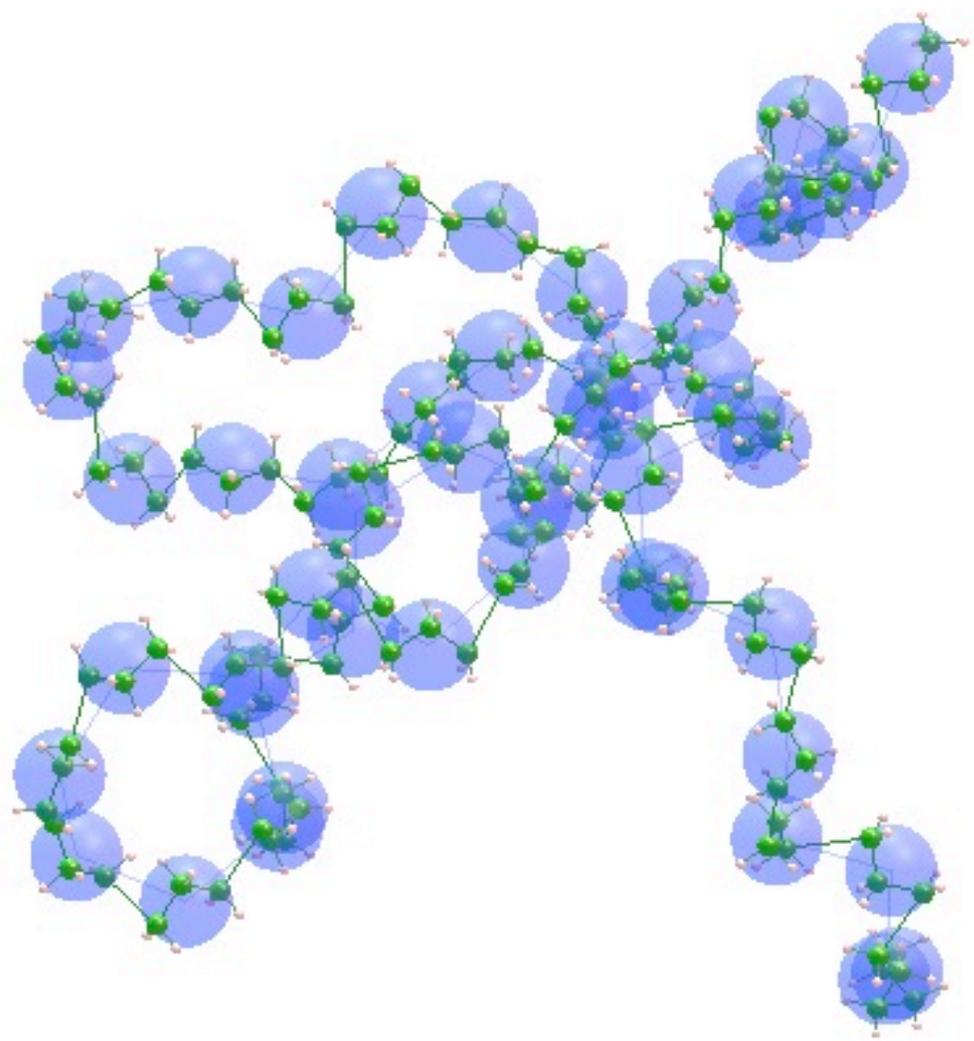


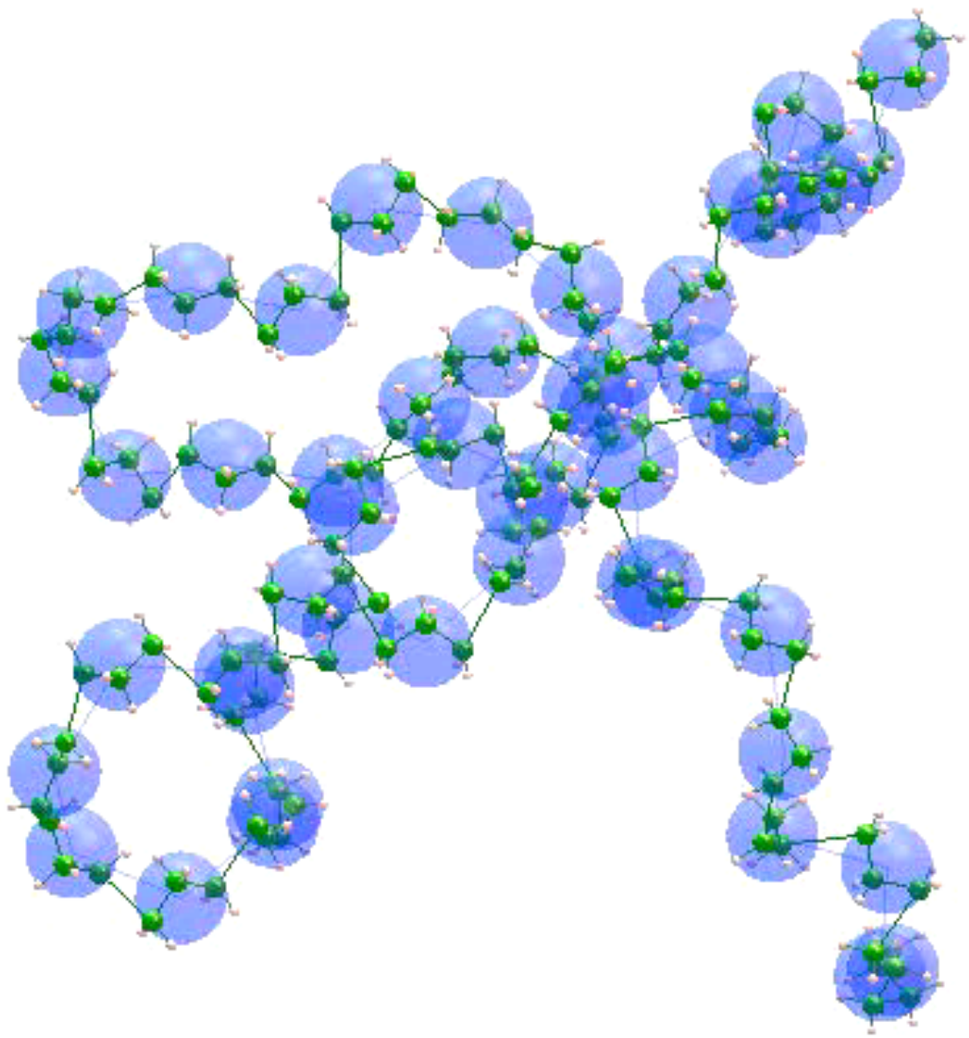
Reverse Mapping

CGMD + Reverse Mapping on the Fly



Reverse Mapping

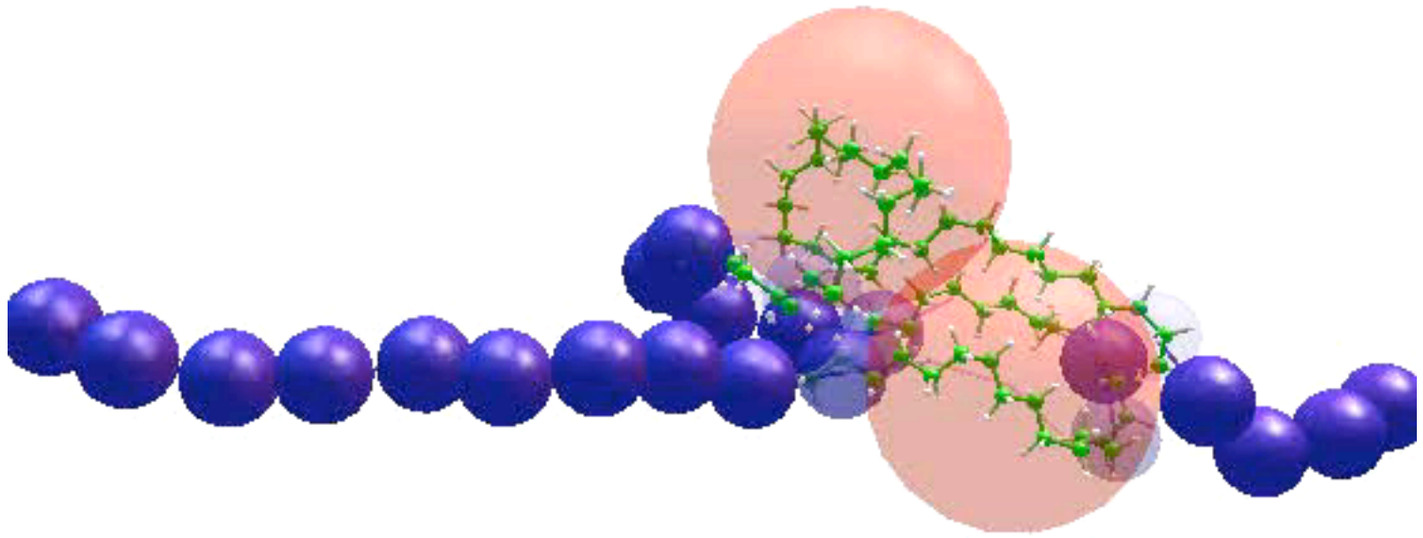
CGMD + Reverse Mapping on the Fly

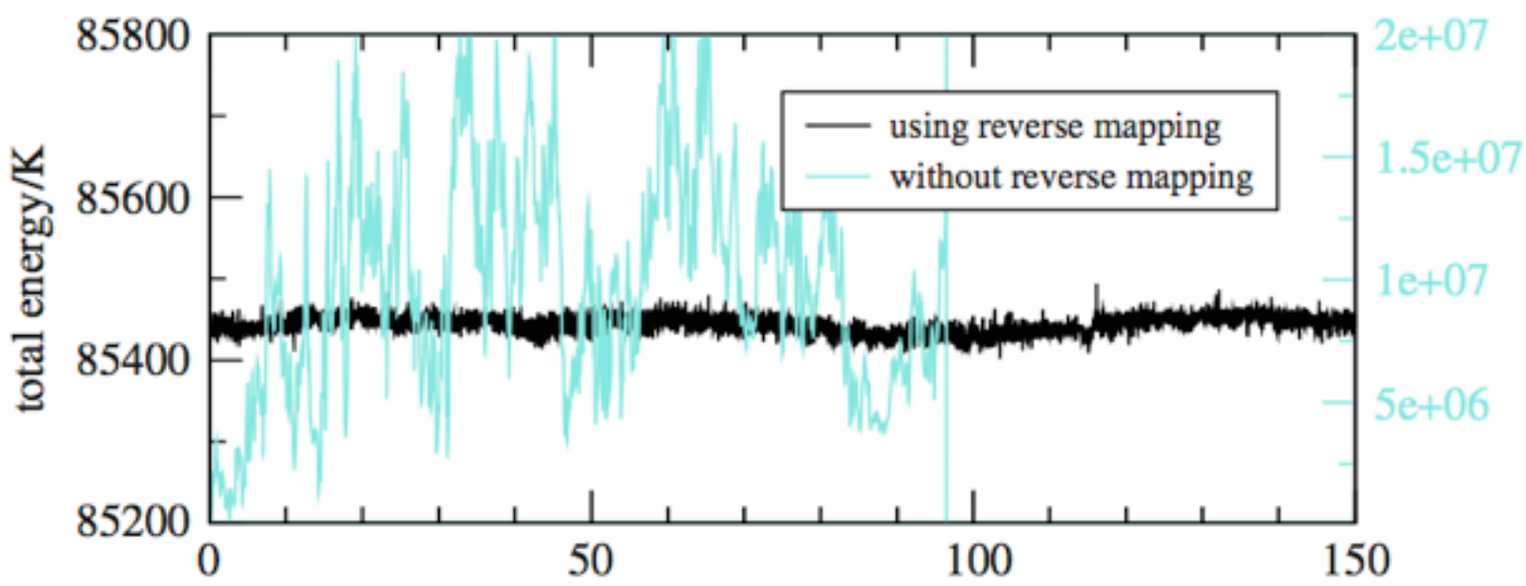


Hybrid Molecular Dynamics

Combined hybrid MD and rotational dynamics

Polyethylene chain, 2 atomistic regions, R_{AR}=6Å





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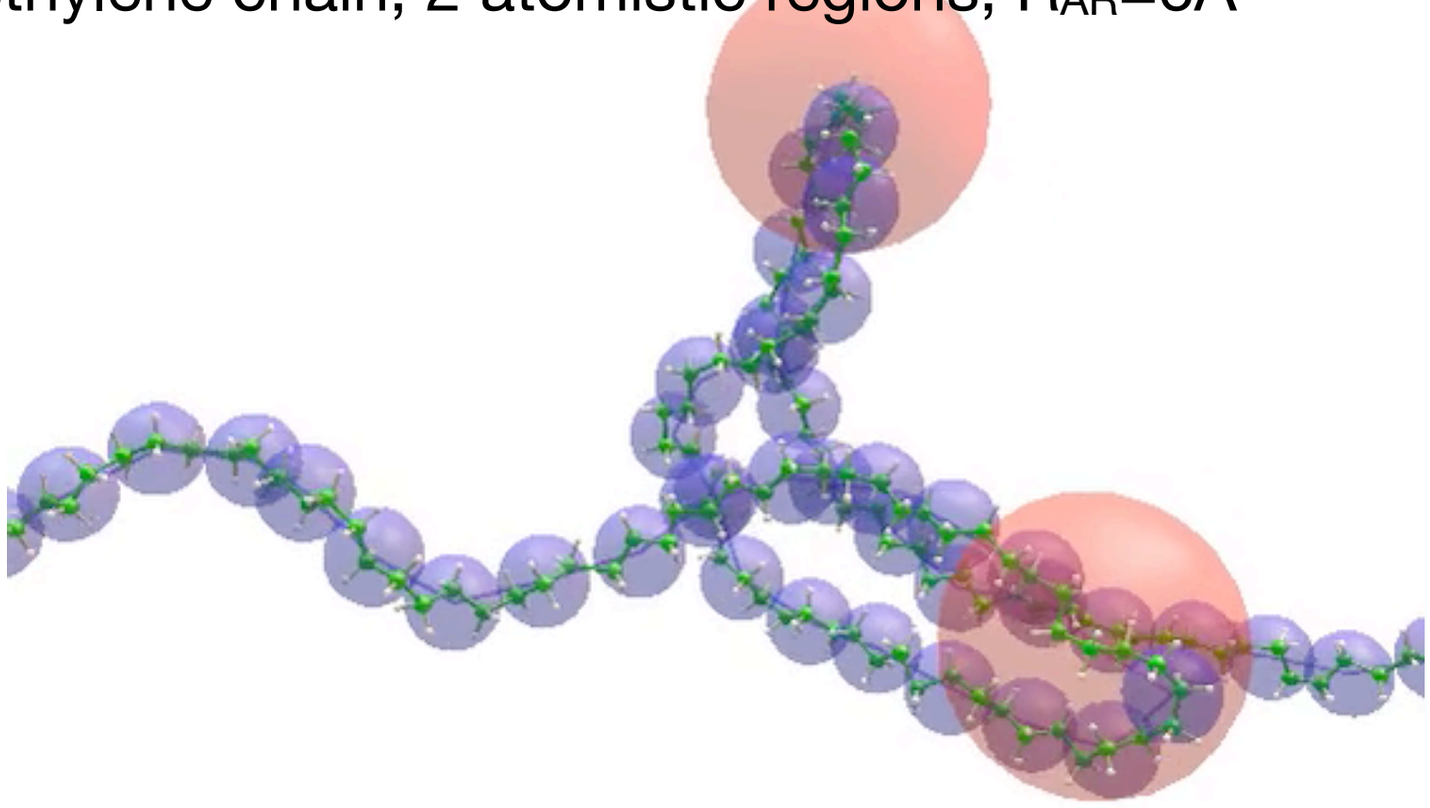
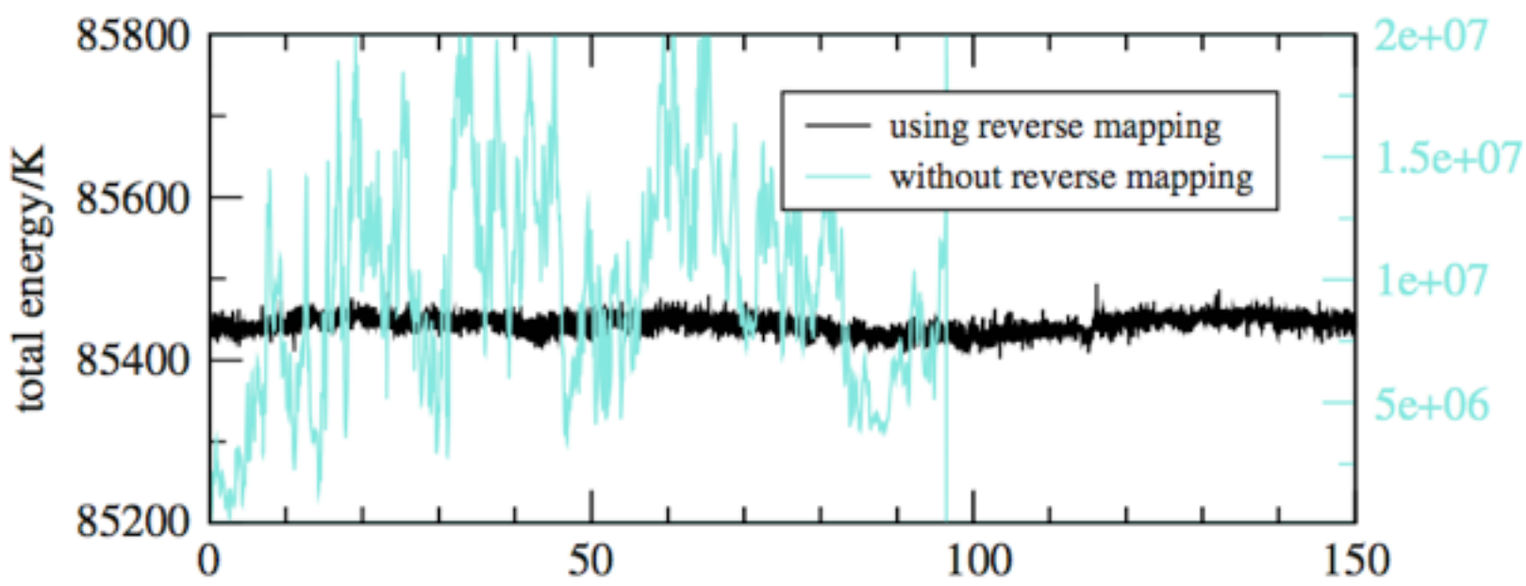
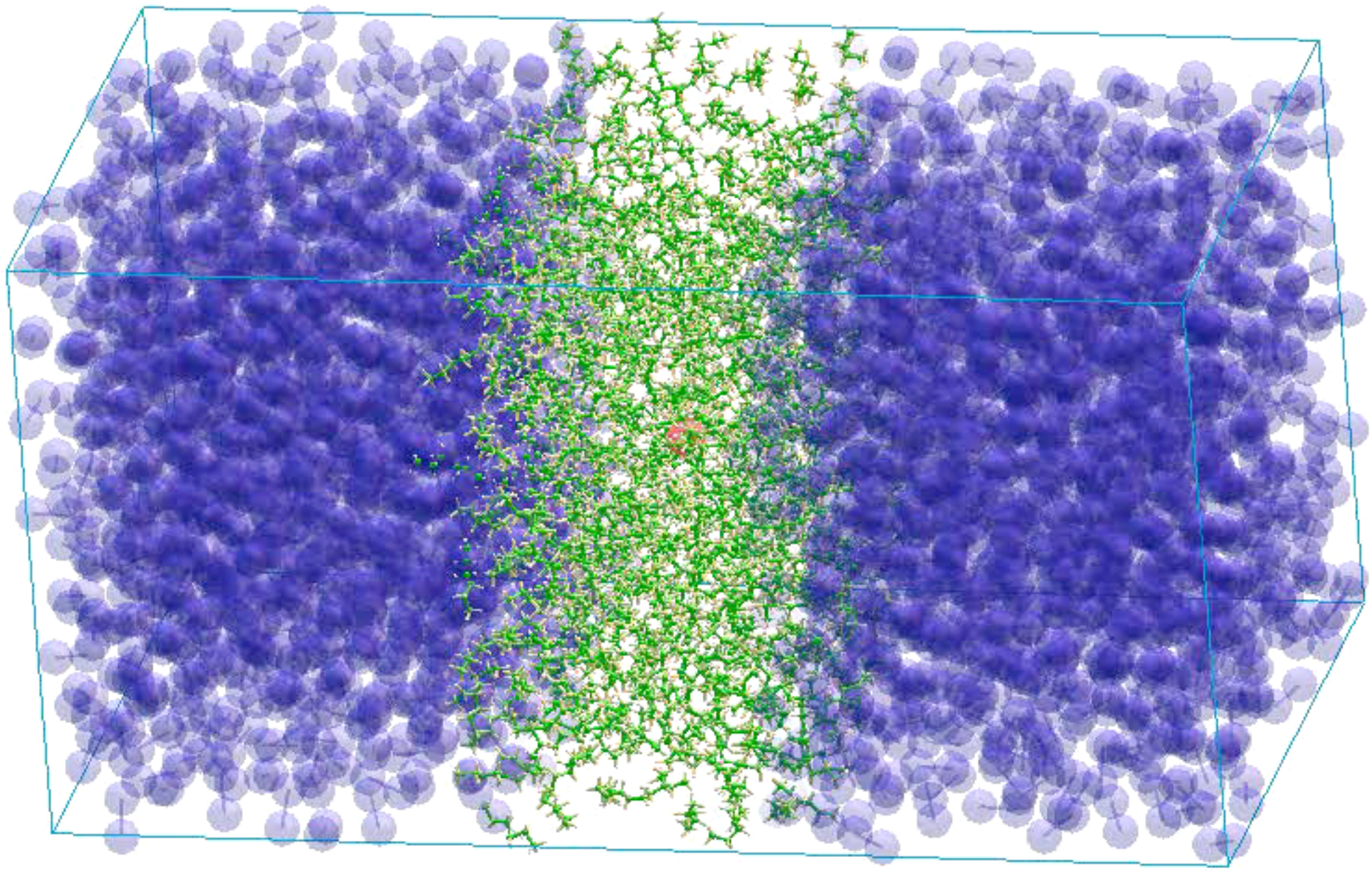




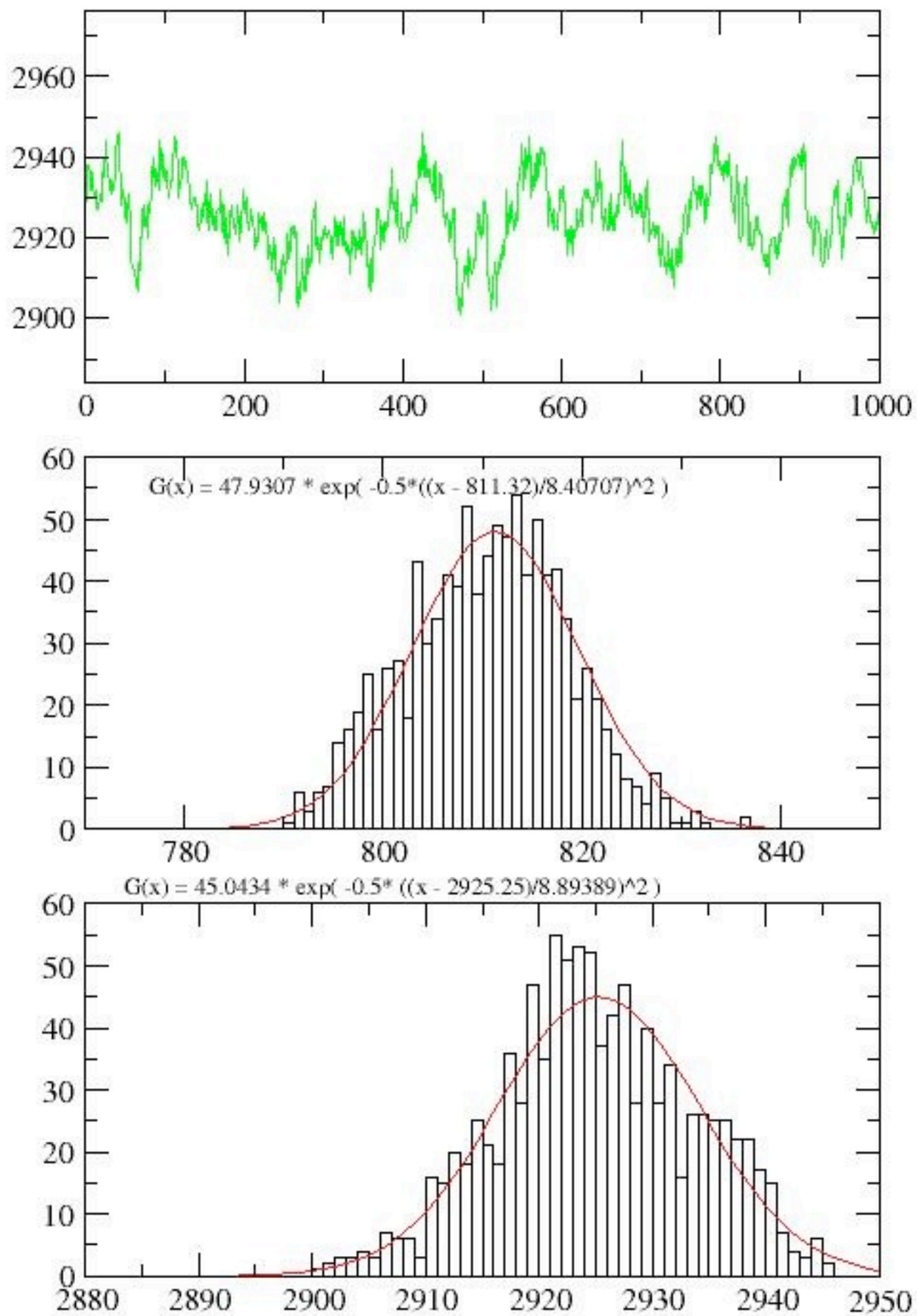
Multiscale MD of hexane

Size: 2000 molecules
AR: 2x 12 Å (2D slice)
HR: 4 Å
Temp: 300 K, NH/particle



particle number fluctuations in hybrid MD of hexane

2000 molecules, slab regions, AR=2x12 Å, HR=4Å, LJ clip 10^6



Grand-canonical ensemble?

Average number of particles (blobs)

Expected N_{AR} = 2000x2 x 2x12/118.147 = 812.547

Measured N_{AR} = 810.979

Particle fluctuations

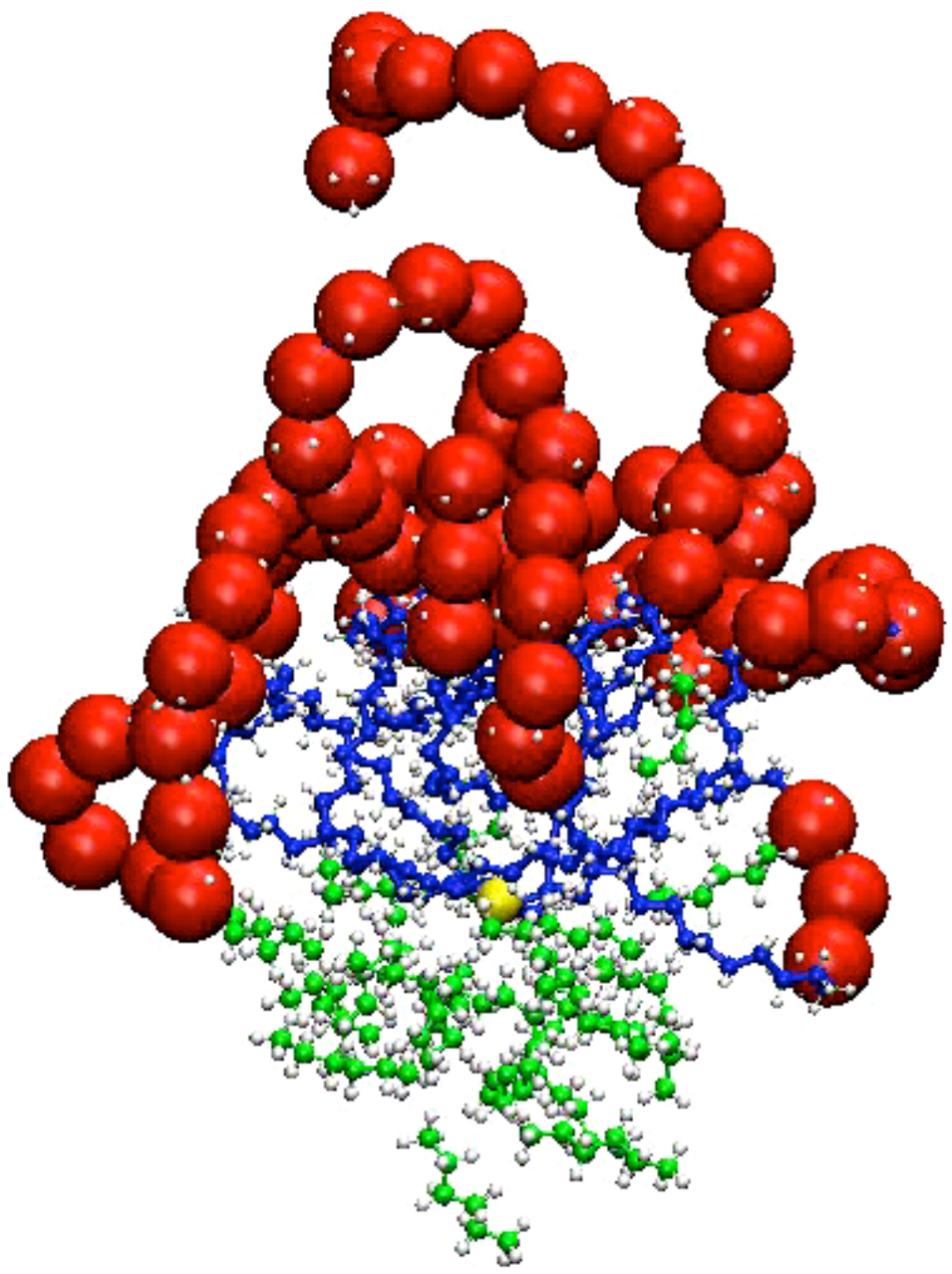
$$\left\langle dN^2 \right\rangle_{\mu VT} = \frac{N^2}{V} * k_B T \beta_T = 67.98$$

$$\beta_T = \left\langle dV^2 \right\rangle_{NPT} (k_B T V)^{-1} = 2.17613 \cdot 10^{-9} Pa^{-1}$$

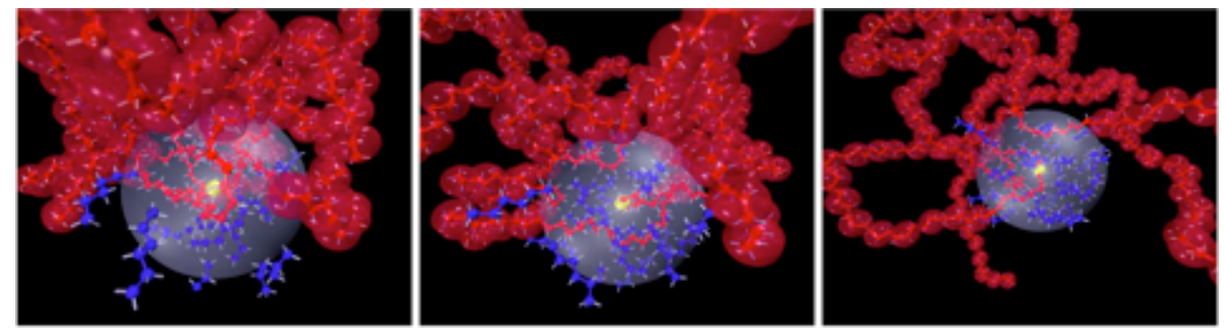
Measured dN^2_{AR} = 65.15

Swelling of $C_{450}H_{902}$ polyethylene chain

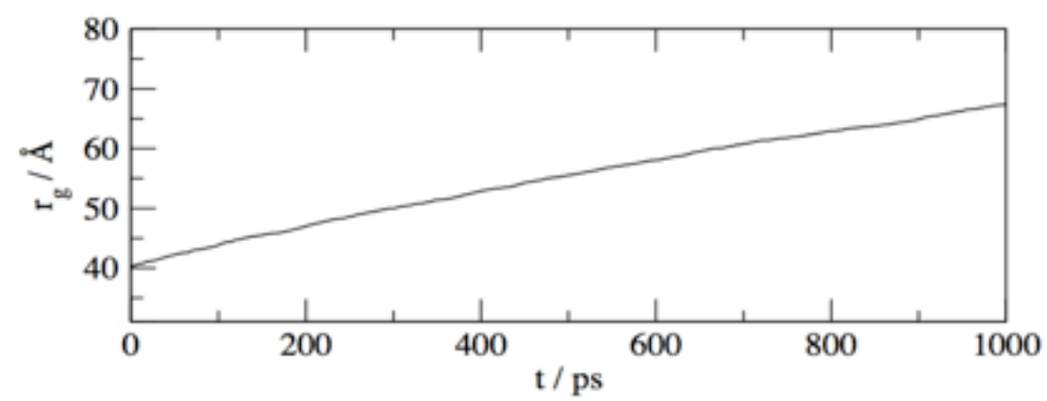
2000 hexane molecules



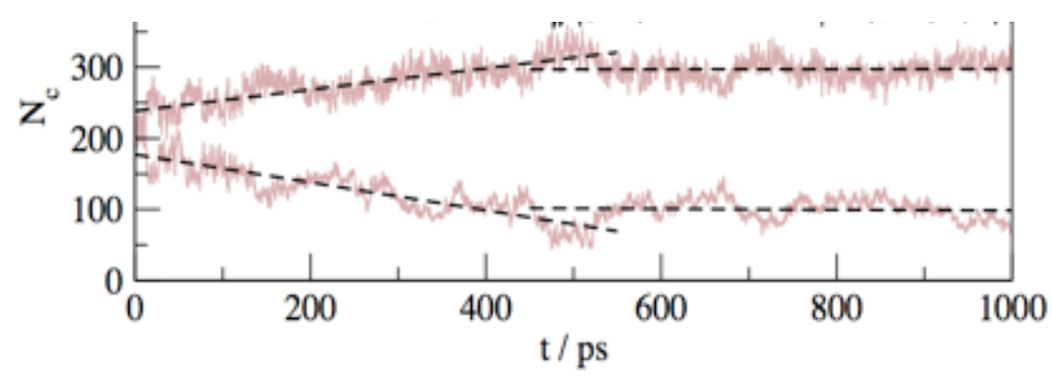
spherical AR of radius 10 Å
centered on 75th polymer bead



radius of gyration of polymer



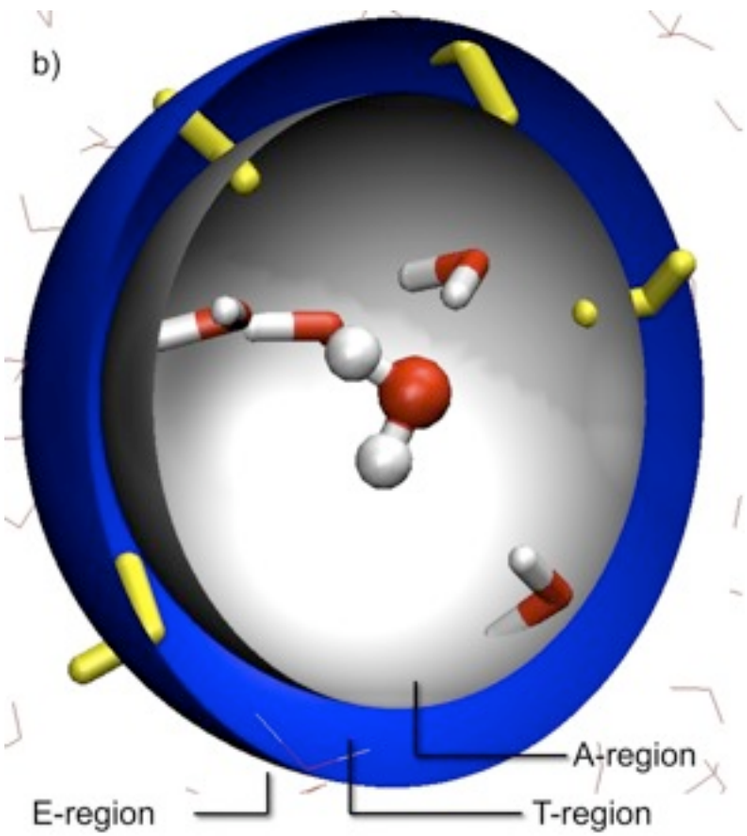
hexane C in AR+HR

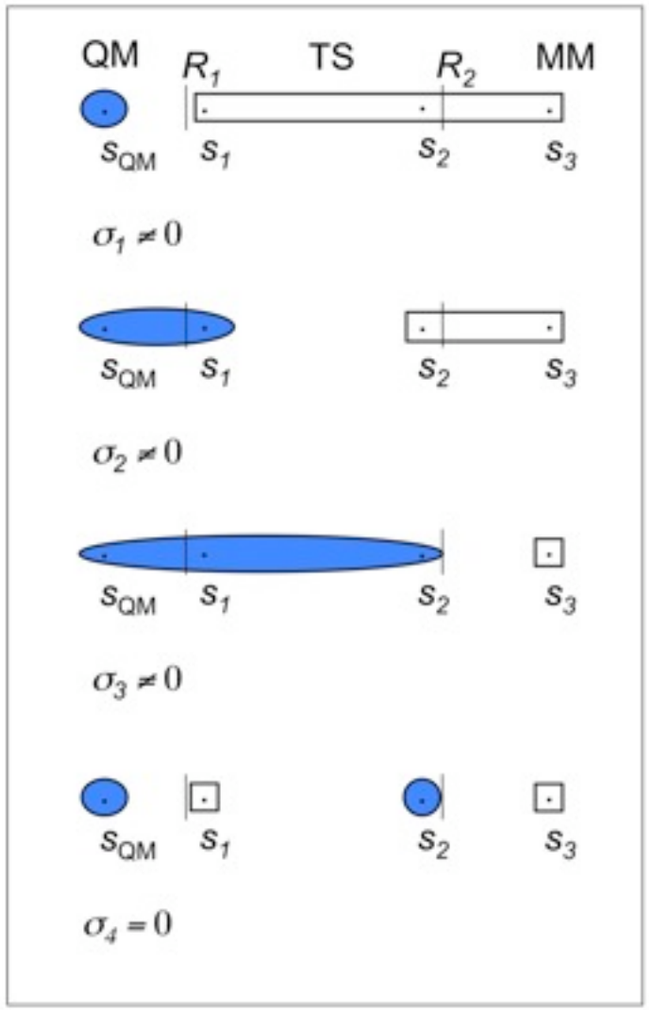


Adaptive QM/MM

Difference-based Adaptive Solvation method

$$V = \sum_{a}^{2^M} \sigma_a V_a$$

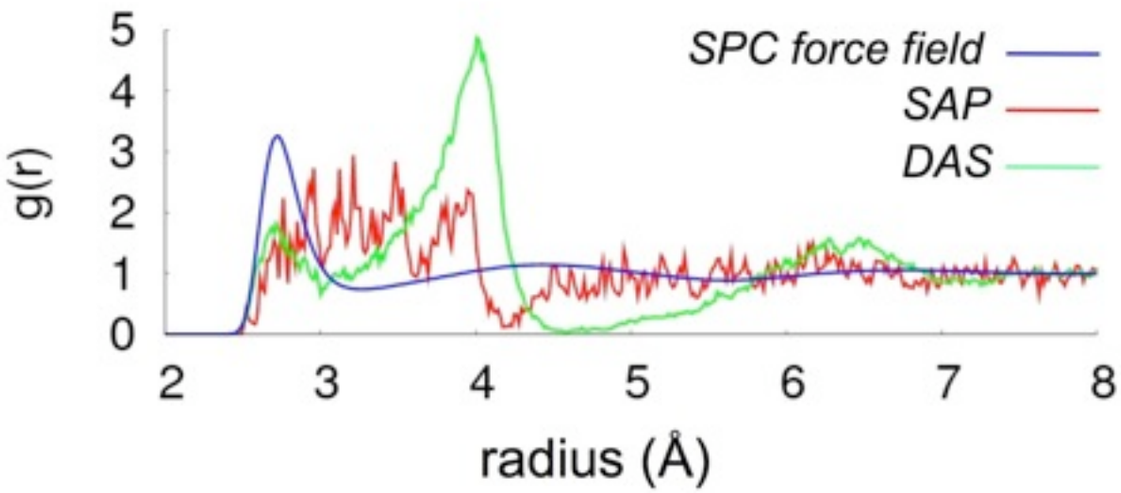




Sorted Adaptive Partitioning (SAP)
A. Heyden, H. Lin and D. G. Truhlar,
J. Phys. Chem. B, 2007, **111**, 2231

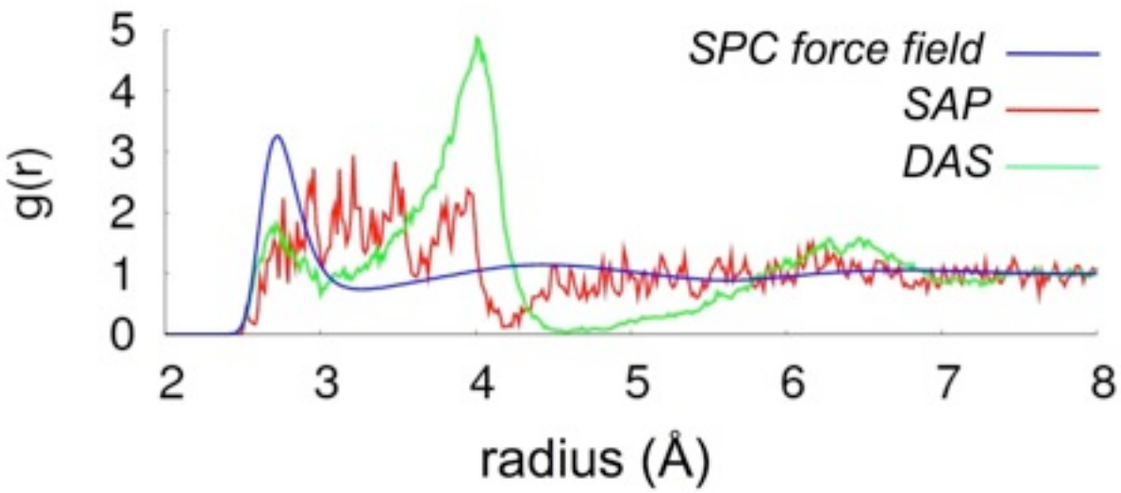
Toward a Practical Method for Adaptive QM/MM Simulations
Rosa E. Bulo, Bernd Ensing, Jetze Sikkema, and Lucas Visscher
J. Chem. Theory Comput. 2009, **5**, 2212–2221

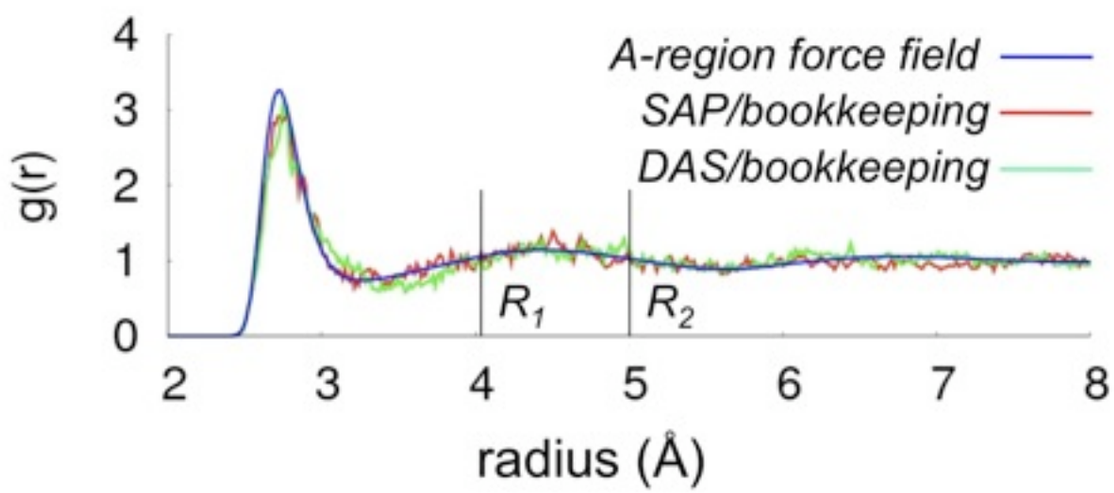
radial distribution



Adaptive QM/MM

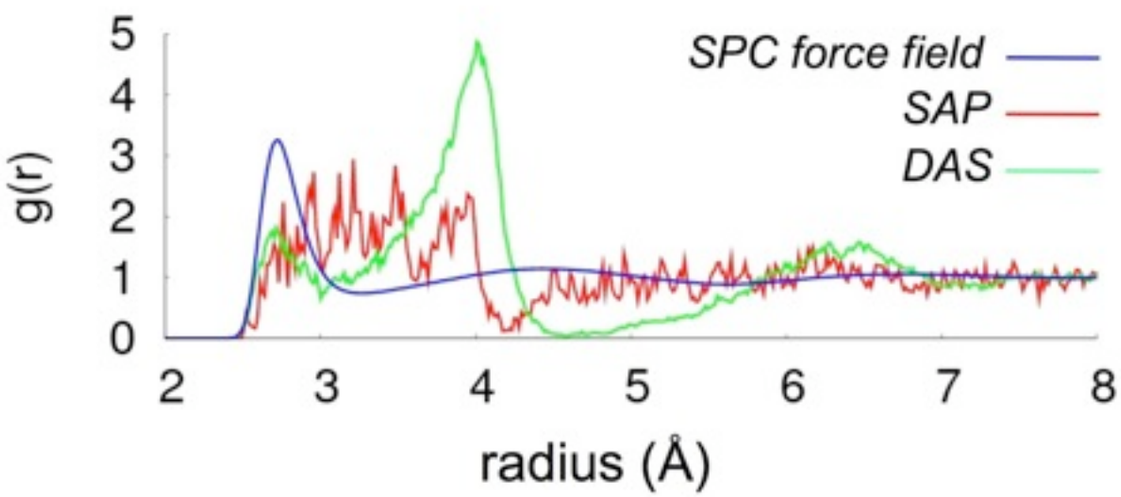
radial distribution

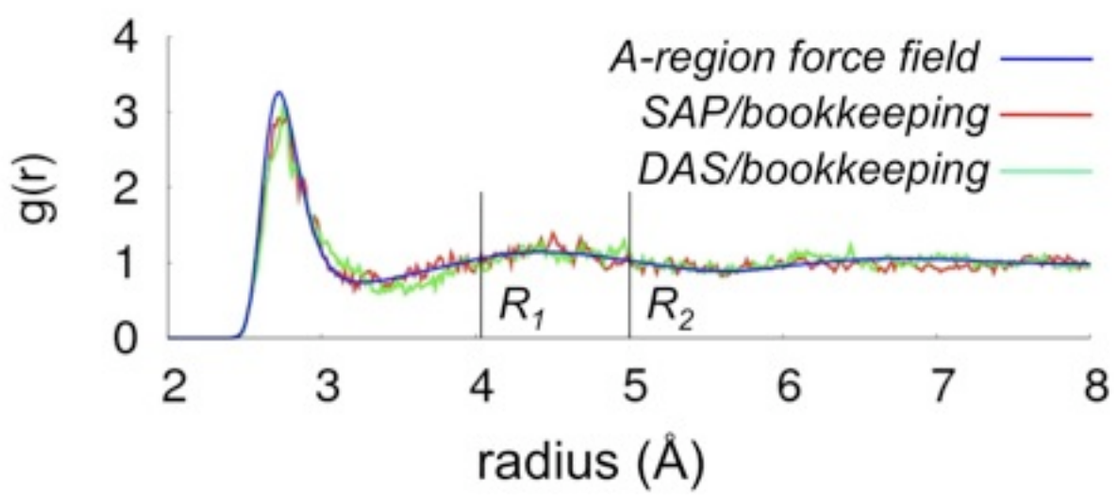




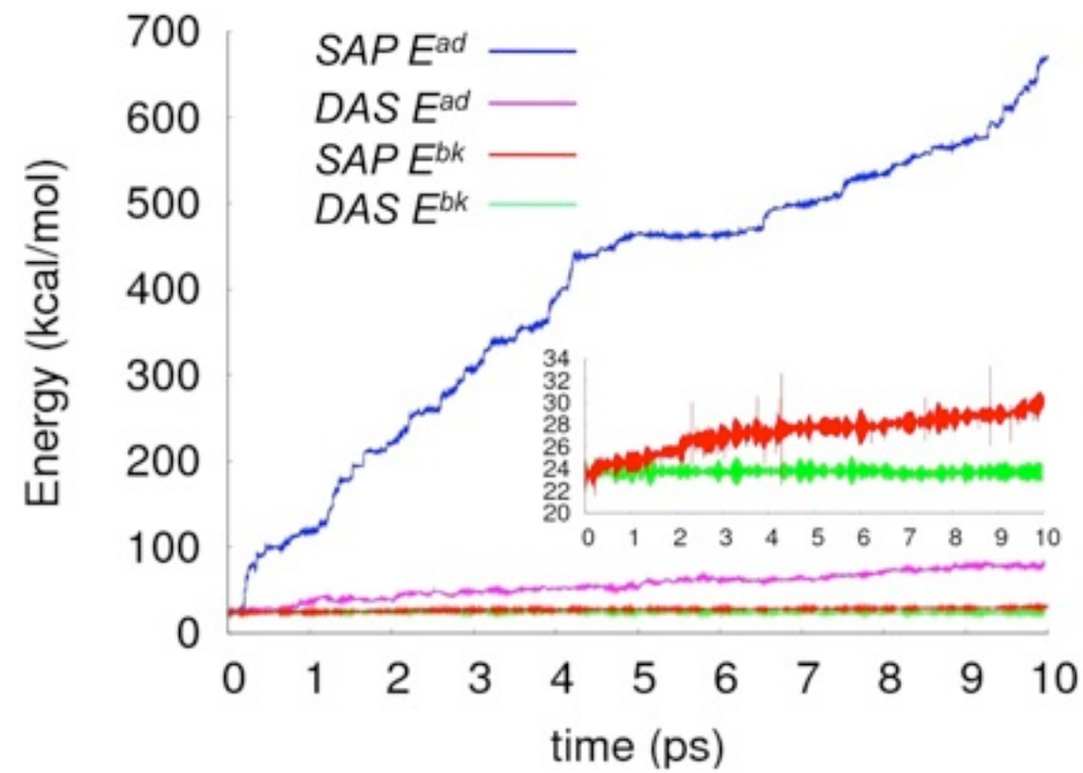
Adaptive QM/MM

radial distribution





total energy



Summary part 2

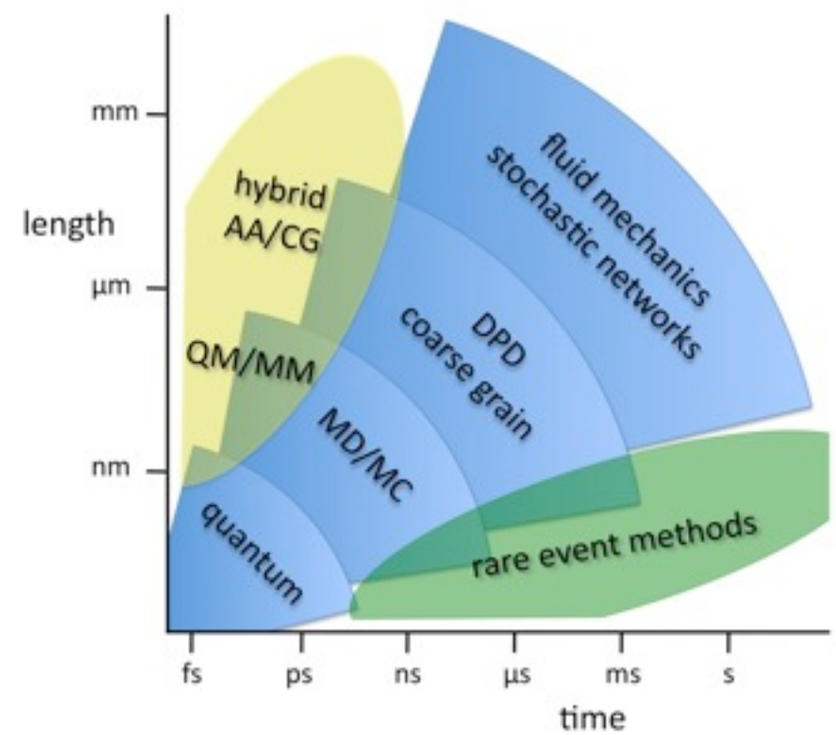
Coarse-graining

- how to choose a atom-CG mapping
- Iterative Boltzmann Inversion
- Inverse Monte Carlo
- Force matching iterative Boltzman
- Targeting selected exp./sim properties

hybrid multiscale MD
- open boundaries/adaptive resolution
- healing region
- non-equilibrium process (equilibration of atoms)
- bookkeeping, auxiliary total energy
- works for spherical CG particles

reverse mapping
- rigid body rotation
- combined with hybrid MD

adaptive QM/MM



fin