CLASSICAL MOLECULAR DYNAMICS

NUMERICAL METHODS FOR THE SIMULATION OF BIOLOGICAL SYSTEMS

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Molecular dynamics simulations FOR DUMMIES

Run your own simulations after only one day of training

Learn to:

- set up your molecular assays
- run your simulations
- perform your own analyses

... and understand what you are doing

SYNOPSIS

1. Introduction
2. Periodic boundary conditions
3. Synopsis of a molecular dynamics simulation
4. The potential energy function
5. The propagators of molecular dynamics
6. Restraints versus constraints
7. In which ensemble should the simulation be performed?
8. Lattice sums: The Ewald–Kornfeld approach
9. Molecular dynamics on parallel architectures
10. Guidelines
11. Properties accessible from the trajectories

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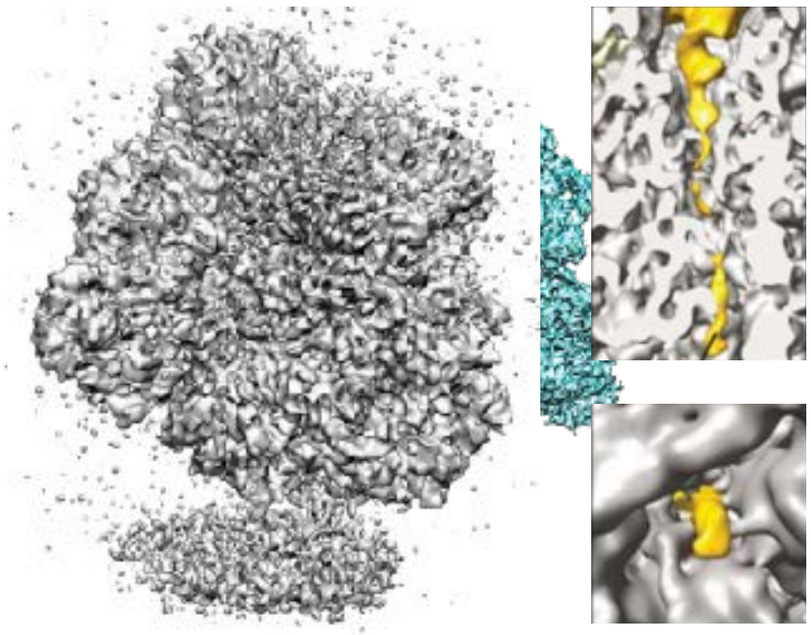
INTRODUCTION

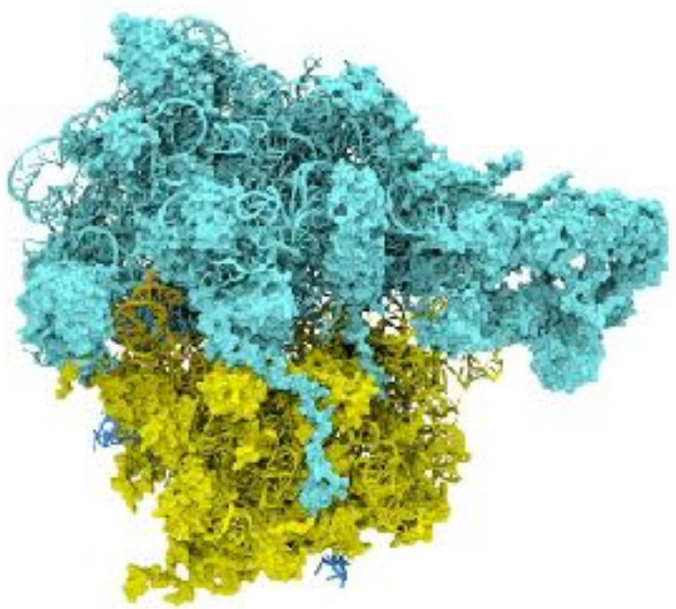
why would we want to turn to MD?

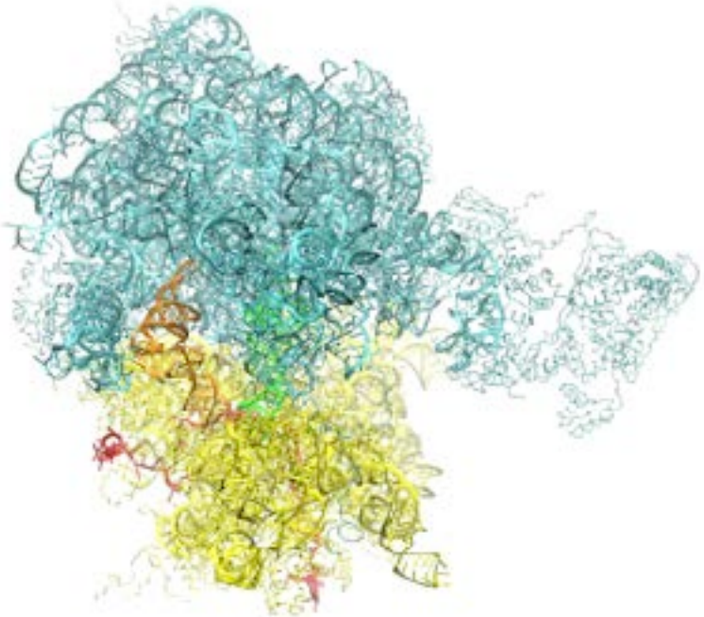
- Supply the microscopic detail that experiment cannot capture;
- Attain key thermodynamic properties of the system,
  e.g., $\Delta G_{\text{adsorption}}$, $\Delta G_{\text{hydration}}$, ...
- Acquire structural information,
  e.g., refinement of three-dimensional structures,
- Acquire dynamic information,
  e.g., $c(t), D(z), \ldots$

The massive increase of computational resources in the past twenty years has opened the way to the investigation of sizable molecular assemblies of chemical, physical and biological interests, over representative time scales.

Complementing experiment — The computational microscope







Ideally, for an N-particle chemical system,

$$i \frac{\partial \left|\Psi(\mathbf{r}^N;t)\right\rangle}{\partial t} = \mathscr{H} \left|\Psi(\mathbf{r}^N;t)\right\rangle$$

In practice, the full quantum treatment of the system is virtually impossible for obvious overwhelming computational reasons.

At the Hartree-Fock level, for N atoms, the CPU investment grows as $\mathscr{O}(N^3)$.

One possible solution: Linear-scaling approaches, or *divide and conquer* growing as $\mathscr{O}(N)$. Currently, they are limited to small systems with a sampling of a few ps. Moreover, they are restrained to the Born-Oppenheimer approximation, and are significantly more costly than molecular mechanics.

Yang, W.; Lee, T. S. *J. Chem. Phys.* **1995**, *103*, 5674-5678

The Born-Oppenheimer approximation: The motion of the electrons and that of the nuclei are dissociated;

The de Broglie wavelength associated to a given particle is substantially smaller than the intermolecular distances in a liquid;

Quantum effects can be globally neglected. It is, therefore, legitimate to turn to the classical equations of motion in molecular dynamics simulations

Time averages and ensemble averages coincide for *ergodic* systems,

$$\lim_{t\to\infty} \overline{\mathscr{A}}_t = \langle \mathscr{A} \rangle$$

Allen, M. P.; Tildesley, D. J. Computer Simulation of Liquids, Clarendon Press, **1987**
Frenkel, D.; Smit, B. Understanding molecular simulations: From algorithms to applications, Academic Press, **2002**
McQuarrie, D. A. Statistical mechanics, Harper and Row, **1976**
Chandler, D. Introduction to modern statistical mechanics Oxford, University Press, **1987**

SUMMARY

We turn to molecular dynamics simulations to access the atomic detail not always accessible to experiment, to gain dynamic information and to predict thermodynamic and kinetic properties.

Molecular dynamics simulations rely on the equations of classical mechanics and, therefore, are restrained to the motion of the nuclei. They are limited to the description of molecular assemblies that do not involve the creation or rupture of chemical bonds.

Ergodicity implies coincidence of ensemble and time averages — and, hence, of properties inferred from Monte-Carlo and molecular dynamics simulations.

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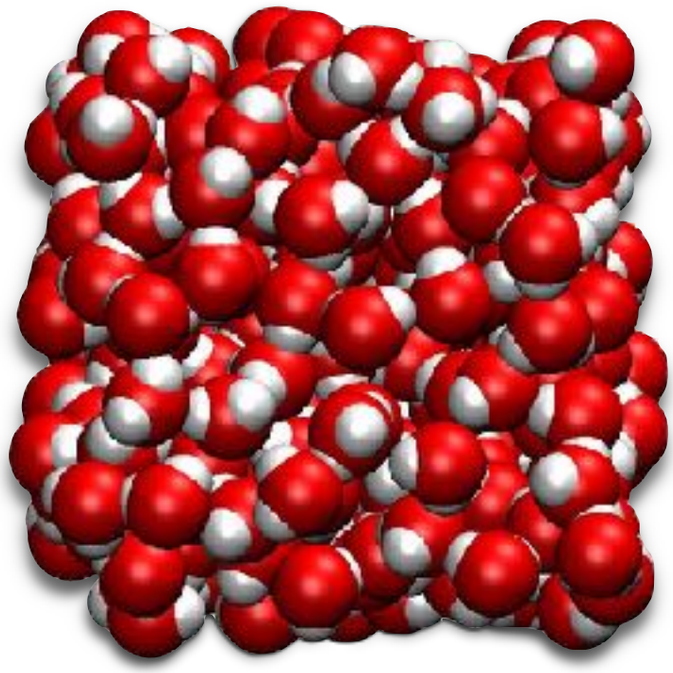
PERIODIC BOUNDARY CONDITIONS



Bridge the macroscopic, or the mesoscopic world to the microscopic one;

Can we relate the properties of a system containing a number of particles on the order of $\mathcal{N}_A$ to those of a system containing only a few hundreds to a few thousands particles?

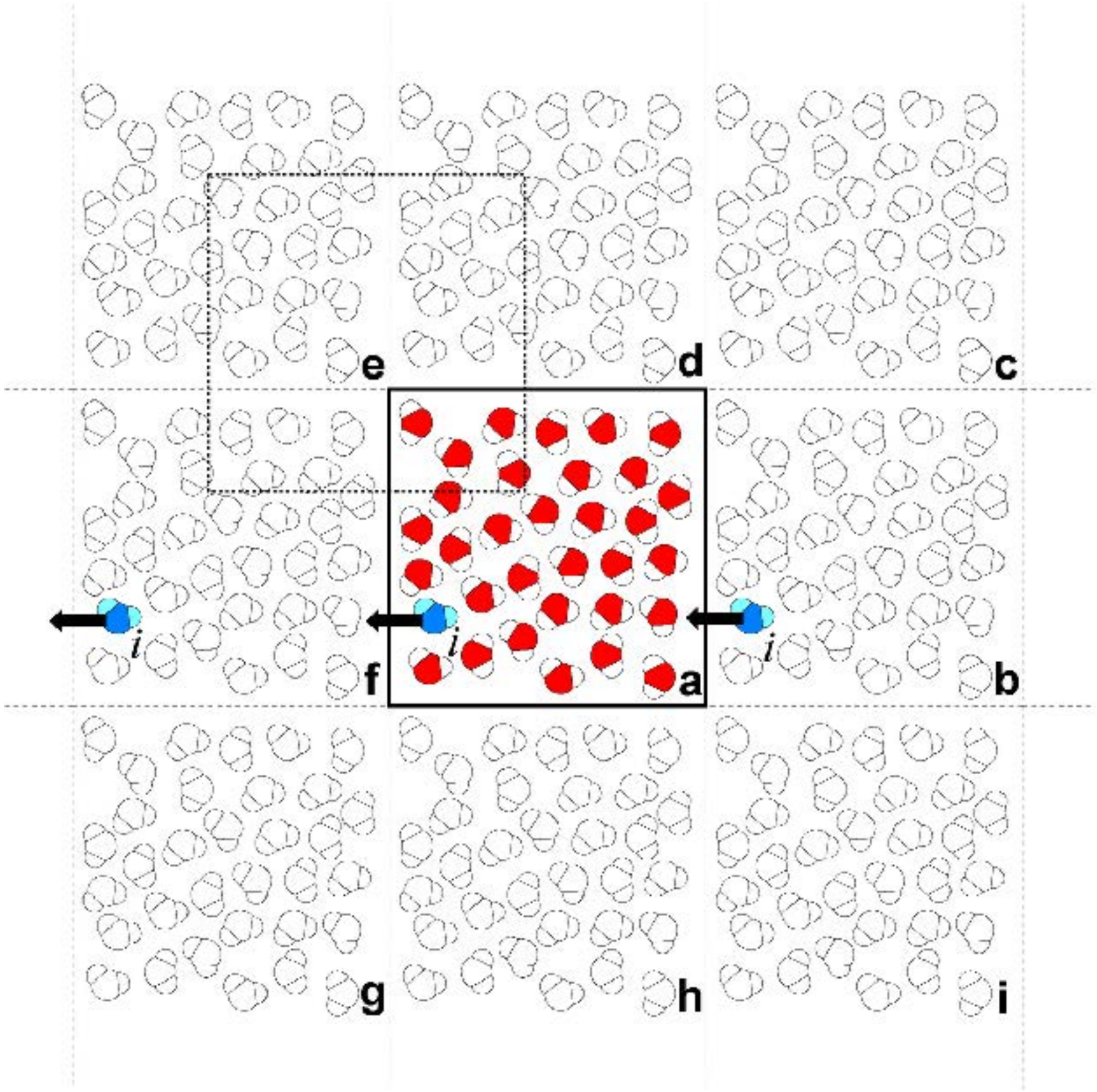
How can we handle edge effects ?

Allen, M. P.; Tildesley, D. J. Computer Simulation of Liquids, Clarendon Press, **1987**

Frenkel, D.; Smit, B. Understanding molecular simulations: From algorithms to applications, Academic Press, **2002**

NAMD
NAnoscale Molecular Dynamics

```
CellBasisVector1    70    0    0
CellBasisVector2     0   70    0
CellBasisVector3     0    0   70
```



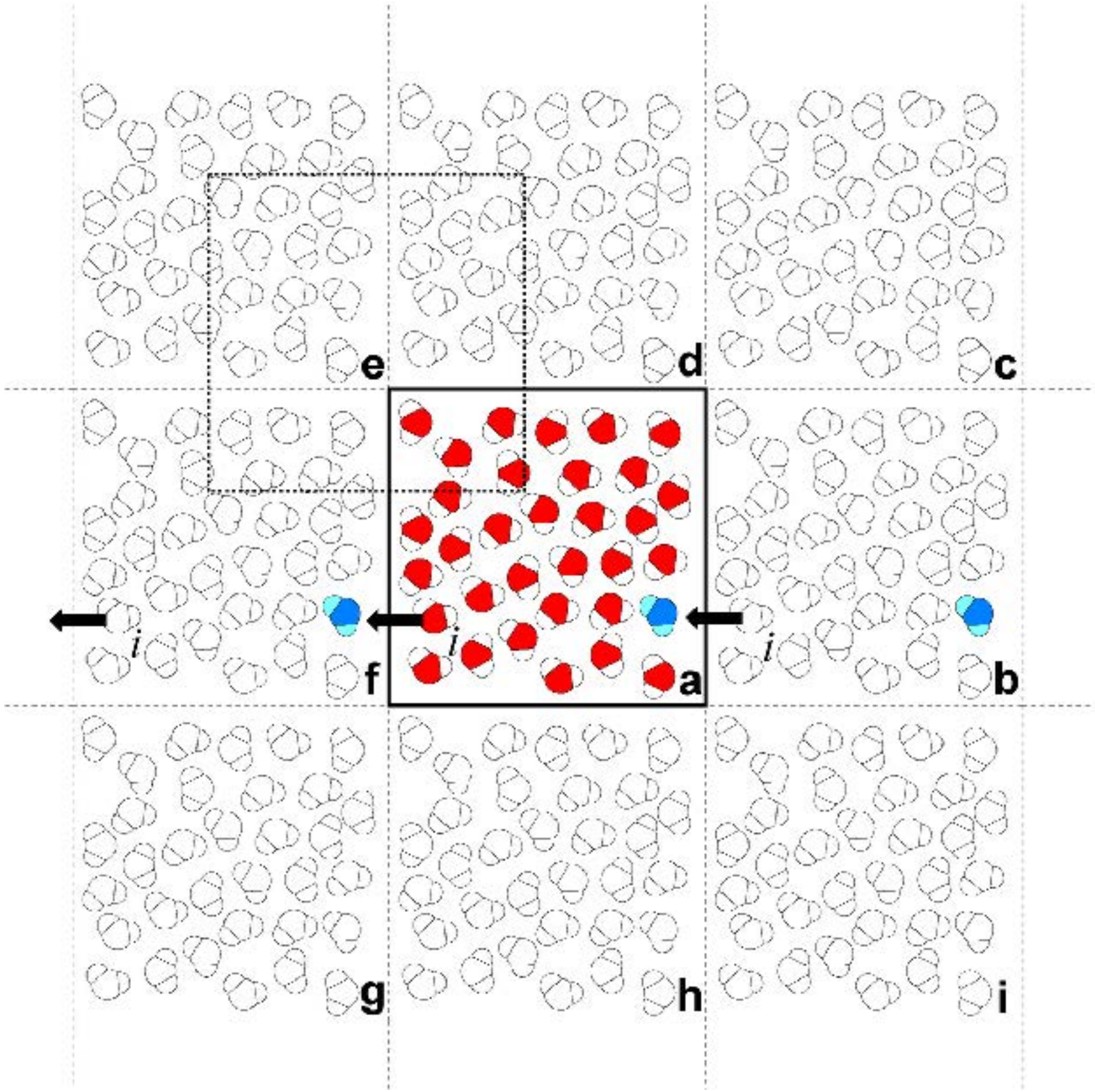
Allen, M. P.; Tildesley, D. J. Computer Simulation of Liquids, Clarendon Press, **1987**

Frenkel, D.; Smit, B. Understanding molecular simulations: From algorithms to applications, Academic Press, **2002**

NAMD
Scalable Molecular Dynamics

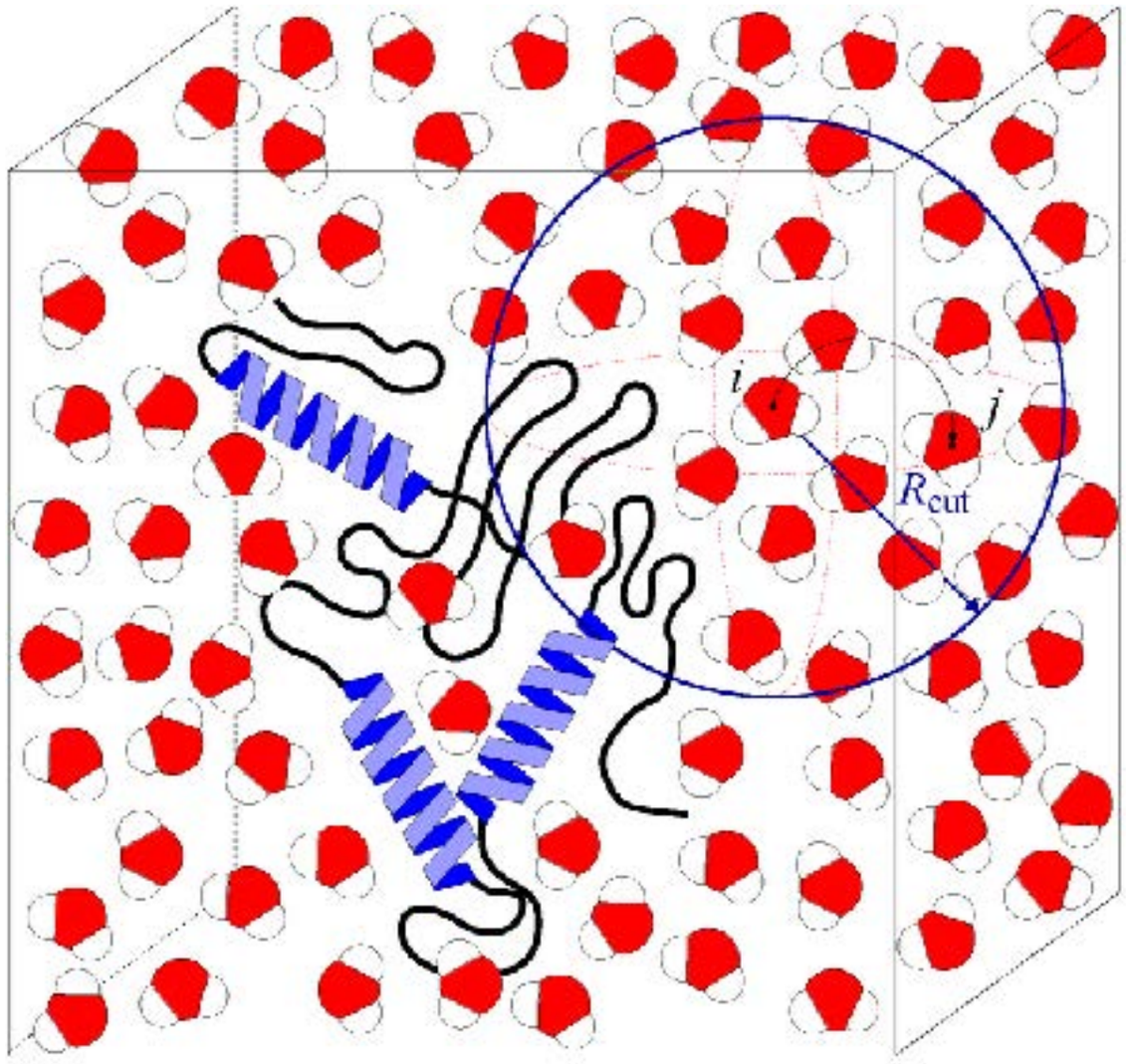
```
CellBasisVector1    70    0    0
CellBasisVector2     0   70    0
CellBasisVector3     0    0   70
```

minimum-image convention: each individual particle in the cell interacts with the closest image of the remaining particles in the assay.



Allen, M. P.; Tildesley, D. J. Computer Simulation of Liquids, Clarendon Press, **1987**

Frenkel, D.; Smit, B. Understanding molecular simulations: From algorithms to applications, Academic Press, **2002**

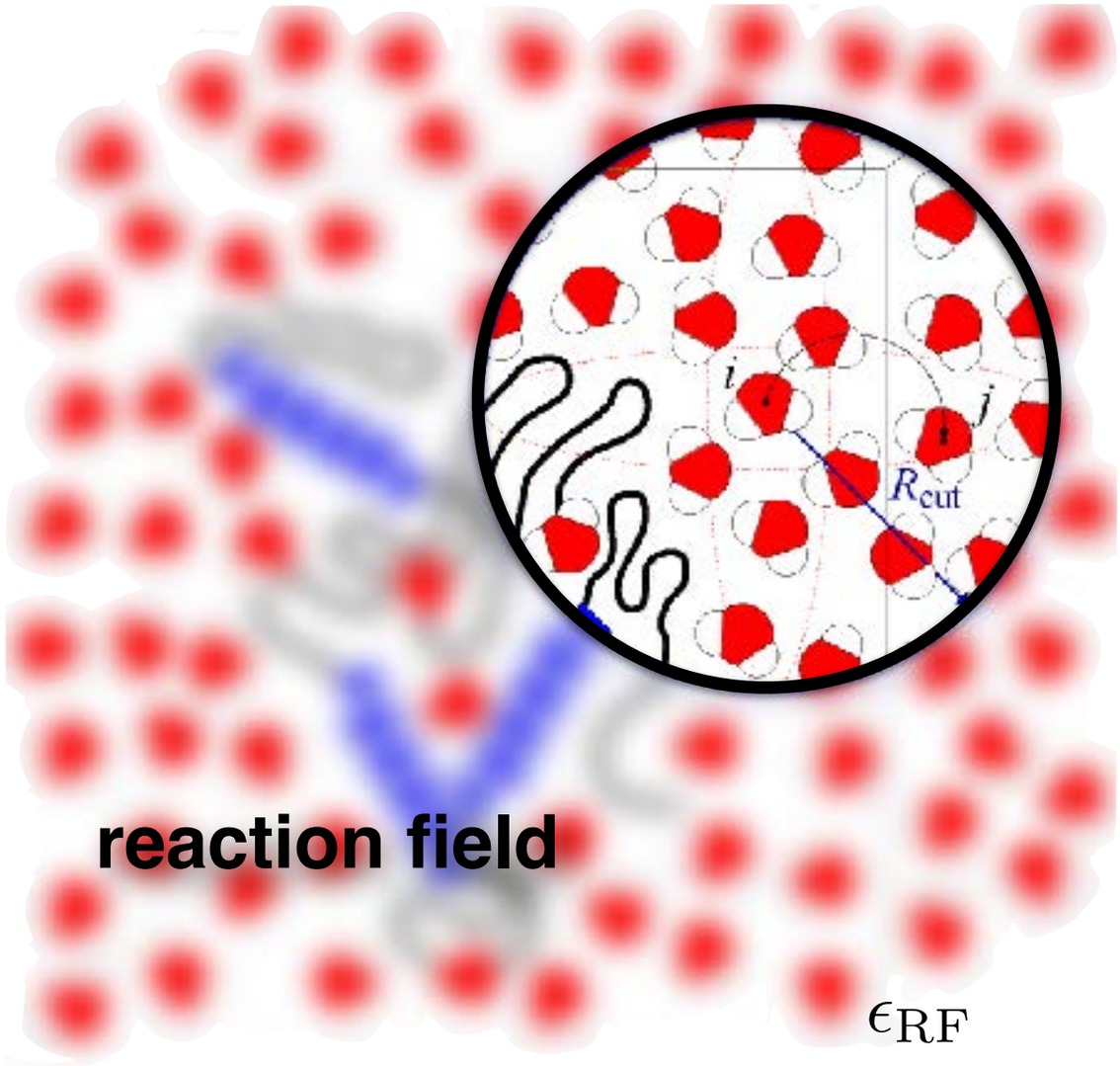


hard cut-off

Conventionally, beyond the spherical truncation, the interaction potential is nil.

Allen, M. P.; Tildesley, D. J. Computer Simulation of Liquids, Clarendon Press, **1987**

Frenkel, D.; Smit, B. Understanding molecular simulations: From algorithms to applications, Academic Press, **2002**

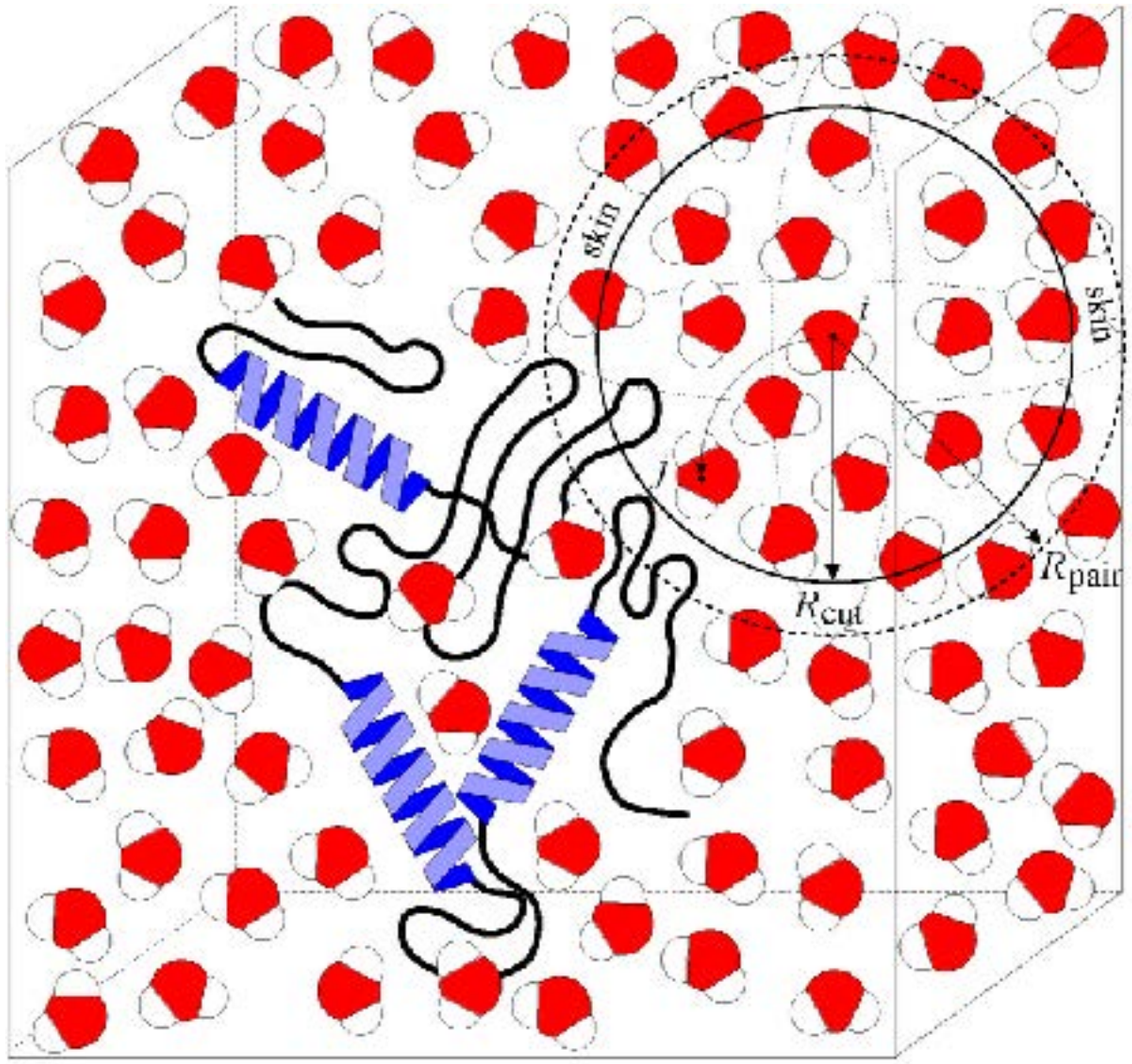


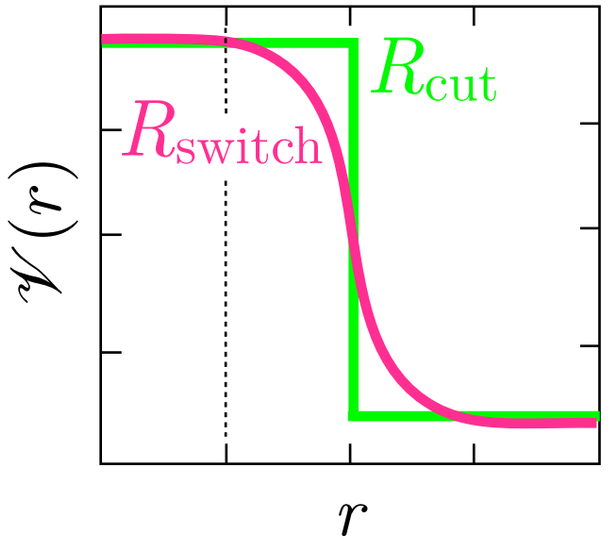
hard cut-off

Conventionally, beyond the spherical truncation, the interaction potential is nil. Yet, it is possible to include a reaction-field term, $\mathscr{V}_{\text{elec}}(r) = \sum_{i<j} q_i q_j \left[\frac{1}{r_{ij}} + \left(\frac{\epsilon_{\text{RF}} - 1}{2\epsilon_{\text{RF}} + 1} \right) \frac{r_i j^2}{R_{\text{cut}}^3} \right]$.

Barker, J. A.;Watts, R. O. *Mol. Phys.* **1973**, *26*, 789-792

hard cut-off ≠
switched cut-off






```
NAMD  Scalable Molecular Dynamics

switchDist                 8
cutoff                     9
pairListDist              10
```

In principle, spherical truncation is acceptable for electrostatic interactions in $1/r^n$, with $n \geq 3$. For $n < 3$, an appropriate treatment is required — e.g., Ewald, or Ladd.

Toukmaji, A. Y. ; Board Jr., J. A. *Comput. Phys. Comm.* **1996**, *95*, 73-92

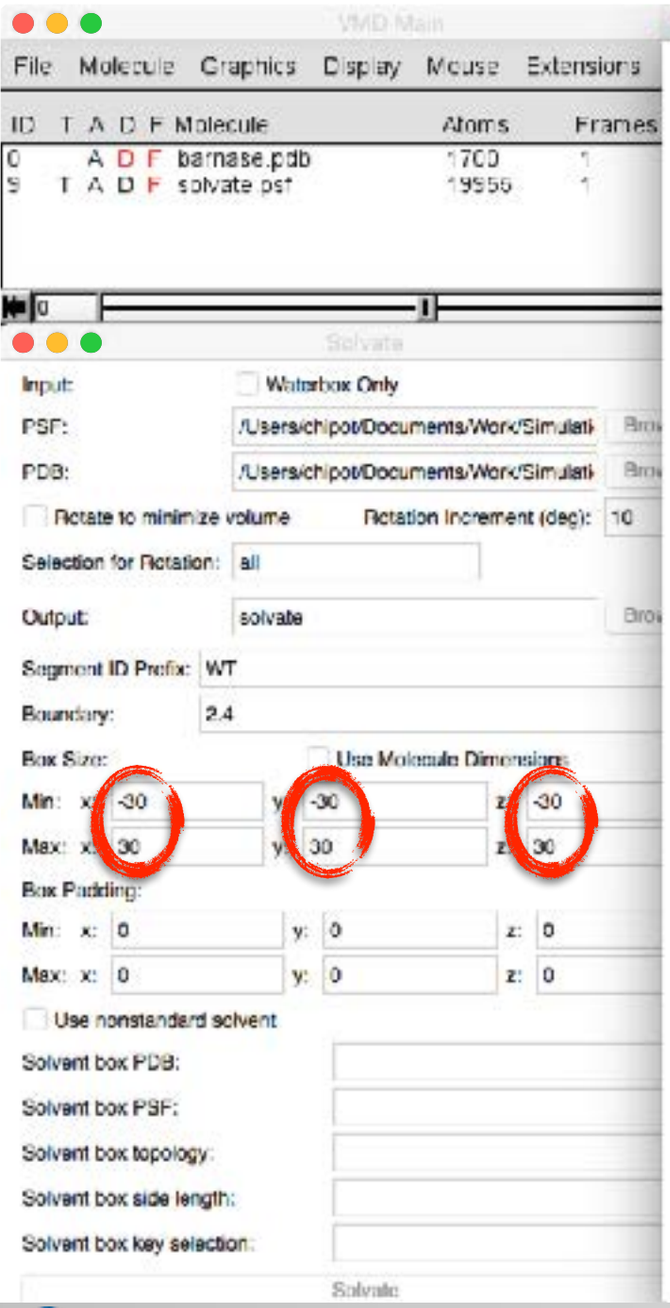
Allen, M. P.; Tildesley, D. J. Computer Simulation of Liquids, Clarendon Press, **1987**

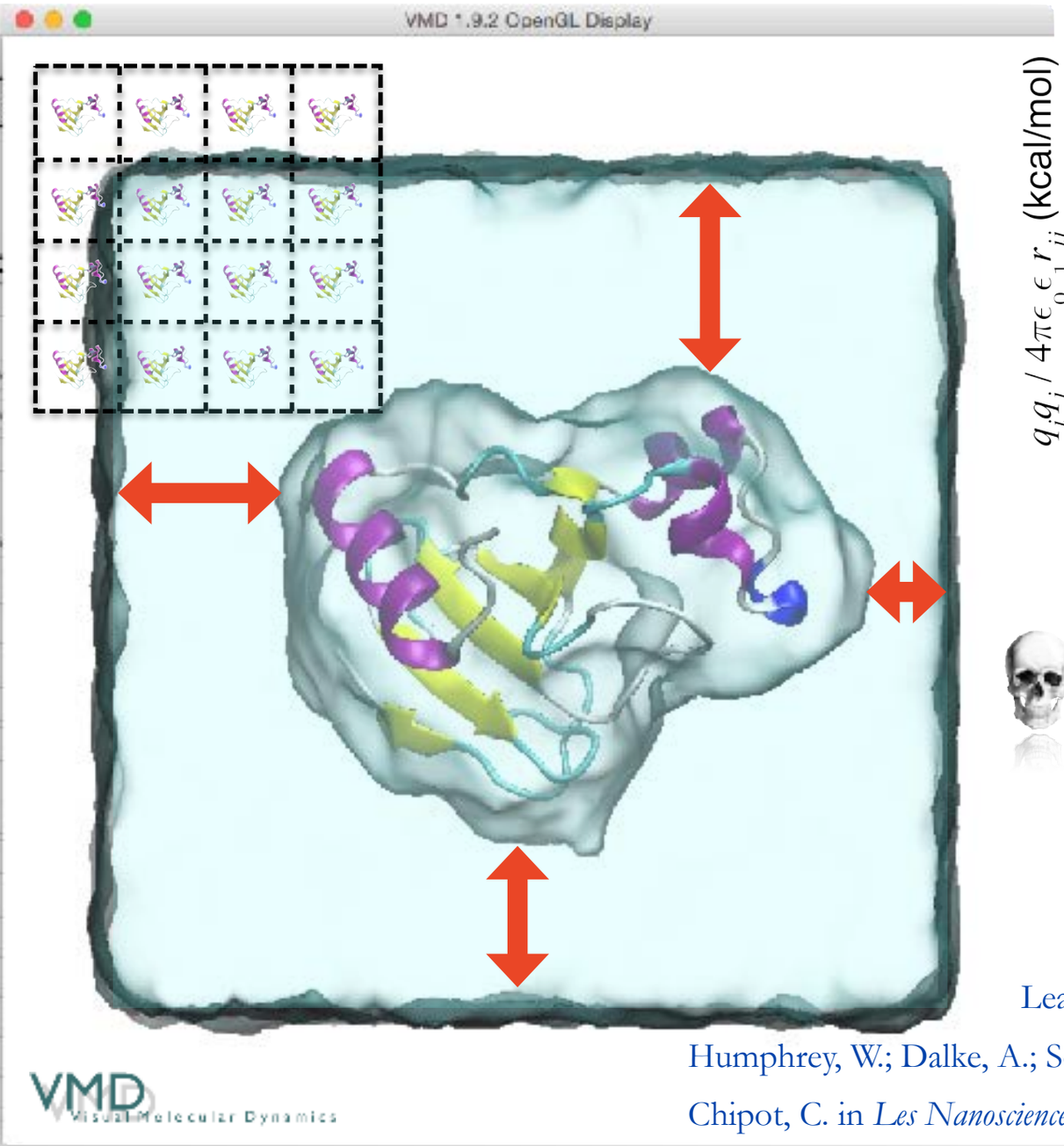
Frenkel, D.; Smit, B. Understanding molecular simulations: From algorithms to applications, Academic Press, **2002**

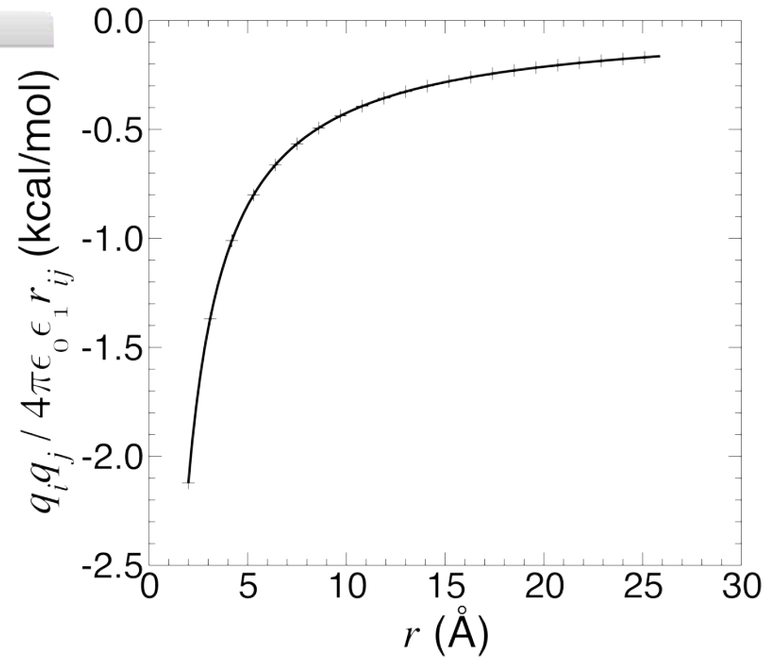
Build a simple molecular assay using VMD

— Load the topology and Cartesian coordinates, $\{\mathbf{x}\}$, of the biological object

— Solvate in a pre-equilibrated solvent cell







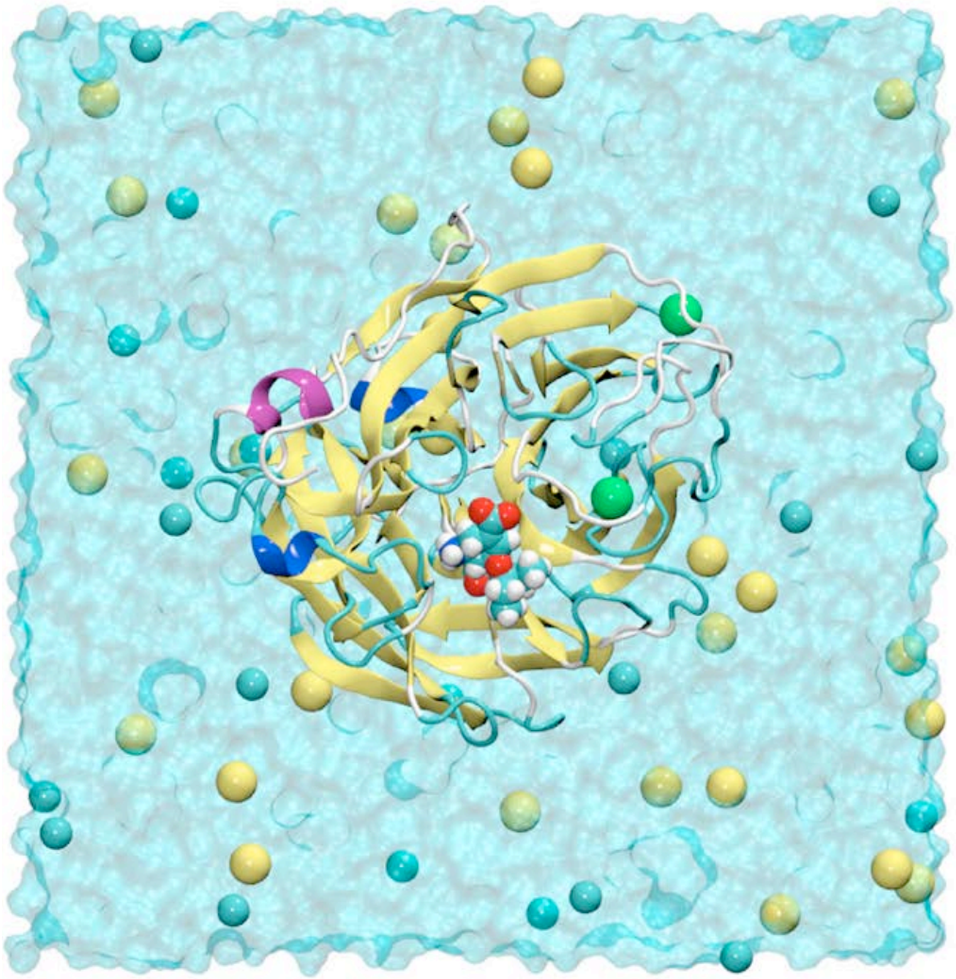
leave enough headspace when solvating to avoid periodicity-induced artifacts

Leach, A. R. *Molecular modeling*. Longman, **1996**

Humphrey, W.; Dalke, A.; Schulten, K. *J. Molec. Graphics* **1996**, *14*, 33-38

Chipot, C. in *Les Nanosciences: Nanotechnologies et nanophysique*, Belin, **2006**

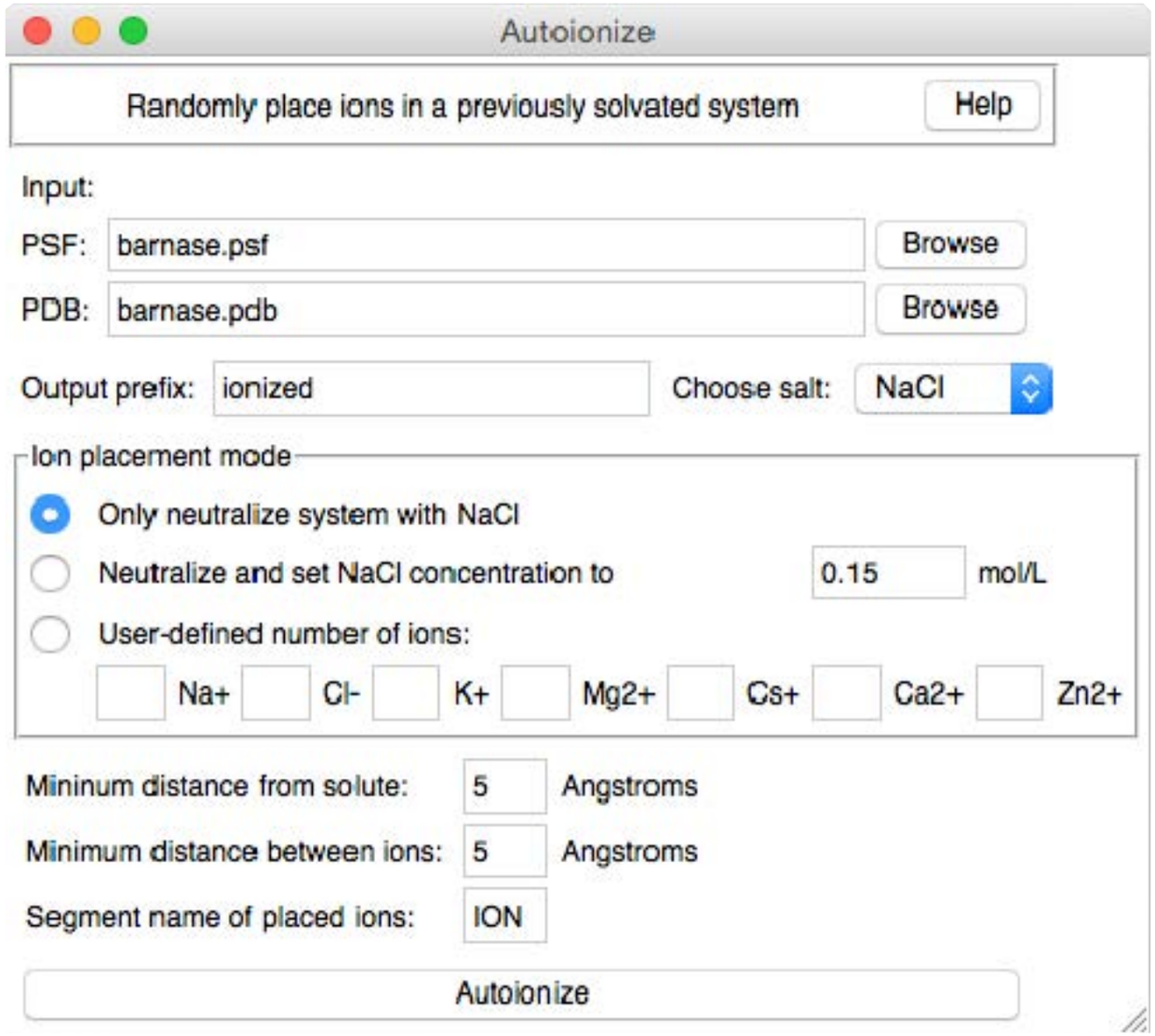
Adding ions to a solvated protein-ligand complex



— At what salinity was the experiment carried out?

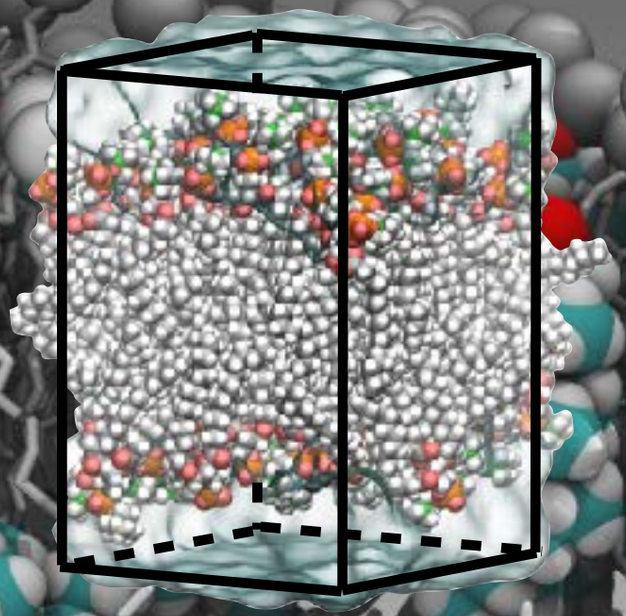
— What ions were used?

— What is the excess charge of the complex?



Humphrey, W.; Dalke, A.; Schulten, K. *J. Molec. Graphics* **1996**, *14*, 33-38

Building a membrane protein assay



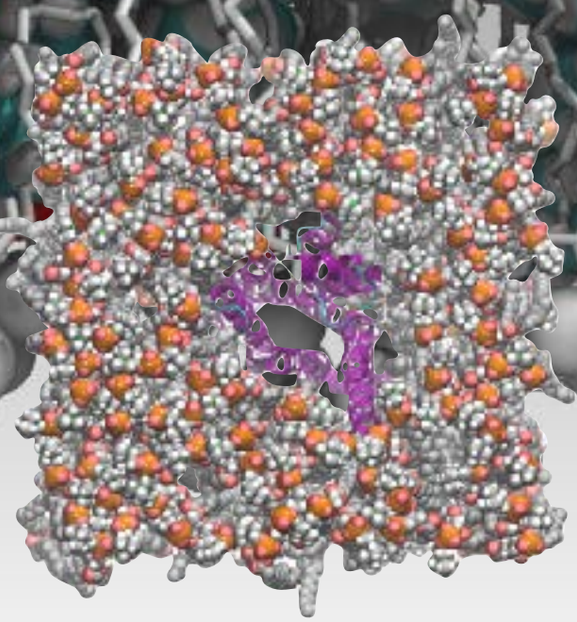
equilibrated membrane patch

insert randomly additives

insert membrane protein

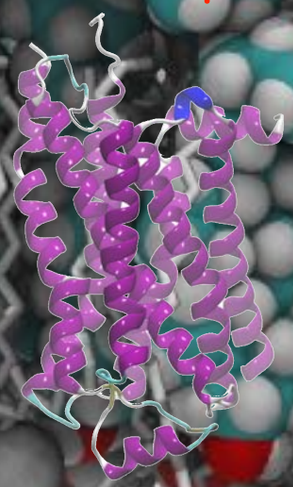
add water if necessary

insert ions if necessary



in what lipids was the experiment conducted?

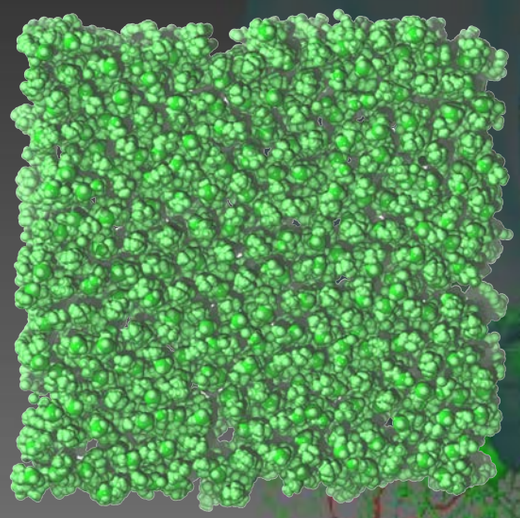
were additives present in the experimental assay?



allow extracellular loops to extend

Humphrey, W.; Dalke, A.; Schulten, K. *J. Molec. Graphics* **1996**, *14*, 33-38

Building a membrane protein assay with different lipids



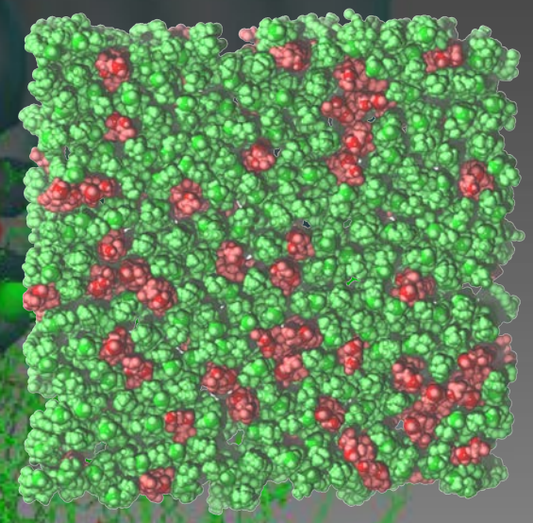
equilibrated pure-lipid patch

random insertion of lipids

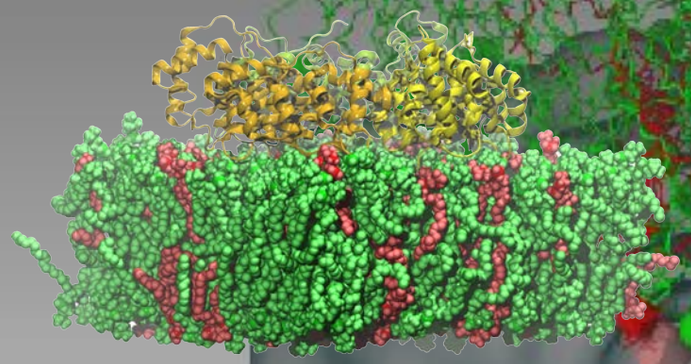
embed membrane protein

add aqueous environment

adjust salinity



replacement of lipids or perturbative insertion



Humphrey, W.; Dalke, A.; Schulten, K. *J. Molec. Graphics* **1996**, *14*, 33-38

CHARMM-GUI

Effective Simulation Input Generator and More

CHARMM is a versatile program for atomic-level simulation of many-particle systems, particularly macromolecules of biological interest. - M. Karplus

about us :: input generator :: archive :: charmm docs :: MD lectures :: movie gallery :: video demo :: citations :: update log

CHARMM-GUI has updated. See our upload log to see what is changed. Contact us (E-mail or CHARMM Forum) if you have any problem/question/comment.

CHARMM-GUI

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Front Page

CHARMM-GUI provides a web-based graphical user interface to generate various molecular simulation systems and input files to facilitate and standardize the usage of common and advanced simulation techniques. Currently, CHARMM-GUI supports CHARMM, NAMD, GROMACS, AMBER, and OpenMM simulation programs mostly based on the CHARMM force fields.

CHARMM-GUI is powered by CHARMM, an academic research program used world-wide for macromolecular dynamics and mechanics (http://www.charmm.org). Its development began in the research group of Professor Martin Karplus at Harvard University and continues throughout the world with contributing developers. CHARMM performs standard molecular dynamics and energy minimization with the potential energy functions for proteins, nucleic acids, lipids, carbohydrates, and various small molecules. In addition, CHARMM can be used for various chemical and conformational free energy calculations with many types of restraints.

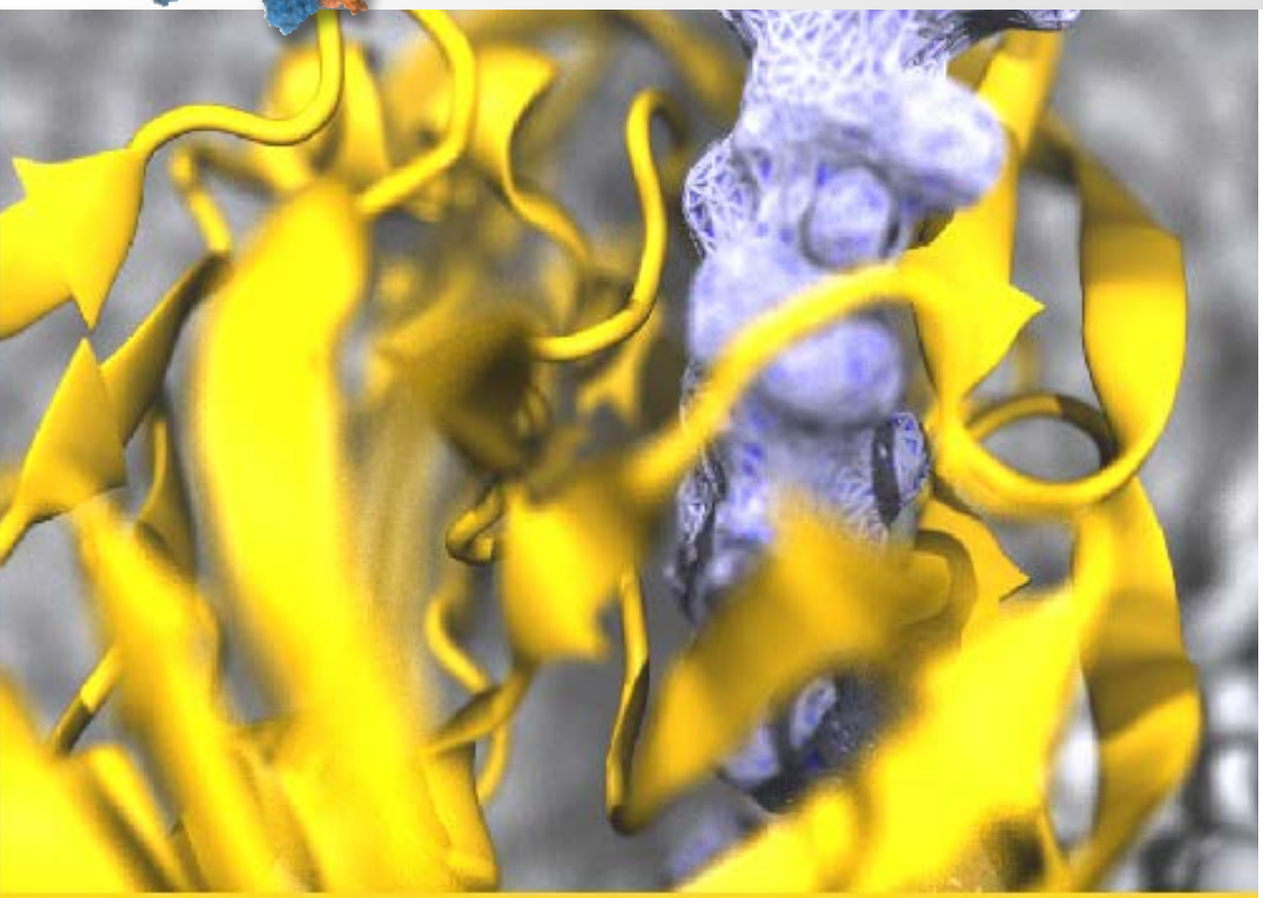
The CHARMM-GUI team hopes that the tools and materials offered here are useful and helpful for your research and education.

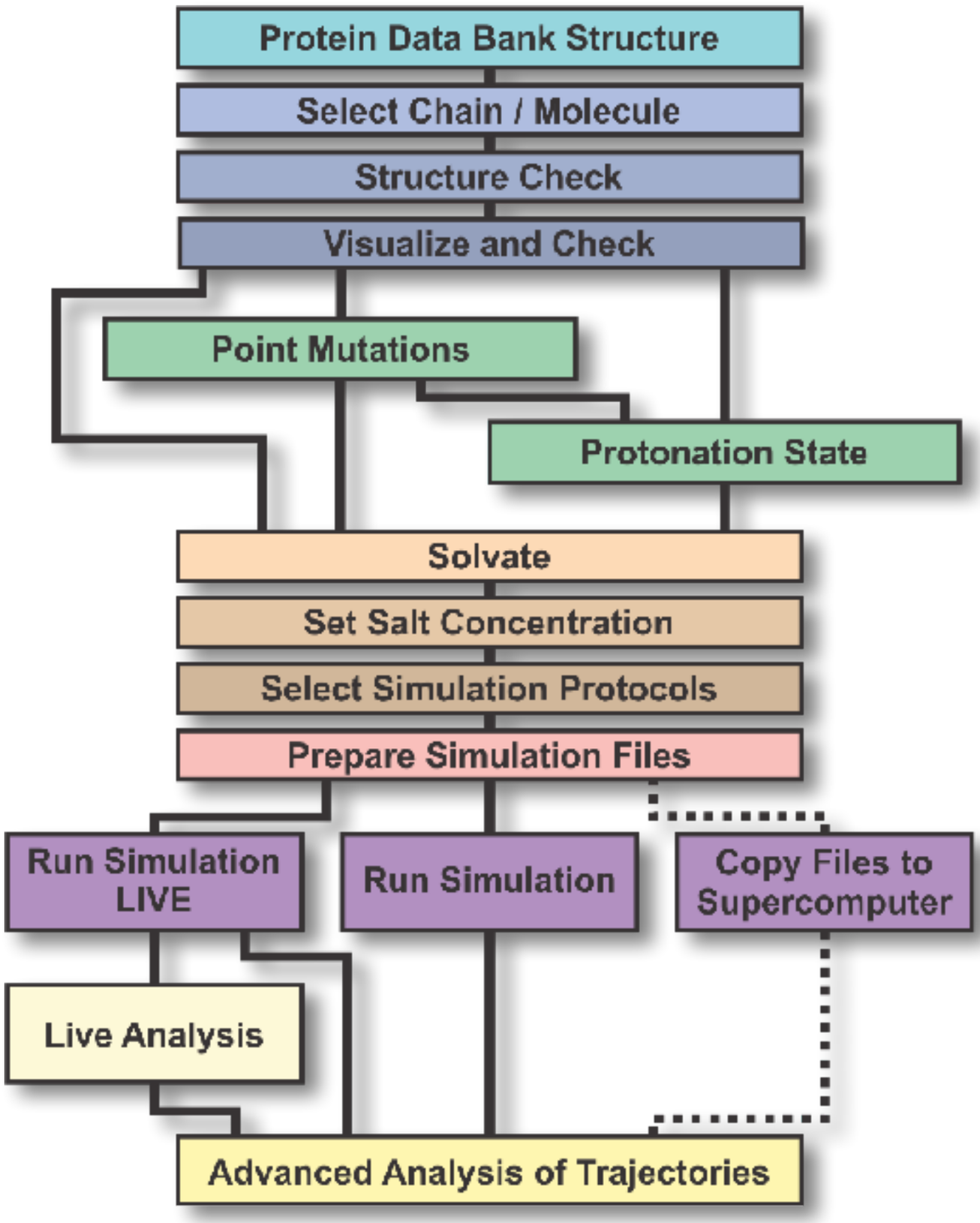
The University of Kansas / Department of Molecular Biosciences / Center for Computational Biology / Im Lab
Problems, Questions, & Comments? CHARMM Forum or E-Mail / Copyright(c) 2006-2015 by the Im Lab

Jo, S.; Lim, J. B.; Klauda, J. B.; Im, W. *Biophys. J.* **2009**, *97*, 50-58

Jo, S.; Jiang, W.; Lee, H. S.; Roux, B.;Im, W. *J. Chem. Inf. Model.* **2013**, *53*, 267-277

Jo, S. et al. *Adv. Protein Chem. Struct. Biol.* **2014**, *96*, 235-265





Ribeiro, J. V. et al. *Sci. Rep.* **2016**, *6*, 26536

SUMMARY

Periodic boundary conditions offer a convenient framework to bridge the microscopic world to the macroscopic one, whilst being emancipated from edge effects.

Spherical truncation is in general valid only for short-range interactions.

Switching is recommended to ensure continuous derivative across the cut-off sphere.

When constructing molecular assays, leave enough headspace to avoid spurious periodicity-induced artifacts.

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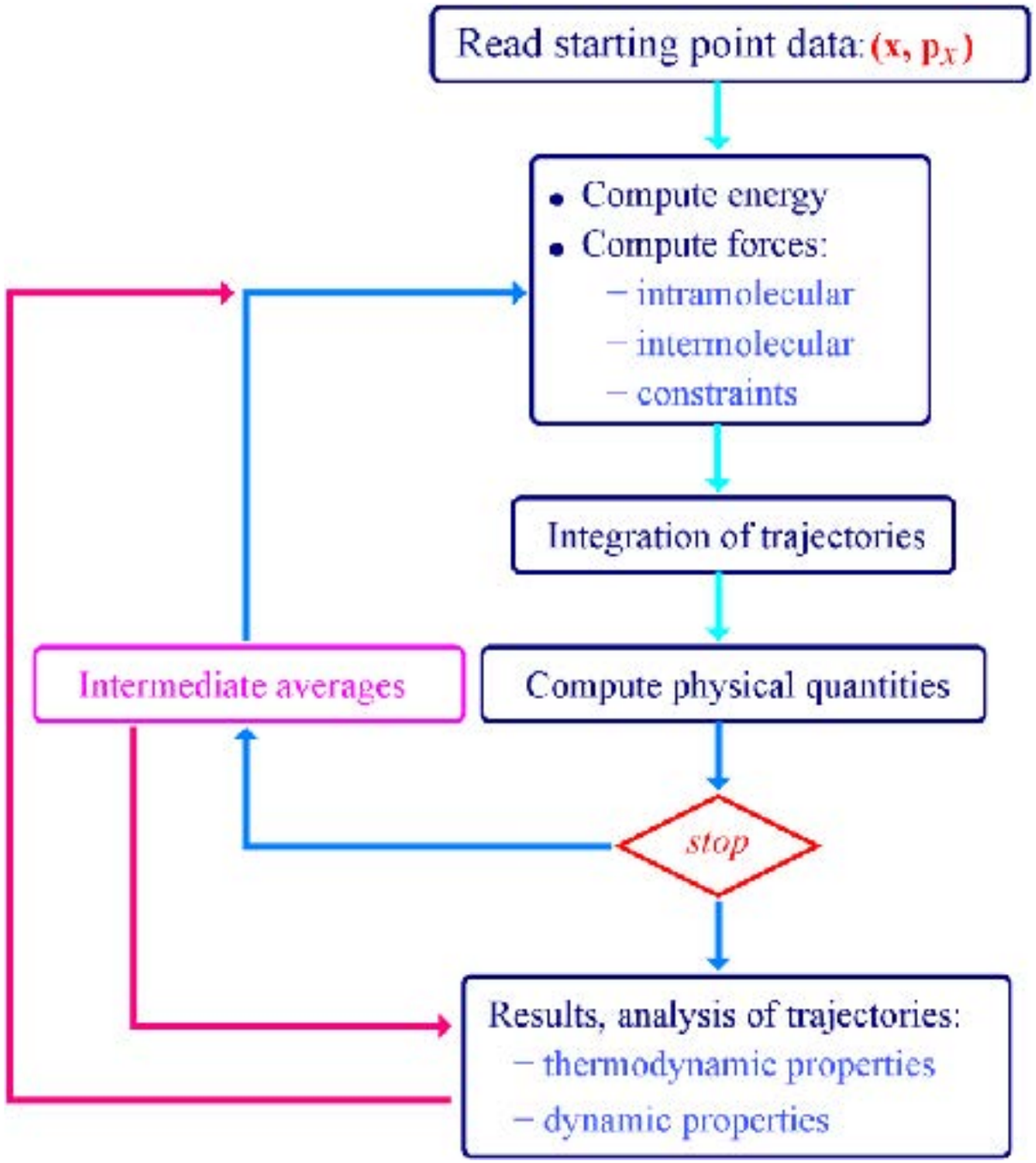
SYNOPSIS OF A MOLECULAR DYNAMICS SIMULATION



Alder, B. J.; Wainwright, T. E. *J. Chem. Phys.* **1957**, *27*, 1208-1209

Allen, M. P.; Tildesley, D. J. Computer Simulation of Liquids, Clarendon Press, **1987**

Frenkel, D.; Smit, B. Understanding molecular simulations: From algorithms to applications, Academic Press, **2002**

Goal: Follow the trajectory of an ensemble of particles with time:

$$\begin{cases} m_i \dfrac{\mathrm{d}^2\mathbf{x}_i(t)}{\mathrm{d}t^2} = \mathbf{f}_i \\ \\ \mathbf{f}_i = -\dfrac{\partial \mathscr{V}(\mathbf{x})}{\partial \mathbf{x}_i} \end{cases}$$

Rely upon a potential energy function capable of describing the chemical system:

$$\mathscr{V}(\mathbf{x}) = \sum_i v_1(\mathbf{x}_i) + \sum_i \sum_{j>i} v_2(\mathbf{x}_i, \mathbf{x}_j) + \sum_i \sum_{j>i} \sum_{k>j>i} v_3(\mathbf{x}_i, \mathbf{x}_j, \mathbf{x}_k) + \dots$$

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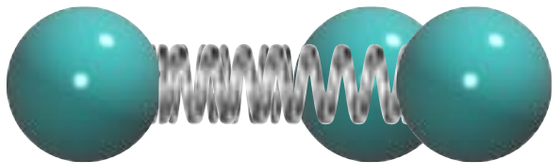
Frenkel, D.; Smit, B. Understanding molecular simulations: From algorithms to applications, Academic Press, **2002**

Goal: Follow the trajectory of an ensemble of particles with time:

$$\begin{cases} m_i \dfrac{\mathrm{d}^2\mathbf{x}_i(t)}{\mathrm{d}t^2} = \mathbf{f}_i \\ \\ \mathbf{f}_i = -\dfrac{\partial \mathscr{V}(\mathbf{x})}{\partial \mathbf{x}_i} \end{cases}$$

Rely upon a potential energy function capable of describing the chemical system:

$$\mathscr{V}(\mathbf{x}) = \sum_i v_1(\mathbf{x}_i) + \sum_i \sum_{j>i} v_2^{\text{effective}}(\mathbf{x}_i, \mathbf{x}_j)$$



Require a numerical integration of the Newtonian equations of motion, utilizing an infinitesimal time-step, namely $\delta t = 1\text{-}2 \times 10^{-15}$ s.

why are we limited to such low δt's ?

$\nu = 1/2\pi c\ (k/\mu)^{1/2}$

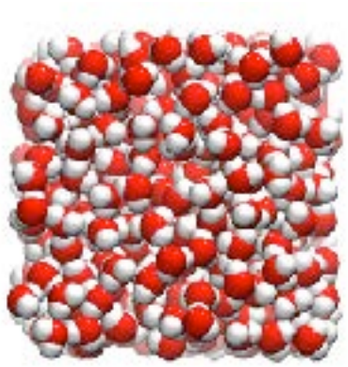
Allen, M. P.; Tildesley, D. J. Computer Simulation of Liquids, Clarendon Press, **1987**

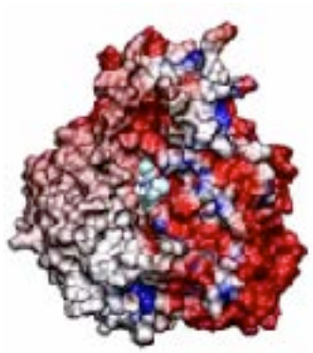
Frenkel, D.; Smit, B. Understanding molecular simulations: From algorithms to applications, Academic Press, **2002**

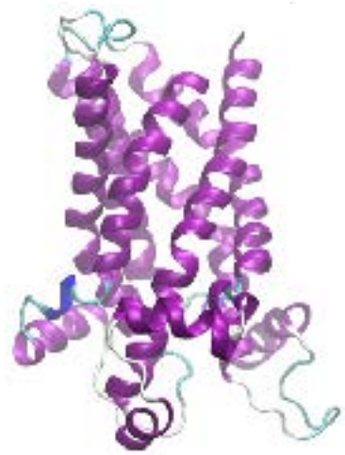
Typical timescales explored in molecular dynamics and the computational resource required to access them.

ps **ns** **μs** **ms** **s** **time**

10^{-12} 10^{-9} 10^{-6} 10^{-3} 1







1 gigaflop **1 teraflop** **100 teraflops** **10 petaflops**

The error associated to the propagator should be bound, that is,

$$\lim_{n_{\text{steps}}\to\infty}\left(\frac{1}{n_{\text{steps}}}\right)\sum_{k=1}^{n_{\text{steps}}}\left|\frac{\mathscr{E}(k\delta t)-\mathscr{E}(0)}{\mathscr{E}(0)}\right|\leq\varepsilon_{\text{MD}}$$

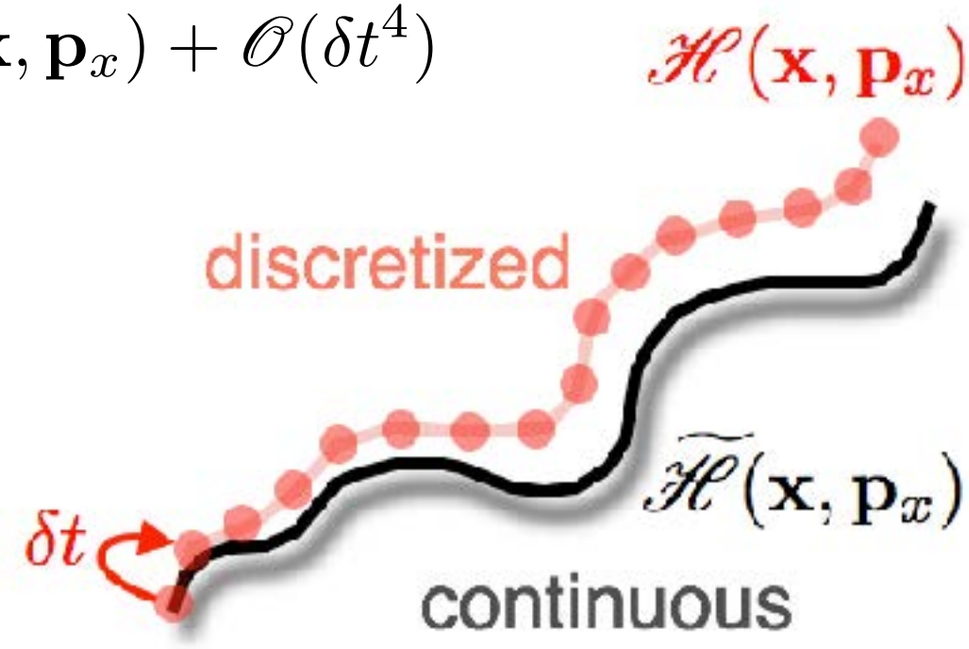
which is true for a *symplectic* propagator.

Energy drifts stem from inaccuracies in the integration of the equations of motion.

These drifts can be in principle monitored by means of a shadow Hamiltonian.

$$\widetilde{\mathscr{H}}(\mathbf{x},\mathbf{p}_x)=\mathscr{H}(\mathbf{x},\mathbf{p}_x)+\frac{\delta t^2}{2!}h(\mathbf{x},\mathbf{p}_x)+\mathscr{O}(\delta t^4)$$

$$h(\mathbf{x},\mathbf{p}_x)=\frac{1}{6}\mathbf{p}_x^{\mathsf{T}}m^{-1}\frac{\partial^2\mathscr{V}(\mathbf{x})}{\partial\mathbf{x}^2}m^{-1}\mathbf{p}_x-\frac{1}{12}\left[\nabla\mathscr{V}(\mathbf{x})\right]^{\mathsf{T}}m^{-1}\nabla\mathscr{V}(\mathbf{x})$$



Candy, J.; Rozmus, W. *J. Comput. Phys.* **1991**, *92*, 230-256

Engle, R. D.; Skeel, R. D.; Drees, M. J. *Comput. Phys.* **2005**, *206*, 432-452

Lagrangian formalism,

$$\mathscr{L}(\mathbf{q},\mathbf{p}) = \mathscr{T}(\mathbf{p}_x) - \mathscr{V}(\mathbf{q})$$

$$\begin{cases} \mathscr{T}(\mathbf{p}_x) & = & \displaystyle\sum_i \frac{1}{2}\frac{p_i^2}{m_i} \\ \mathscr{V}(\mathbf{x}) & = & \displaystyle\sum_i v_1(\mathbf{q}_i) \\ & + & \displaystyle\sum_i \sum_{j>i} v_2(\mathbf{q}_i,\mathbf{q}_j) + \dots \end{cases}$$

Lagrange's equation of motion,

$$\frac{\mathrm{d}}{\mathrm{d}t}\left(\frac{\partial\mathscr{L}(\mathbf{q},\mathbf{p})}{\partial\dot{q}}\right) - \frac{\partial\mathscr{L}(\mathbf{q},\mathbf{p})}{\partial q} = 0$$

Derivative of the Lagrangian,

$$\frac{\mathrm{d}\mathscr{L}(\mathbf{q},\mathbf{p})}{\mathrm{d}t} = \sum_i \frac{\partial\mathscr{L}(\mathbf{q},\mathbf{p})}{\partial q_i}\,\dot{q}_i + \sum_i \frac{\partial\mathscr{L}(\mathbf{q},\mathbf{p})}{\partial\dot{q}_i}\,\ddot{q}_i$$

Goldstein, H. *Classical mechanics.* Addison-Wesley, **1980**

Lagrange's equation of motion,

$$\frac{\mathrm{d}}{\mathrm{d}t}\left(\frac{\partial \mathscr{L}(\mathbf{q},\mathbf{p})}{\partial \dot{q}}\right) - \frac{\partial \mathscr{L}(\mathbf{q},\mathbf{p})}{\partial q} = 0$$

Newton's equations of motion,

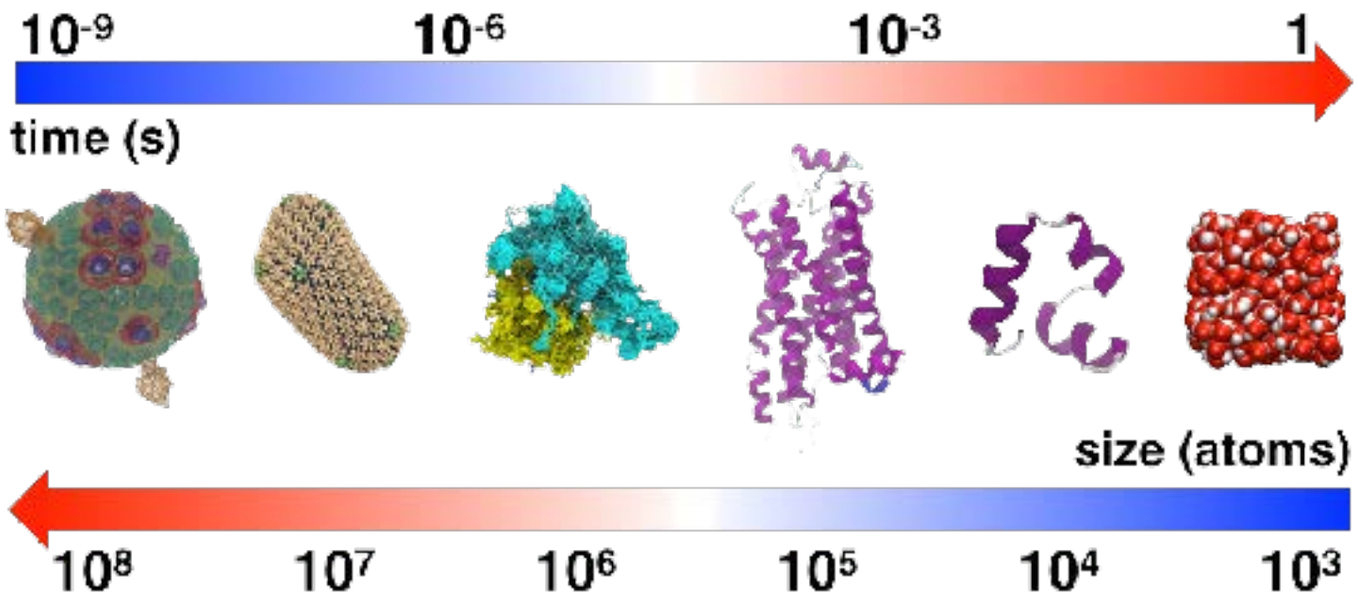
$$\begin{cases} m_i\ \mathbf{a}_i(t) &= \mathbf{f}_i \\ \mathbf{f}_i &= \boldsymbol{\nabla}_{(\boldsymbol{q_i})}\mathscr{L}(\mathbf{q},\mathbf{p}) = -\boldsymbol{\nabla}_{(\boldsymbol{r_i})}\mathscr{V}(\mathbf{x}) \end{cases}$$

Hamilton's equations of motion,

$$\begin{cases} \dot{q}_i &= \dfrac{\partial \mathscr{H}(\mathbf{q},\mathbf{p}_x)}{\partial p_i} \\ \dot{p}_i &= -\dfrac{\partial \mathscr{H}(\mathbf{q},\mathbf{p}_x)}{\partial q_i} \end{cases}$$

Goldstein, H. *Classical mechanics.* Addison-Wesley, **1980**

Leimkuhler, B.; Reich, S. *Simulating Hamiltonian Dynamics.* Cambridge University Press, **2005**



$$\begin{cases} m_i \dfrac{\mathrm{d}^2\mathbf{x}_i(t)}{\mathrm{d}t^2} = \mathbf{f}_i \\ \mathbf{f}_i = -\dfrac{\partial \mathscr{V}(\mathbf{x})}{\partial \mathbf{x}_i} \end{cases}$$

where we stand now…

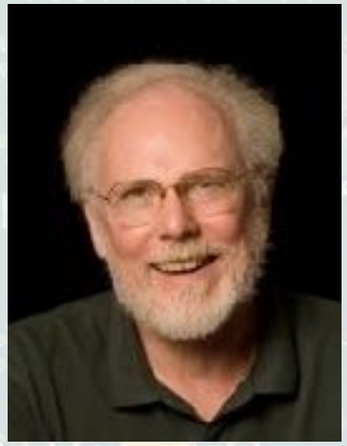
Use of massively parallel architectures (e.g., NUMA, or PC clusters) to spread the task over several processors;

Moore's law suggests longer and more affordable simulations;

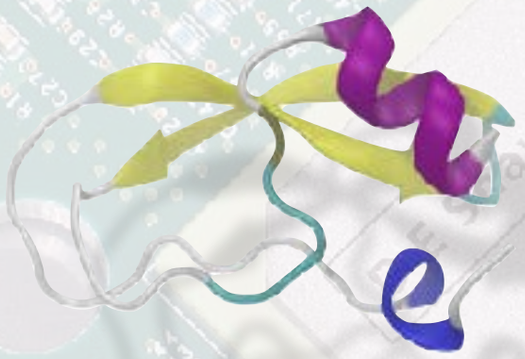
Robust methodology, allowing the modeler to work in realistic conditions and apt thermodynamic ensembles.

Historical perspective

A turning point in computational structural biology



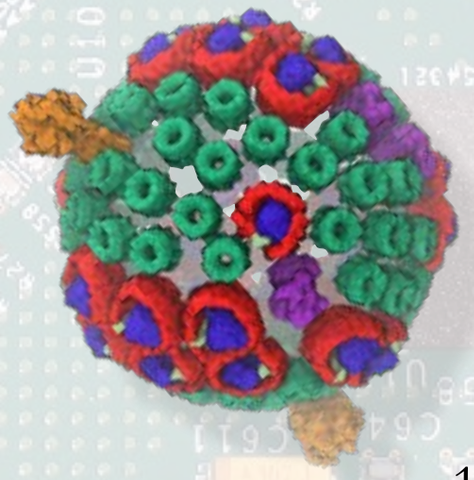
First molecular dynamics simulation applied to a small protein, BPTI, over 8 ps.



time scale

17 µs per day for about 24,000 atoms

size scale



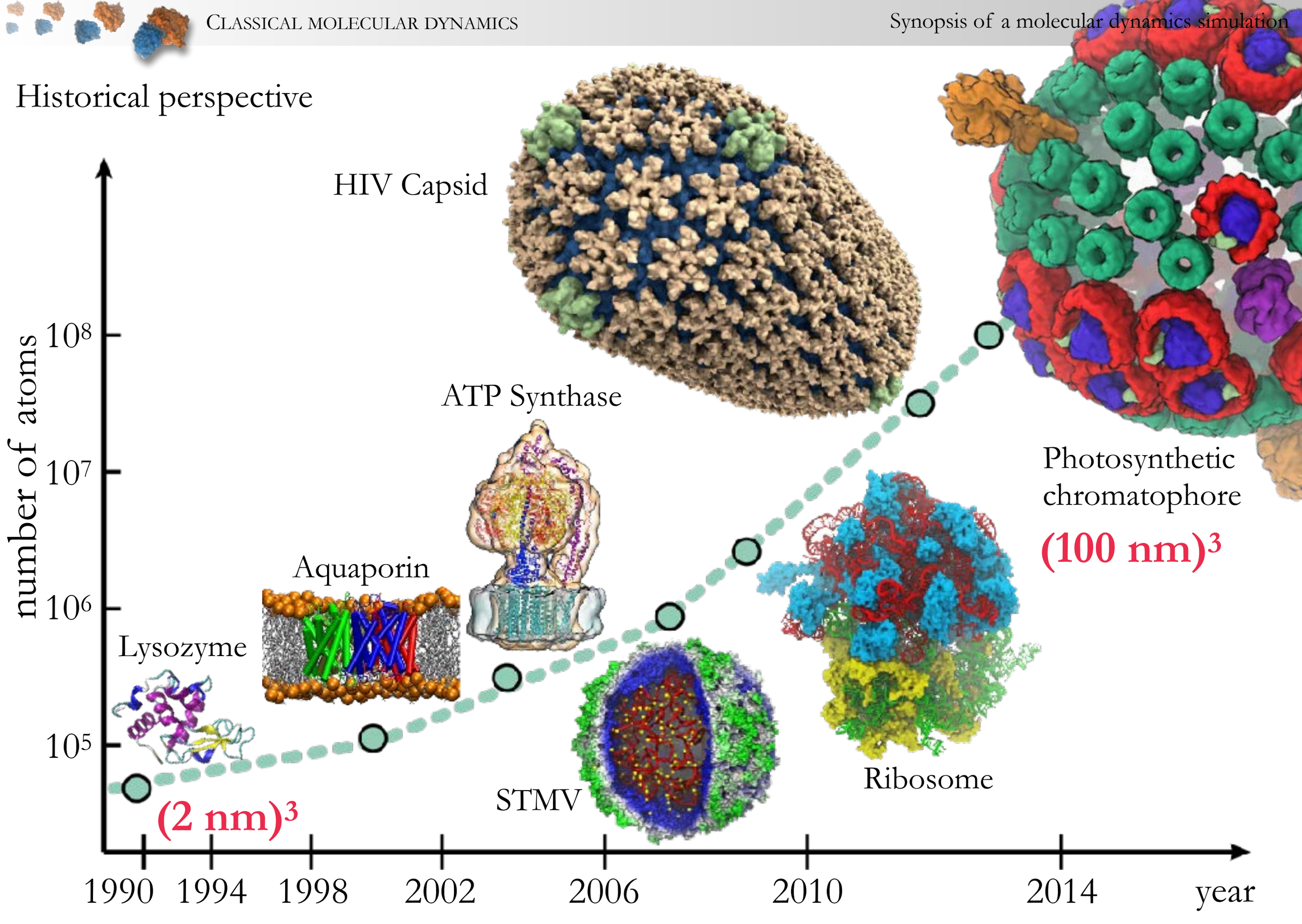
100 million atoms

McCammon, J. A.; Gelin, B. R.; Karplus, M. *Nature* **1977**, *267*, 585-590

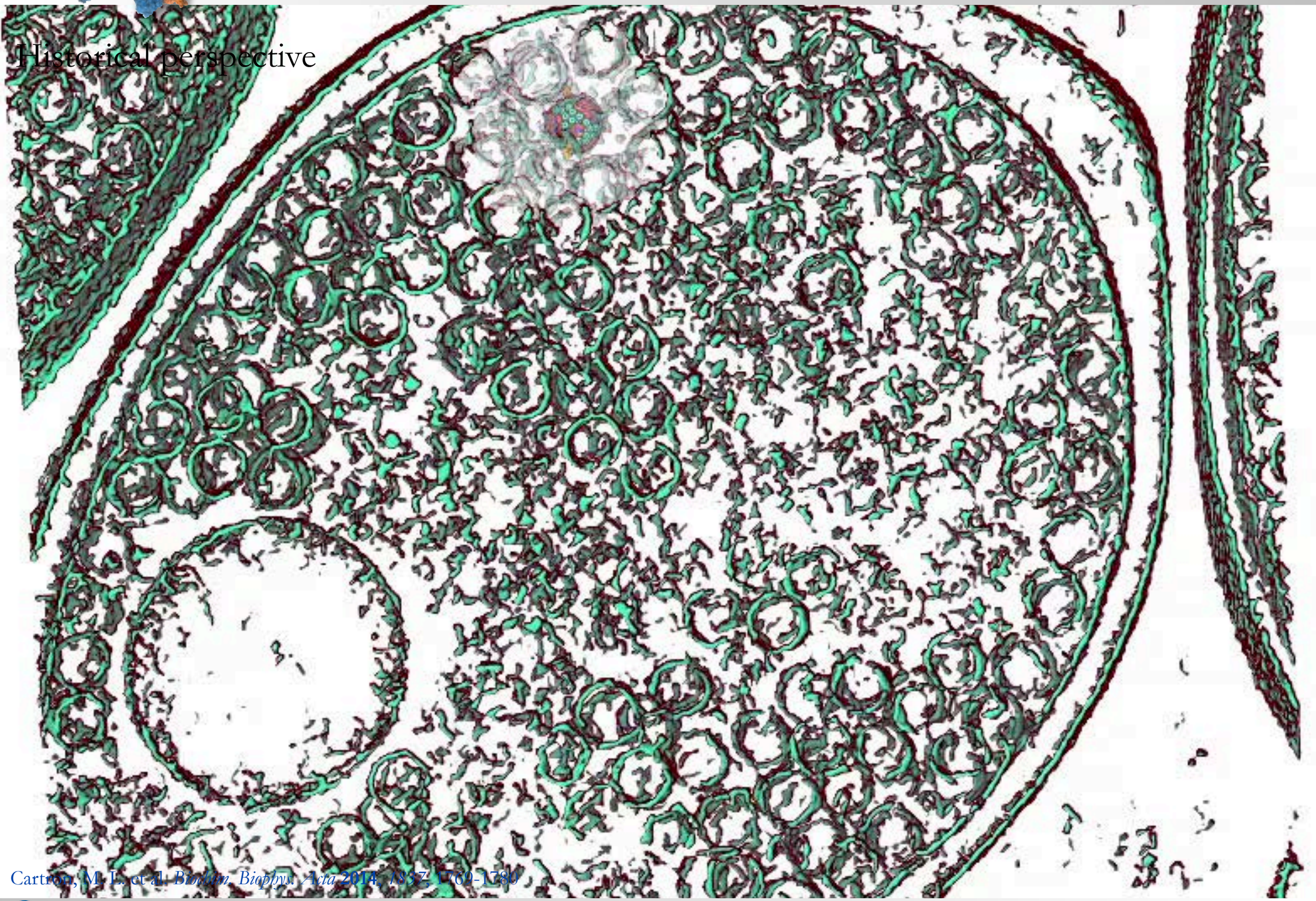
Shaw, D. E.et al. *SIGARCH Comput. Archit. News, ACM* **2007**, *35*, 1-12

Cartron, M. L. et al. *Biochim. Biophys. Acta* **2014**, *1837*, 1769-1780

Historical perspective



Historical perspective



Cartron, M. L. et al. *Biochim. Biophys. Acta* 2014, *1837*: 1769-1780

In its simplest acceptation, molecular dynamics consists in solving the Newton equations of motion, using small time increments.

Choice of the time increment is dictated by the fastest vibration in the molecular assay.

Discretization errors are bounded provided that a symplectic integrator is used.

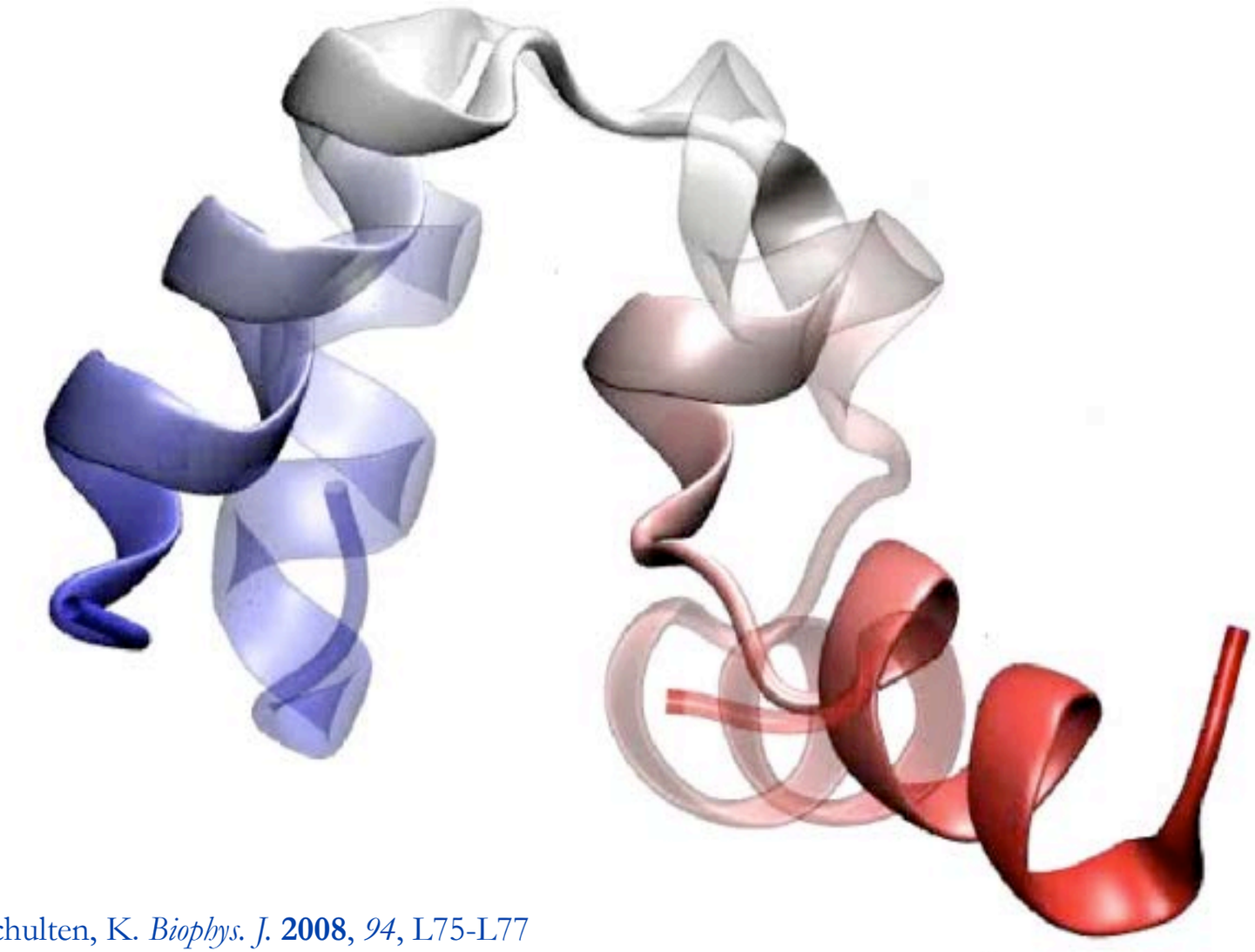
Current molecular dynamics simulations attain the millisecond timescale and the hundred-million-atom size scale.

SYNOPSIS

1. Introduction
2. Periodic boundary conditions
3. Synopsis of a molecular dynamics simulation
4. The potential energy function
5. The propagators of molecular dynamics
6. Restraints versus constraints
7. In which ensemble should the simulation be performed?
8. Lattice sums: The Ewald–Kornfeld approach
9. Molecular dynamics on parallel architectures
10. Guidelines
11. Properties accessible from the trajectories

THE POTENTIAL ENERGY FUNCTION

Modeling a complex reality with a rudimentary toolkit



villin headpiece

Freddolino, P. L.; L., F.; Gruebele, M.; Schulten, K. *Biophys. J.* **2008**, *94*, L75-L77

Freddolino, P. L.; Schulten, K. *Biophys. J.* **2009**, *97*, 2338-2347

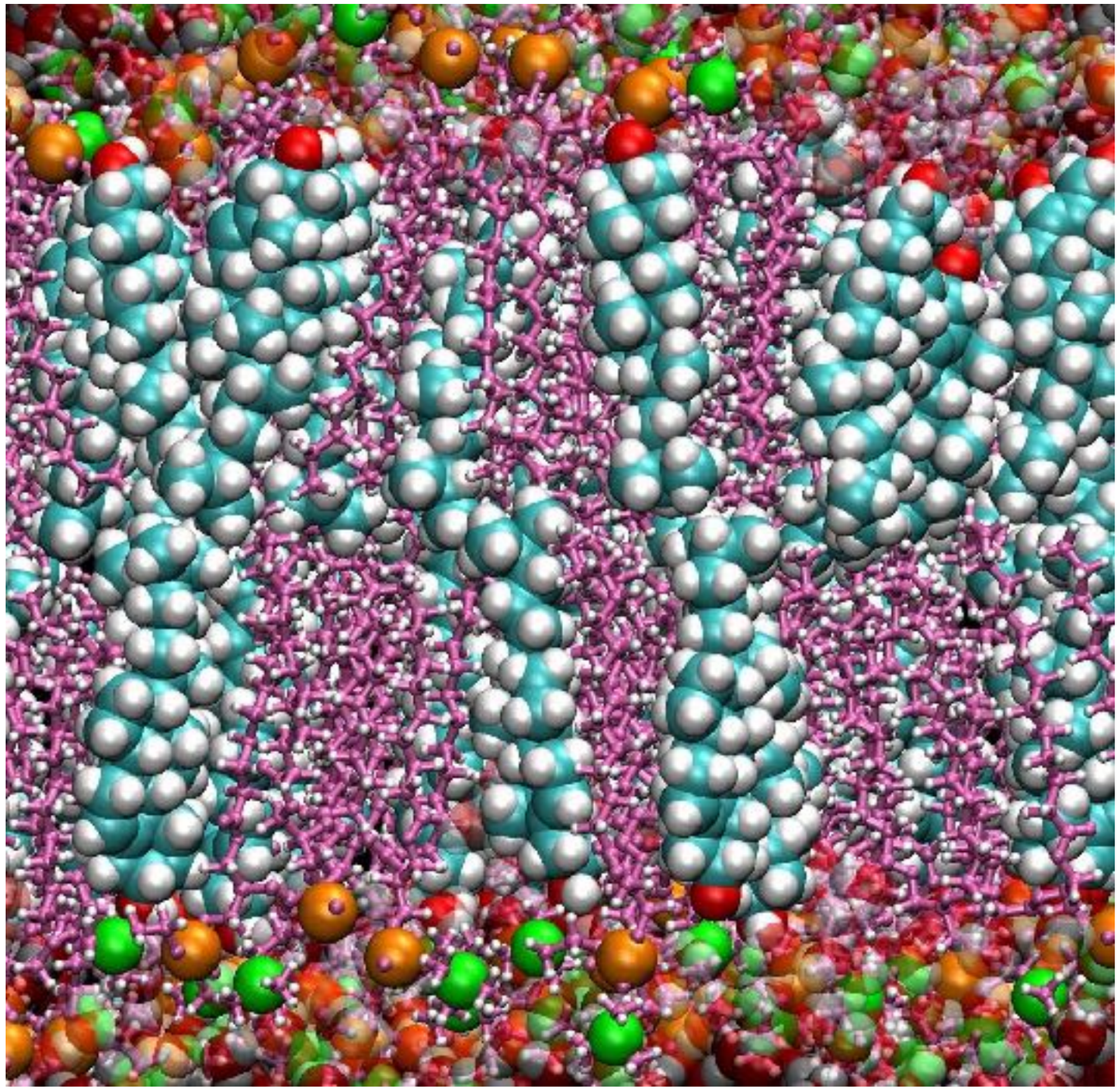
Freddolino, P. L.; Harrison, C. B.; Liu, Y.; Schulten, K. *Nat. Phys.* **2010**, *6*, 751-758

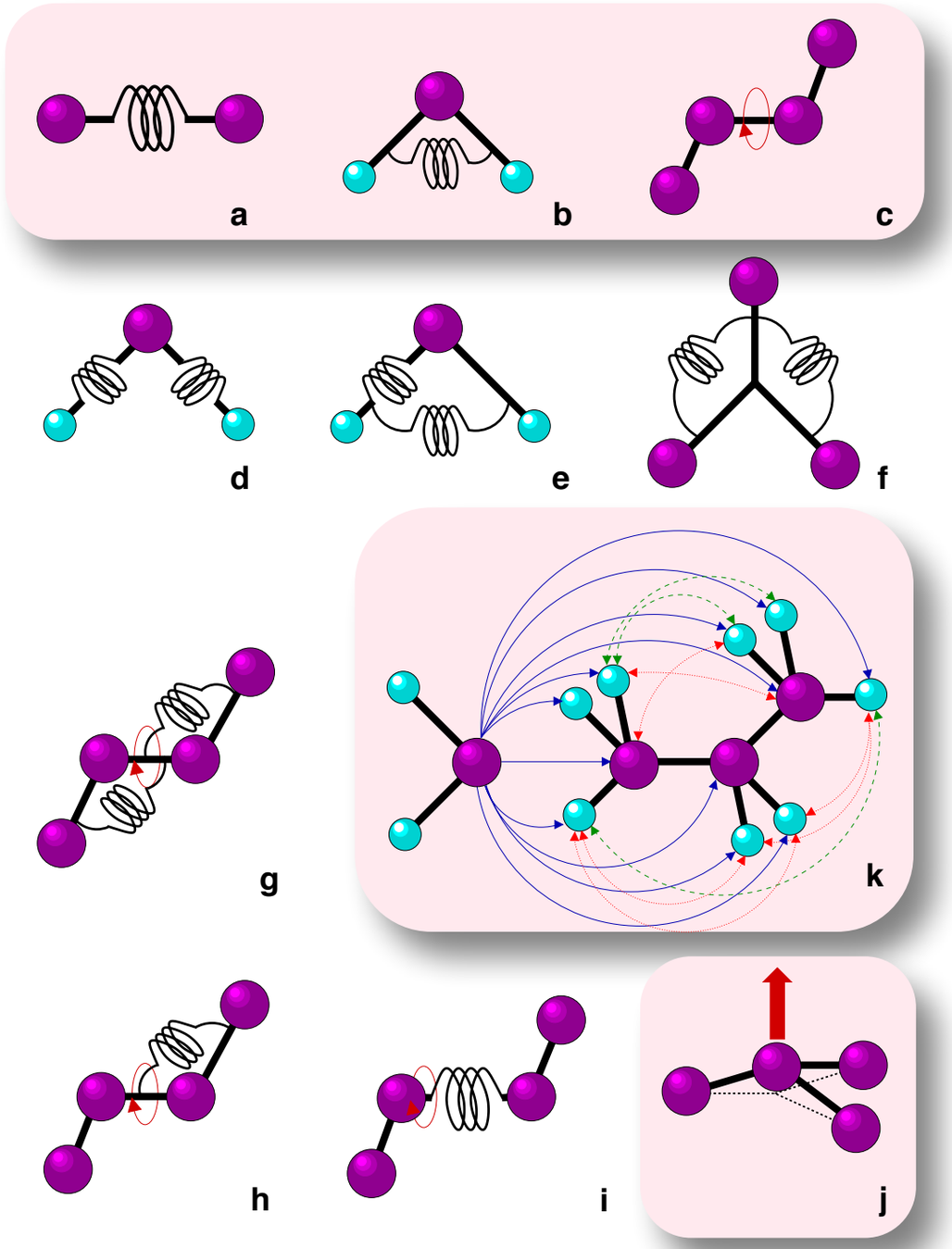
Bowman, G. R.; Voelz, V. A.; Pande, V. S. *J. Am. Chem. Soc.* **2011**, *133*, 664-667

Lindorff-Larsen, K.; Piana, S.; Dror, R. O.; Shaw, D. E. *Science* **2011**, *334*, 517-520

THE POTENTIAL ENERGY FUNCTION

Modeling a complex reality with a rudimentary toolkit





Case example of the macromolecular AMBER force field,

$$\mathscr{V}(\mathbf{x}) = \sum_{\text{bonds}} k_r\ (r - r_0)^2 + \sum_{\text{valence angles}} k_\theta\ (\theta - \theta_0)^2$$

$$+ \sum_{\text{torsions}} \frac{V_n}{2}\ [1 + \cos(n\phi - \gamma)]$$

$$+ \frac{1}{k^{1\text{-}4}_{\text{vdW}}} \sum_{\substack{i<j \\ \{i,j\}\in 1\text{-}4}} \varepsilon_{ij} \left[\left(\frac{R^*_{ij}}{r_{ij}} \right)^{12} - 2 \left(\frac{R^*_{ij}}{r_{ij}} \right)^{6} \right] + \frac{1}{k^{1\text{-}4}_{\text{Coulomb}}} \sum_{\substack{i<j \\ \{i,j\}\in 1\text{-}4}} \frac{q_i q_j}{4\pi\epsilon_0\epsilon_1 r_{ij}}$$

$$+ \sum_{\substack{i<j \\ \{i,j\}>1\text{-}4}} \varepsilon_{ij} \left[\left(\frac{R^*_{ij}}{r_{ij}} \right)^{12} - 2 \left(\frac{R^*_{ij}}{r_{ij}} \right)^{6} \right] + \sum_{\substack{i<j \\ \{i,j\}>1\text{-}4}} \frac{q_i q_j}{4\pi\epsilon_0\epsilon_1 r_{ij}}$$

Other macromolecular force fields — CHARMM, MM3, OPLS.

Cornell, W. D. et al. *J. Am. Chem. Soc.*, **1995**, *117*, 5179-5197

MacKerell Jr., A. D. et al. *J. Phys. Chem. B* **1998**, *102*, 3586-3616

Lii, J. H.; Allinger, N. L. *J. Comput. Chem.* **1991**, *12*, 186-199

Kaminski, G. A.; Friesner, R. A.; Tirado-Rives, J.; Jorgensen, W. L. *J. Phys. Chem. B* **2001**, *105*, 6474-6487

Parametrization of a concise set of chemically unique atoms;

Underlying hypothesis: The parameters describing a given atom are essentially local, and may, therefore, be ported to different chemical environments.

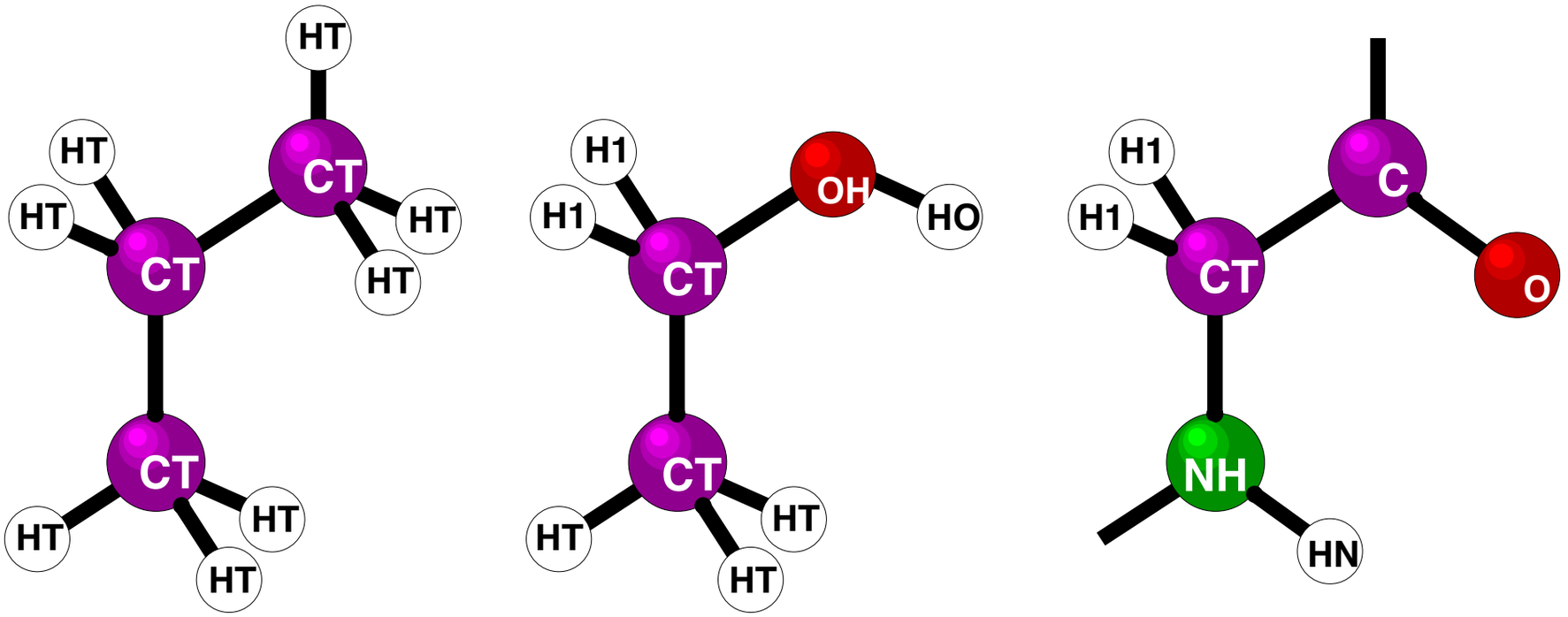
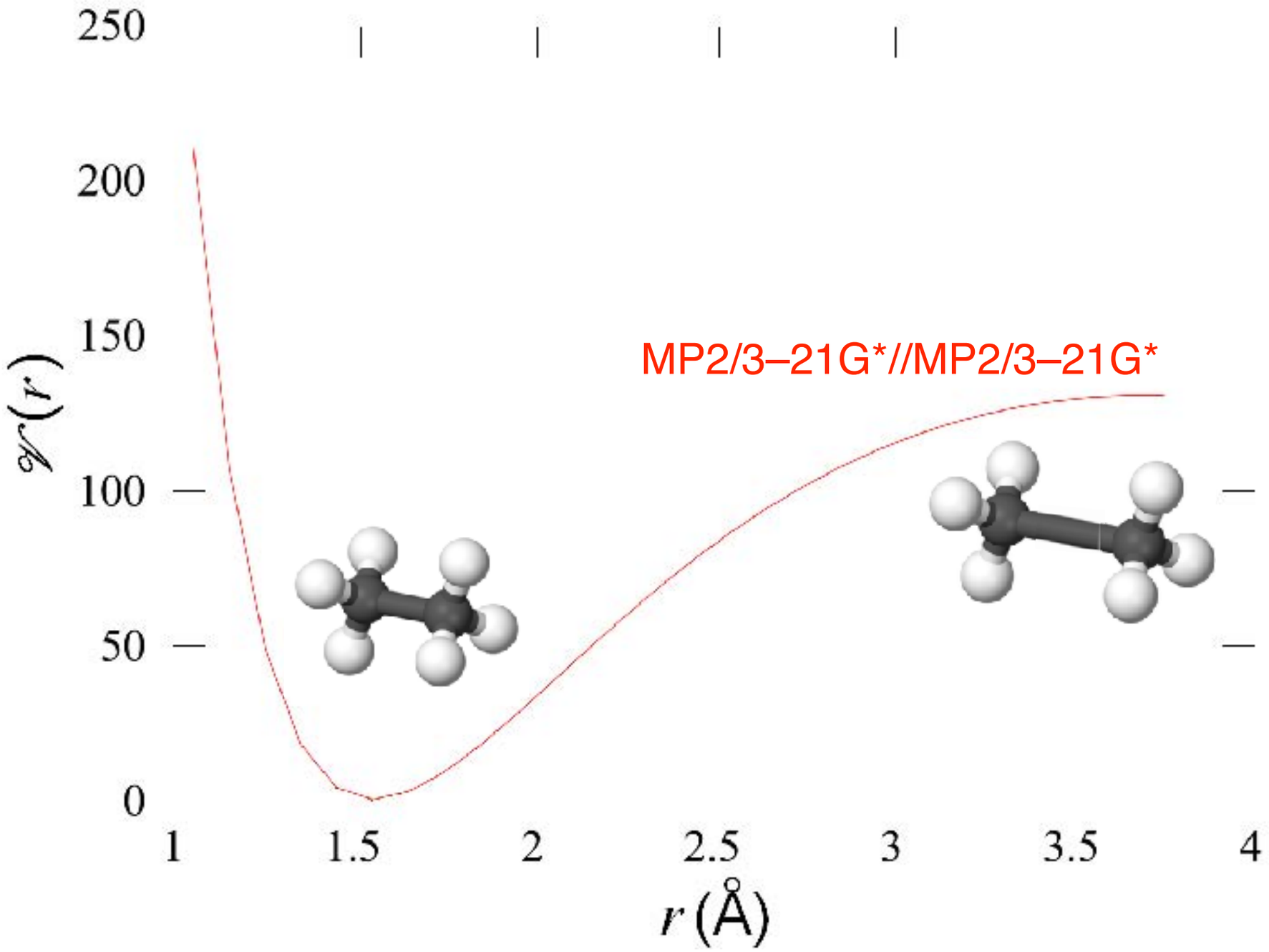


Table 1. List of Atom Types[a]

atom	type	description
carbon	CT	any sp^3 carbon
	C	any carbonyl sp^2 carbon
	CA	any aromatic sp^2 carbon and (Cϵ of Arg)
	CM	any sp^2 carbon, double bonded
	CC	sp^2 aromatic in 5-membered ring with one substituent + next to nitrogen (Cγ in His)
	CV	sp^2 aromatic in 5-membered ring next to carbon and lone pair nitrogen (e.g. Cδ in His (δ))
	CW	sp^2 aromatic in 5-membered ring next to carbon and NH (e.g. Cδ in His (ϵ) and in Trp)
	CR	sp^2 aromatic in 5-membered ring next to two nitrogens (Cγ and Cϵ in His)
	CB	sp^2 aromatic at junction of 5- and 6-membered rings (Cδ in Trp) and both junction atoms in Ade and Gua
	C*	sp^2 aromatic in 5-membered ring next to two carbons (e.g. Cγ in Trp)
	CN	sp^2 junction between 5- and 6-membered rings and bonded to CH and NH (Cϵ in Trp)
	CK	sp^2 carbon in 5-membered aromatic between N and N-R (C8 in purines)
	CQ	sp^2 carbon in 6-membered ring between lone pair nitrogens (e.g. C2 in purines)
nitrogen	N	sp^2 nitrogen in amides
	NA	sp^2 nitrogen in aromatic rings with hydrogen attached (e.g. protonated His, Gua, Trp)
	NB	sp^2 nitrogen in 5-membered ring with lone pair (e.g. N7 in purines)
	NC	sp^2 nitrogen in 6-membered ring with lone pair (e.g. N3 in purines)
	N*	sp^2 nitrogen in 5-membered ring with carbon substituent (in purine nucleosides)
	N2	sp^2 nitrogen of aromatic amines and guanidinium ions
	N3	sp^3 nitrogen
oxygen	OW	sp^3 oxygen in TIP3P water
	OH	sp^3 oxygen in alcohols, tyrosine, and protonated carboxylic acids
	OS	sp^3 oxygen in ethers
	O	sp^2 oxygen in amides
	O2	sp^2 oxygen in anionic acids
sulfur	S	sulfur in methionine and cysteine
	SH	sulfur in cysteine
phosphorus	P	phosphorus in phosphates
hydrogen	H	H attached to N
	HW	H in TIP3P water
	HO	H in alcohols and acids
	HS	H attached to sulfur
	HA	H attached to aromatic carbon
	HC	H attached to aliphatic carbon with no electron-withdrawing substituents
	H1	H attached to aliphatic carbon with one electron-withdrawing substituent
	H2	H attached to aliphatic carbon with two electron-withdrawing substituents
	H3	H attached to aliphatic carbon with three electron-withdrawing substituents
	HP	H attached to carbon directly bonded to formally positive atoms (e.g. C next to NH_3^+ of lysine)
	H4	H attached to aromatic carbon with one electronegative neighbor (e.g. hydrogen on C5 of Trp, C6 of Thy)
	H5	H attached to aromatic carbon with two electronegative neighbors (e.g. H8 of Ade and Gua and H2 of Ade)

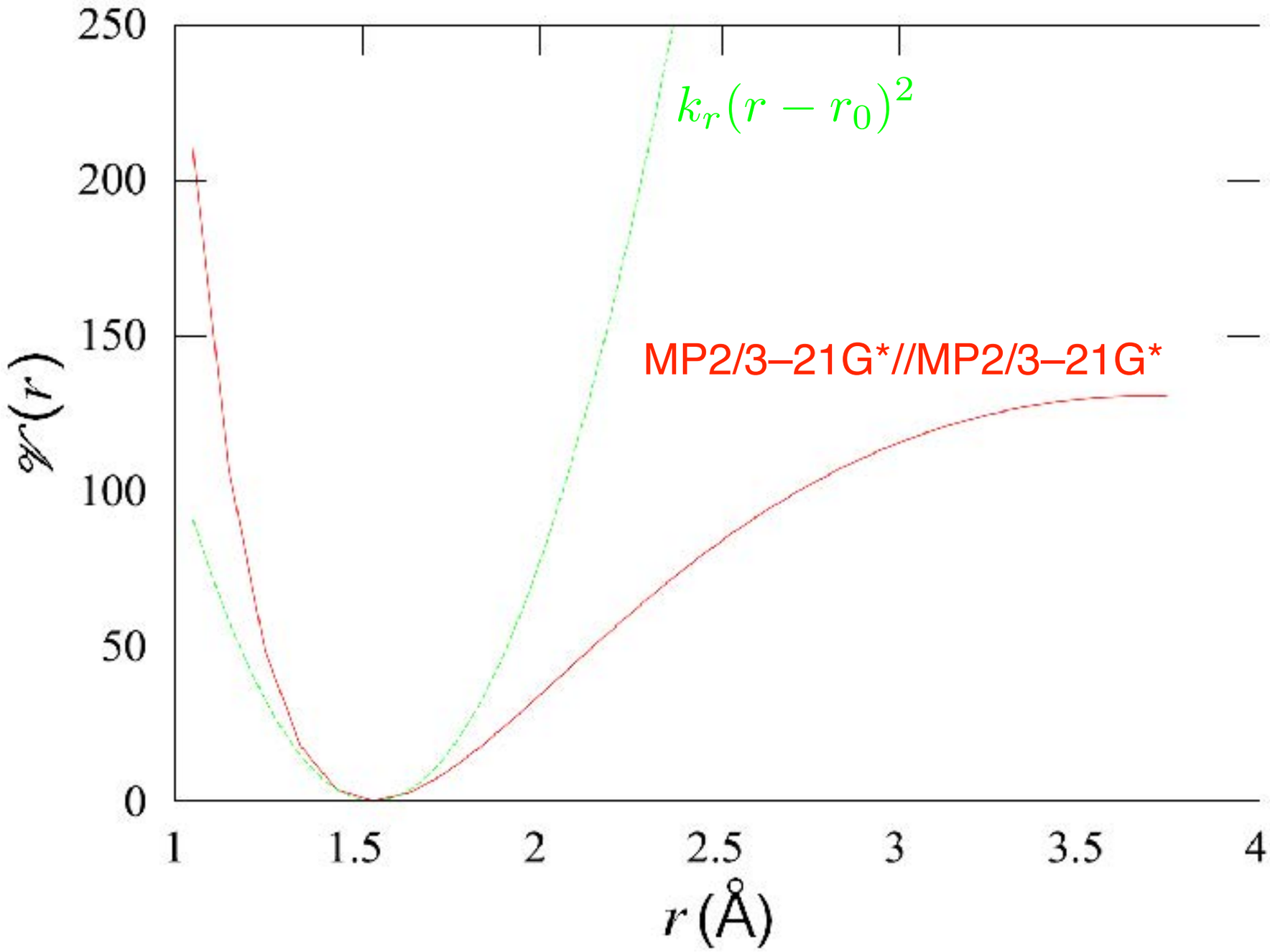
Cornell, W. D. et al. *J. Am. Chem. Soc.*, **1995**, *117*, 5179-5197

Bond-stretching potential



Leach, A. R. *Molecular modeling*. Longman, **1996**

Bond-stretching potential



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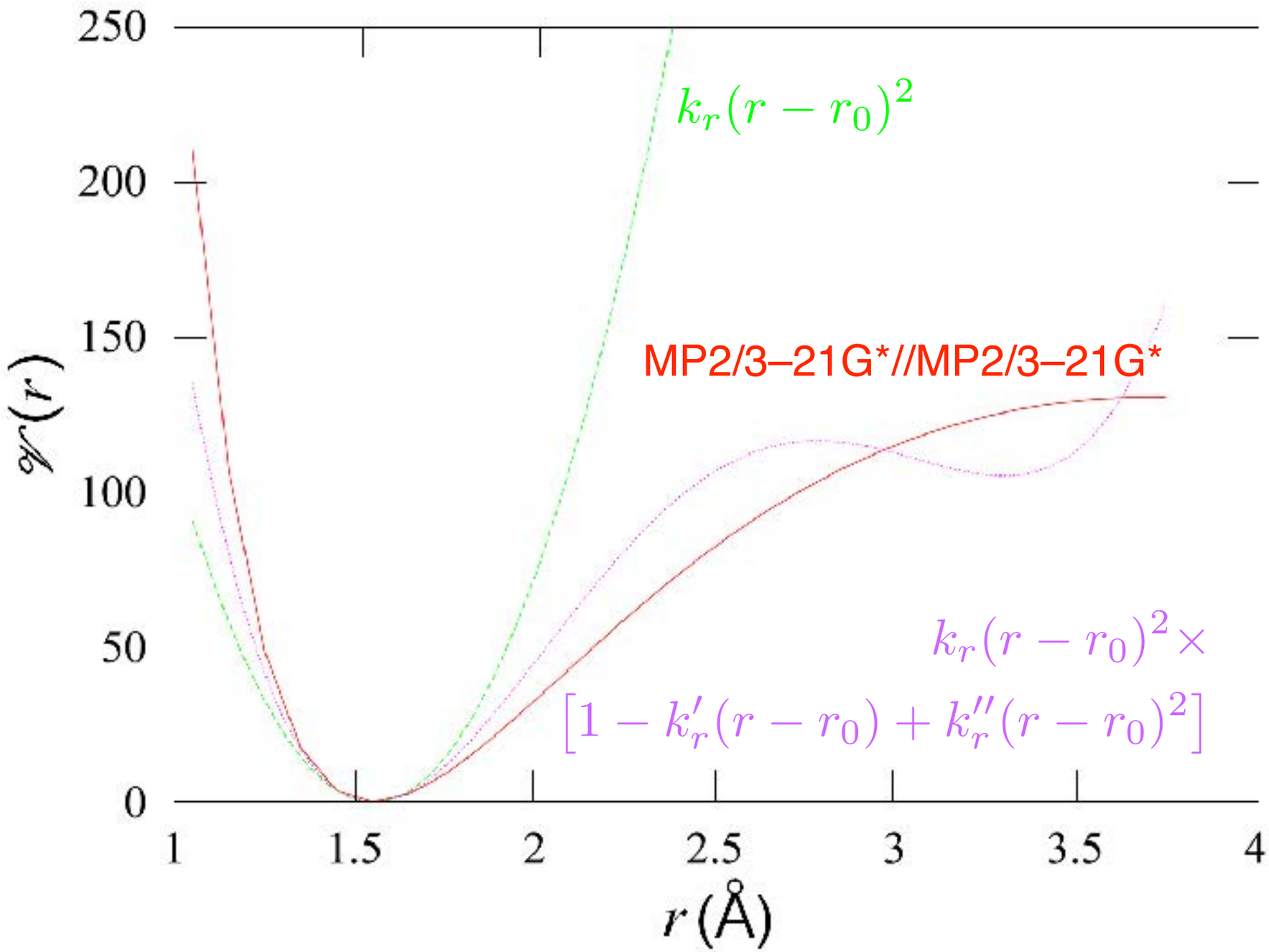
Bond-stretching potential



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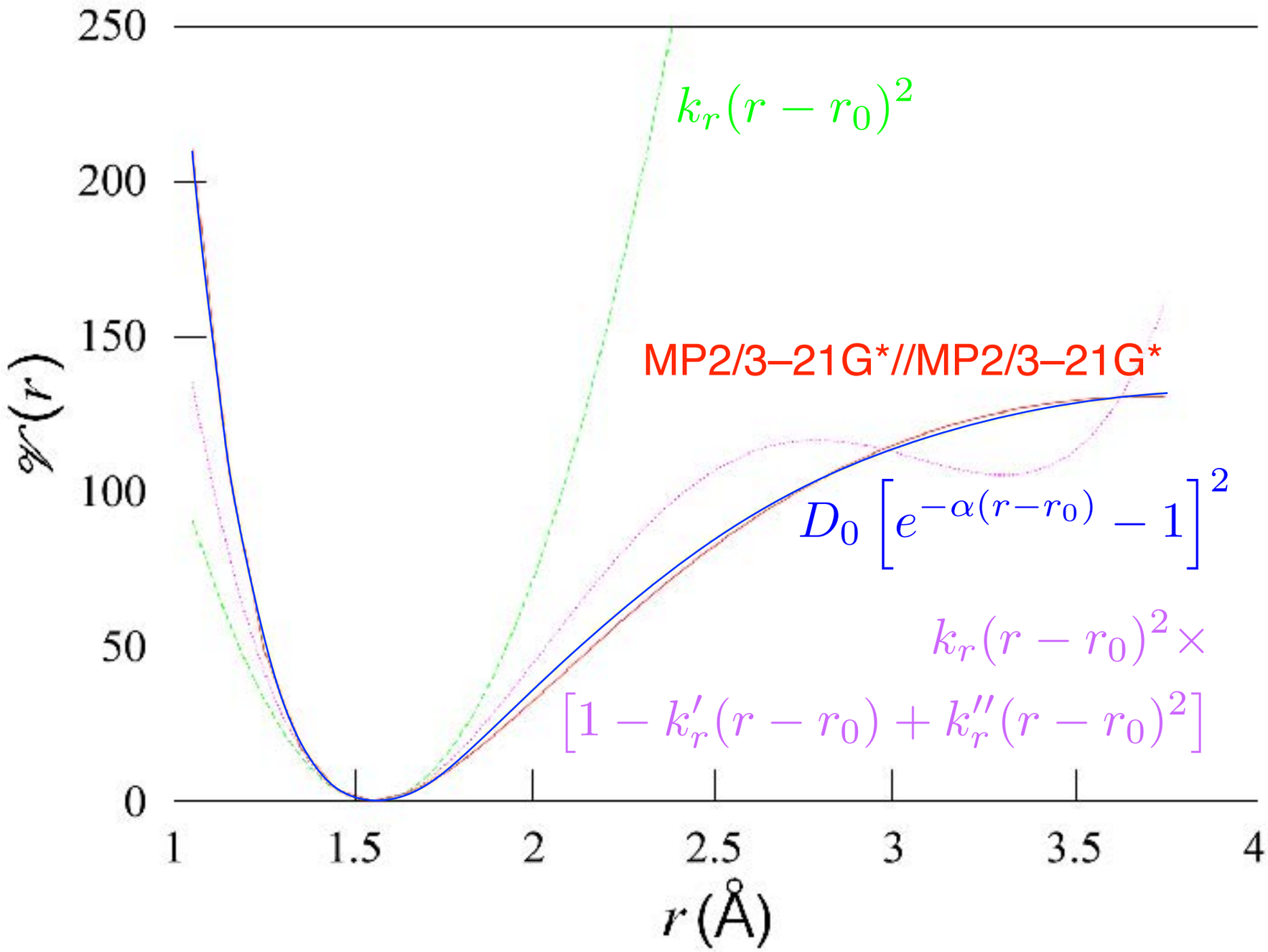
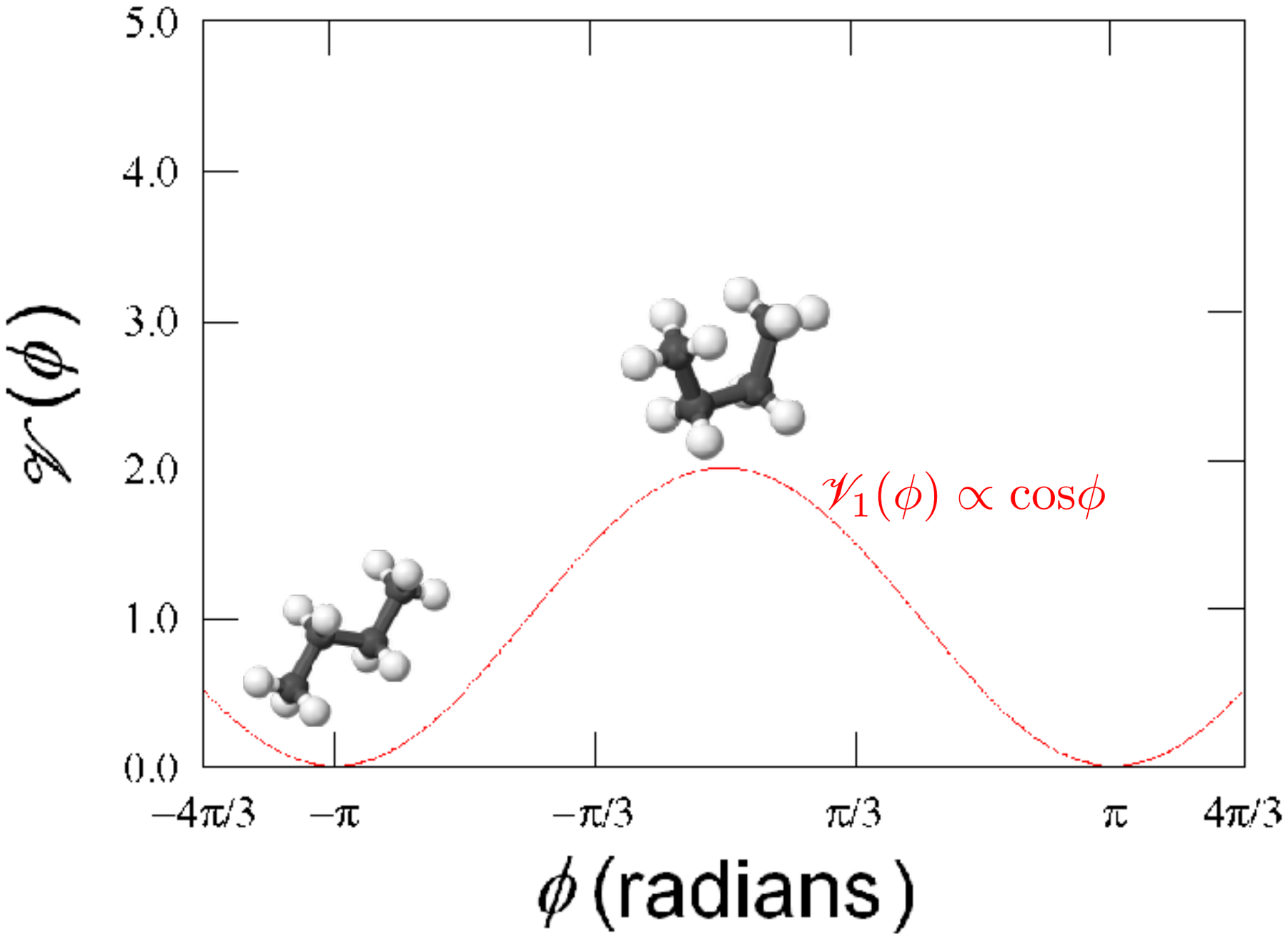


Leach, A. R. *Molecular modeling*. Longman, **1996**

Torsional potential — description of a complex potential requires several terms,



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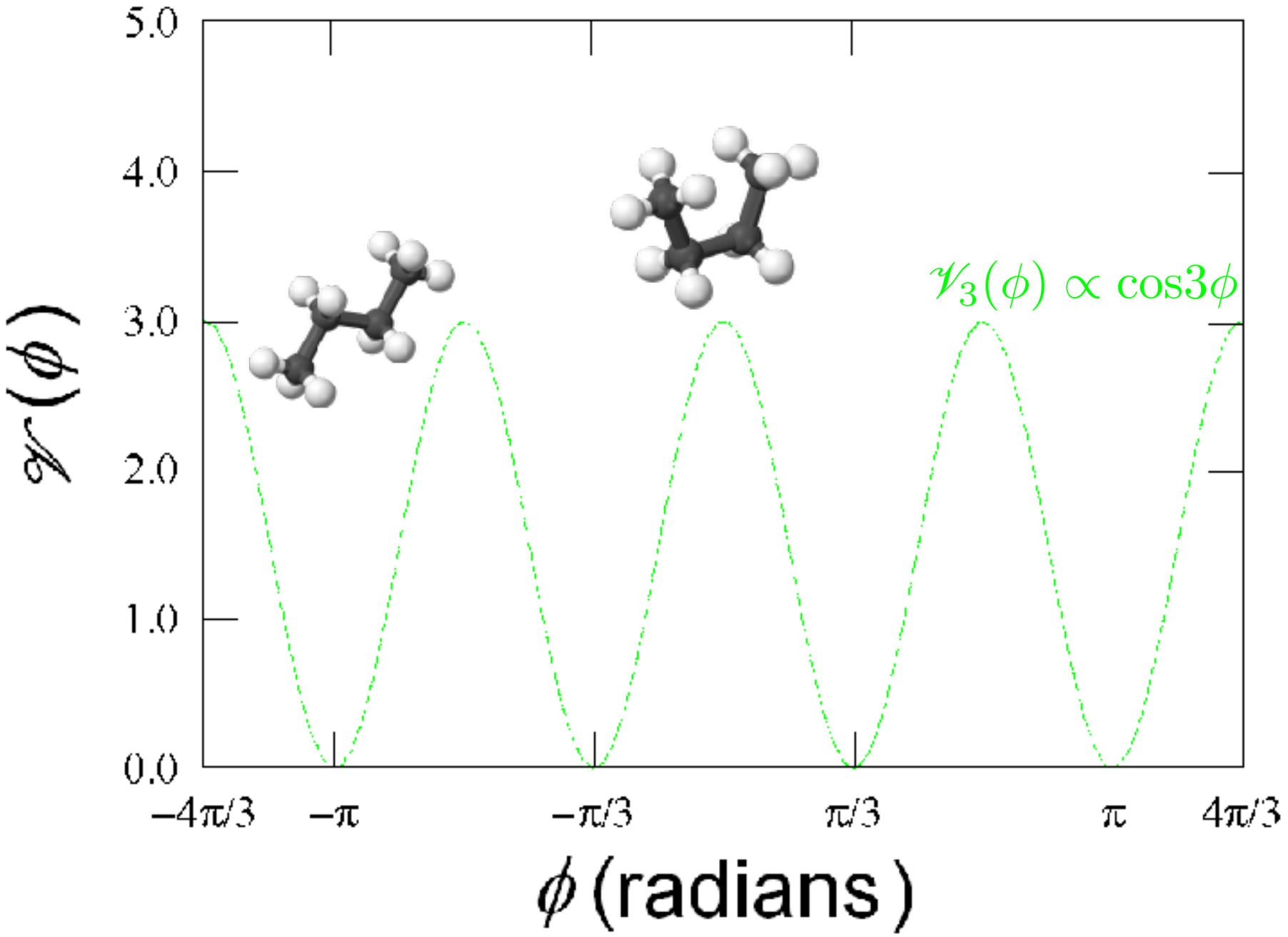
Torsional potential — description of a complex potential requires several terms,



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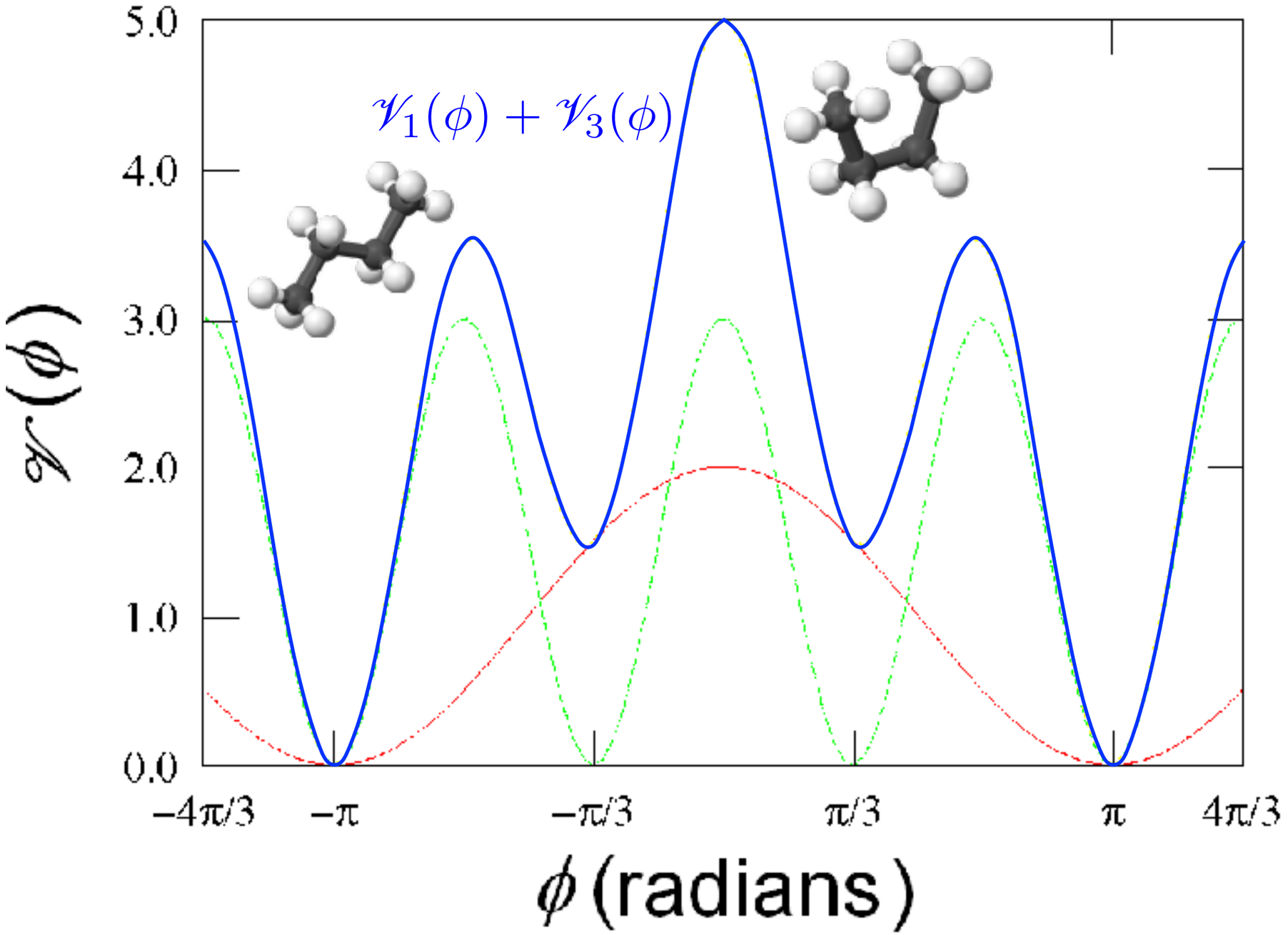
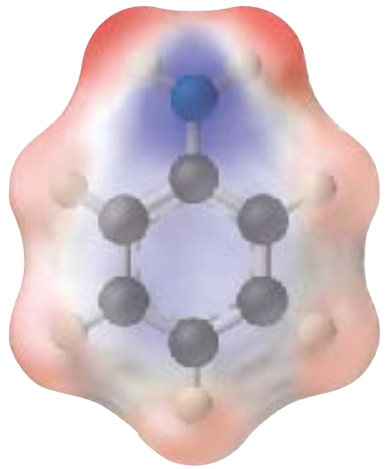
Torsional potential — description of a complex potential requires several terms,



Modeling the electrostatic contribution

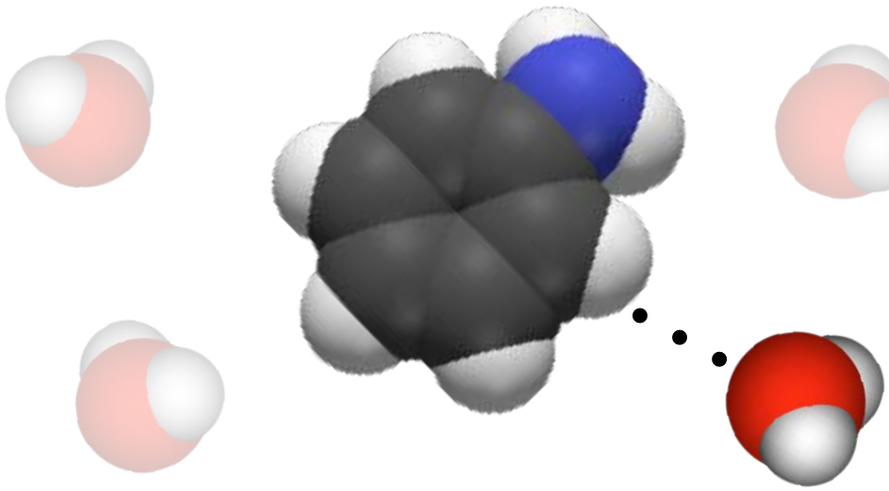


Two distinct philosophies:

AMBER: The electrostatic potential is the *fingerprint* of the molecule

$$V^{\text{reference}}(\mathbf{r}_k) = \sum_A \frac{Z_A}{|\mathbf{r}_k - \mathbf{R}_A|} - \sum_i^{\text{occ.}} \sum_\mu \sum_\nu c^*_{\mu i}\, c_{\nu i} \left\langle \phi_\mu \left| \frac{1}{|\mathbf{r}_k - \mathbf{r}|} \right| \phi_\nu \right\rangle$$

CHARMM: The electrostatic term is parameterized from intermolecular interactions

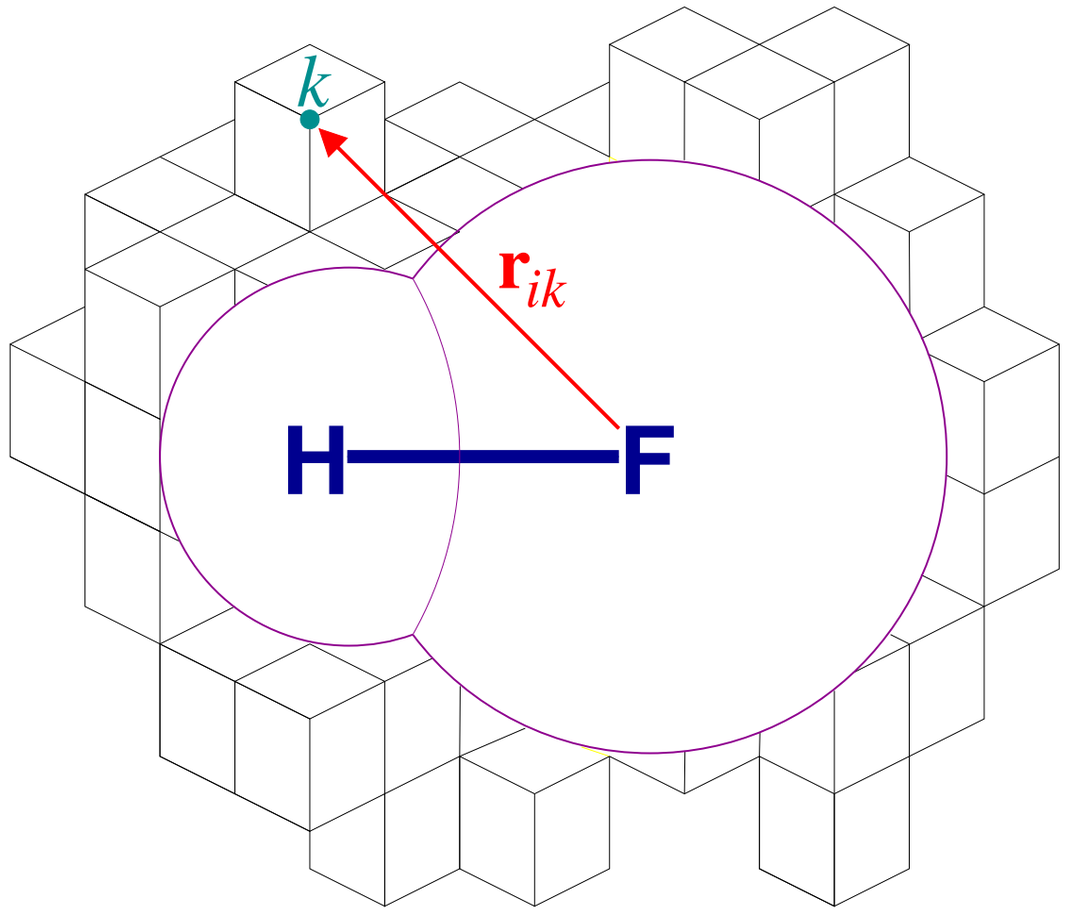


$$E^{\text{QM}}_{\text{interaction}} = E^{\text{QM}}_{\text{molecule:water}} - E^{\text{QM}}_{\text{molecule}} - E^{\text{QM}}_{\text{water}}$$

Cornell, W. D. et al. *J. Am. Chem. Soc.*, **1995**, *117*, 5179-5197

MacKerell Jr., A. D. et al. *J. Phys. Chem. B* **1998**, *102*, 3586-3616

Charges derived from the molecular electrostatic potential,



$$f(\{q_k\}) = \sum_{i=1}^{N_{\text{points}}} \left[V^{\text{reference}}(\mathbf{r}_i) - \sum_{j=1}^{N_{\text{atoms}}} \frac{q_j}{r_{ij}} \right]^2$$

Cox, S. R.; Williams, D. E. *J. Comput. Chem.* **1981**, *2*, 304-323

Cornell, W. D.; Chipot, C. in Schleyer, P. v. R. et al. Eds. *Encyclopedia of computational chemistry*, Wiley and Sons, Chichester, **1998**, *1*, 258-263.

Beyond the simple and limited monopole approximation,

$$g(\{q_k\},\{\boldsymbol{\mu_{k'}}\}) = \sum_{i=1}^{N_{\text{points}}} \left[V^{\text{reference}}(\mathbf{r}_i) - \left(\sum_j \frac{q_j}{r_{ij}} - \sum_{j'} \frac{\boldsymbol{\mu}_{j'} \cdot \mathbf{r}_{ij'}}{r_{ij'}^3} \right) \right]^2 = \min$$

Including intramolecular induction effects,

$$h(\{q_k\}) = \sum_{k=1}^{N_{\text{conformations}}} w_k \sum_{i=1}^{N_{\text{points}}} \left(V_k^{\text{reference}}(\mathbf{r}_i) - \sum_j \frac{q_j}{r_{ij}} \right)^2 = \min$$

Including intermolecular induction effects,

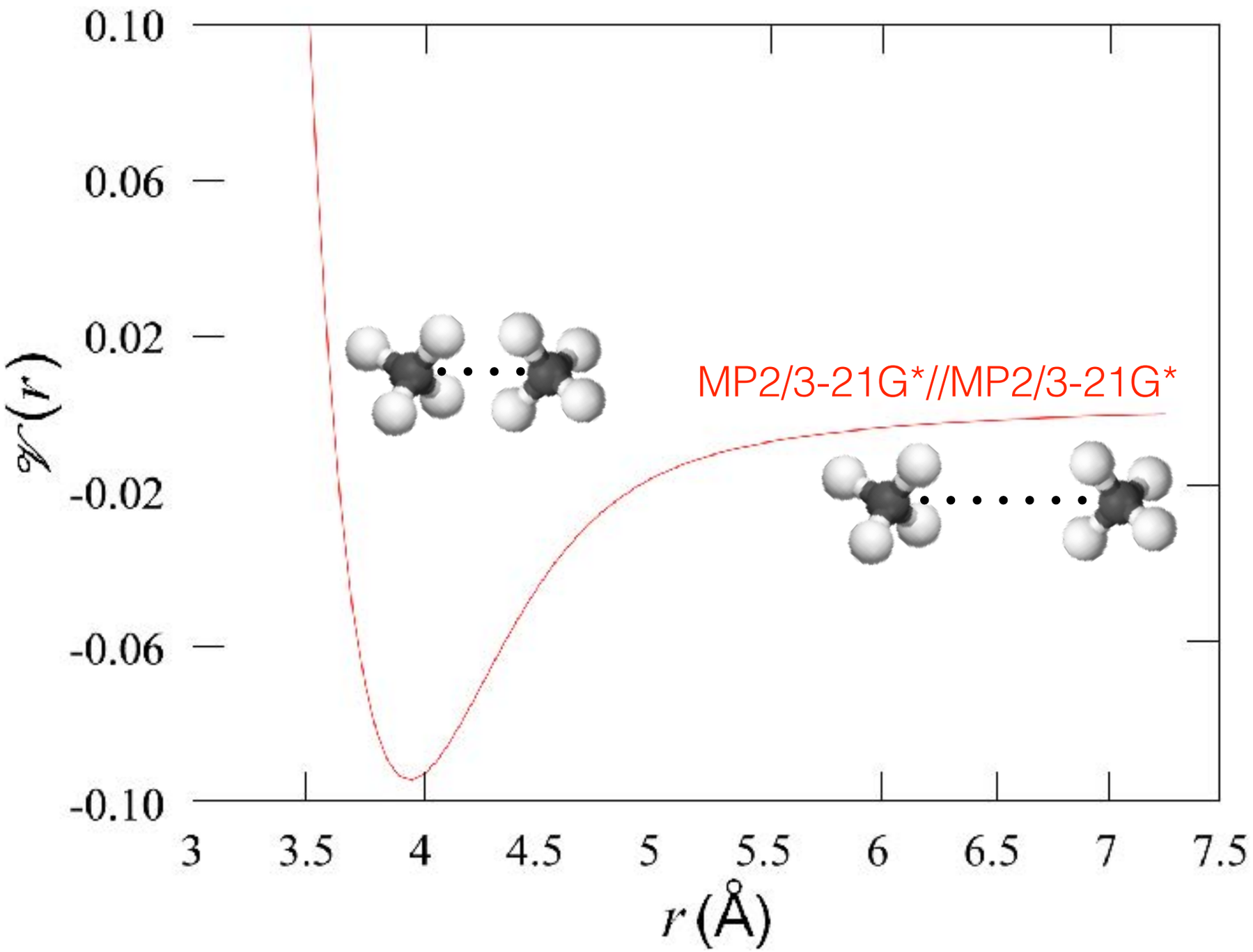
$$\mathscr{H} = \mathscr{H}^0 - \sum_{\ell m} \sum_{\ell' m'} Q_{\ell m} \; f_{\ell\ell'}^{mm'} \; \langle \Psi \, | Q_{\ell' m'} | \, \Psi \rangle$$

Chipot, C.; Ángyán, J. G. *New J. Chem.* **2005**, *29*, 411-420

Reynolds, C. A.; Essex, J. W.; Richards, W. G. *J. Am. Chem. Soc.* **1992**, *114*, 9075-9079

Chipot, C. *J. Comput. Chem.* **2003**, *24*, 409-415

Modeling van der Waals interactions



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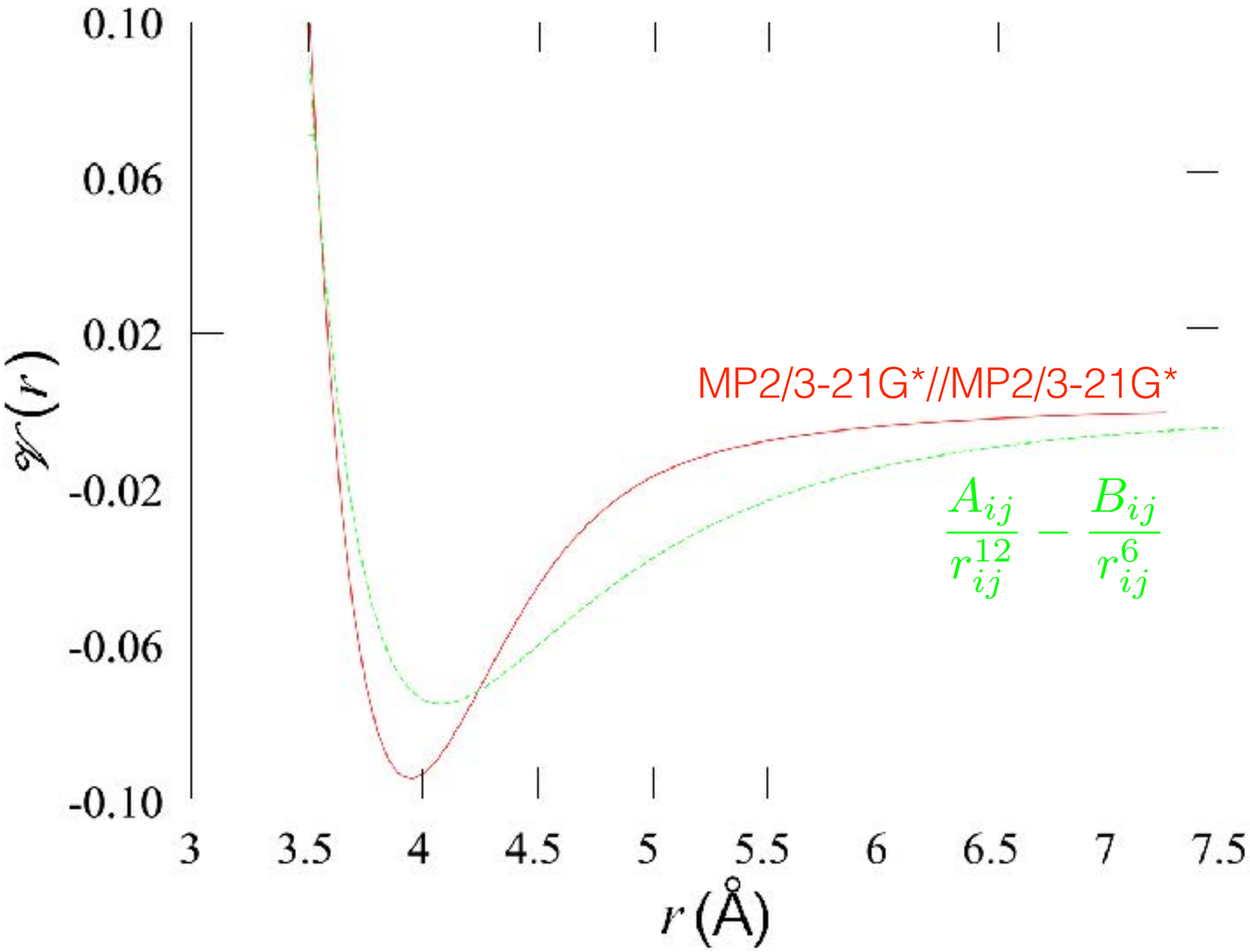
Modeling van der Waals interactions



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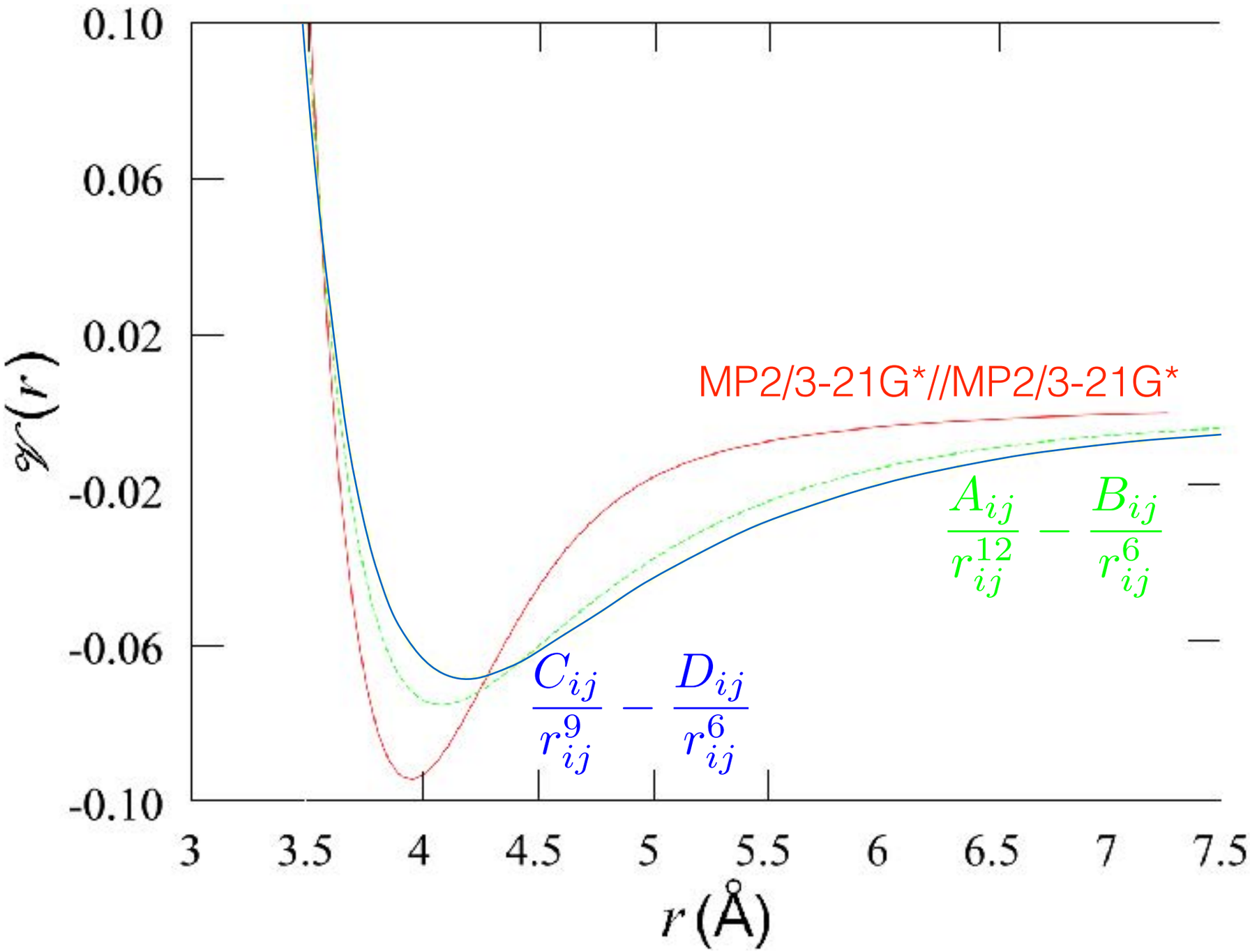
Modeling van der Waals interactions



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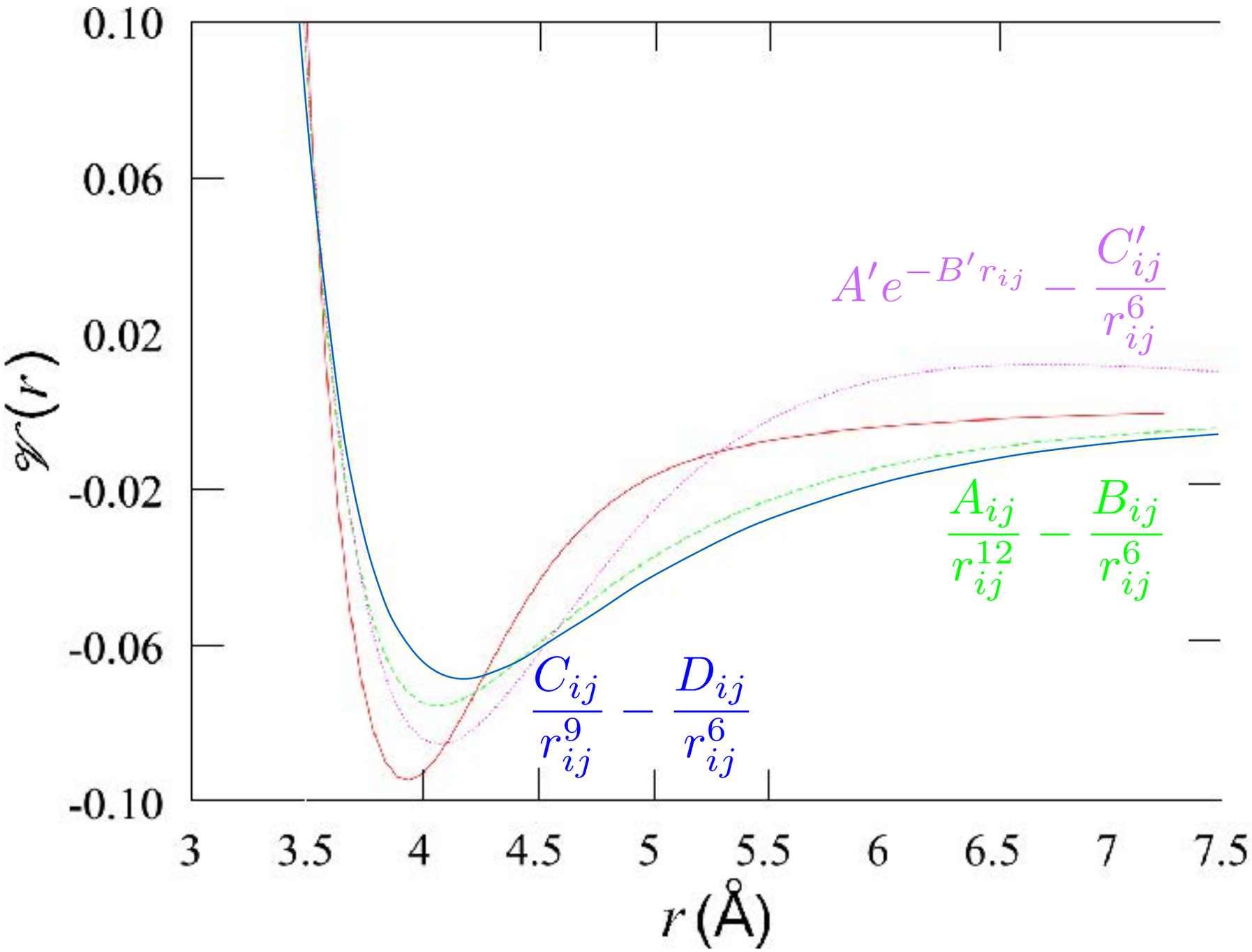
Modeling van der Waals interactions



Leach, A. R. *Molecular modeling*. Longman, **1996**

SUMMARY

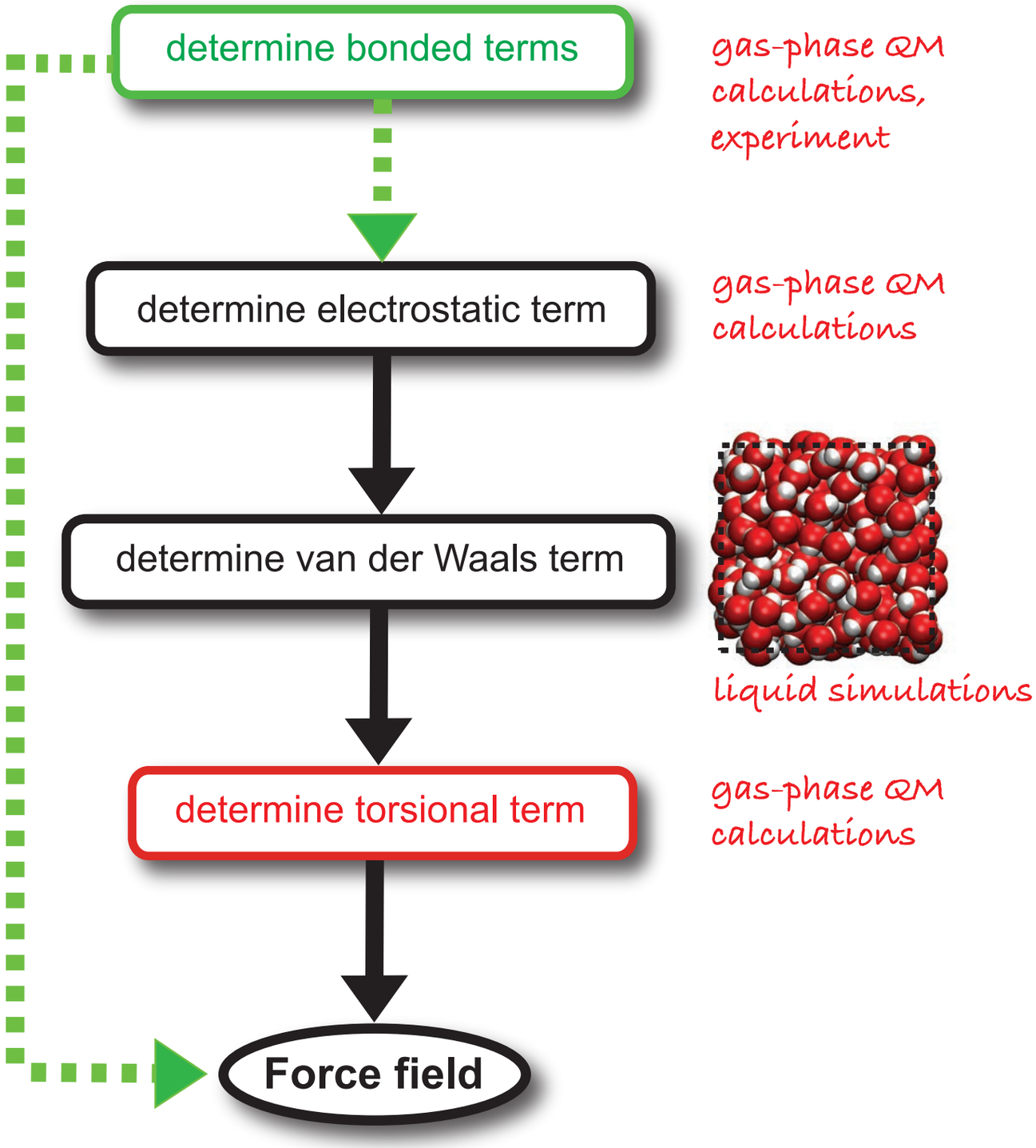
Transferability of parameters constitutes one of the key assumptions of macromolecular force fields.

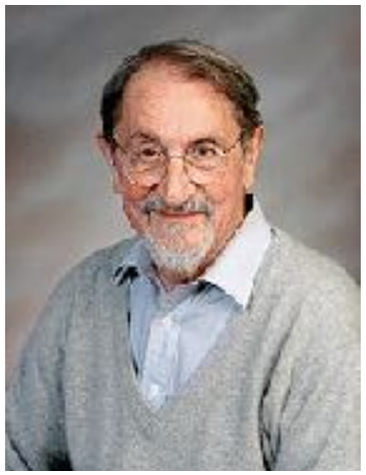
The underlying idea of macromolecular force fields is a minimalist description of complex chemical objects, based on a limited number of terms — often ad hoc.

Parametrization of different macromolecular force fields rely on distinct philosophies.

Parameters are not interchangeable between different potential energy functions.

Synopsis of a force-field parametrization

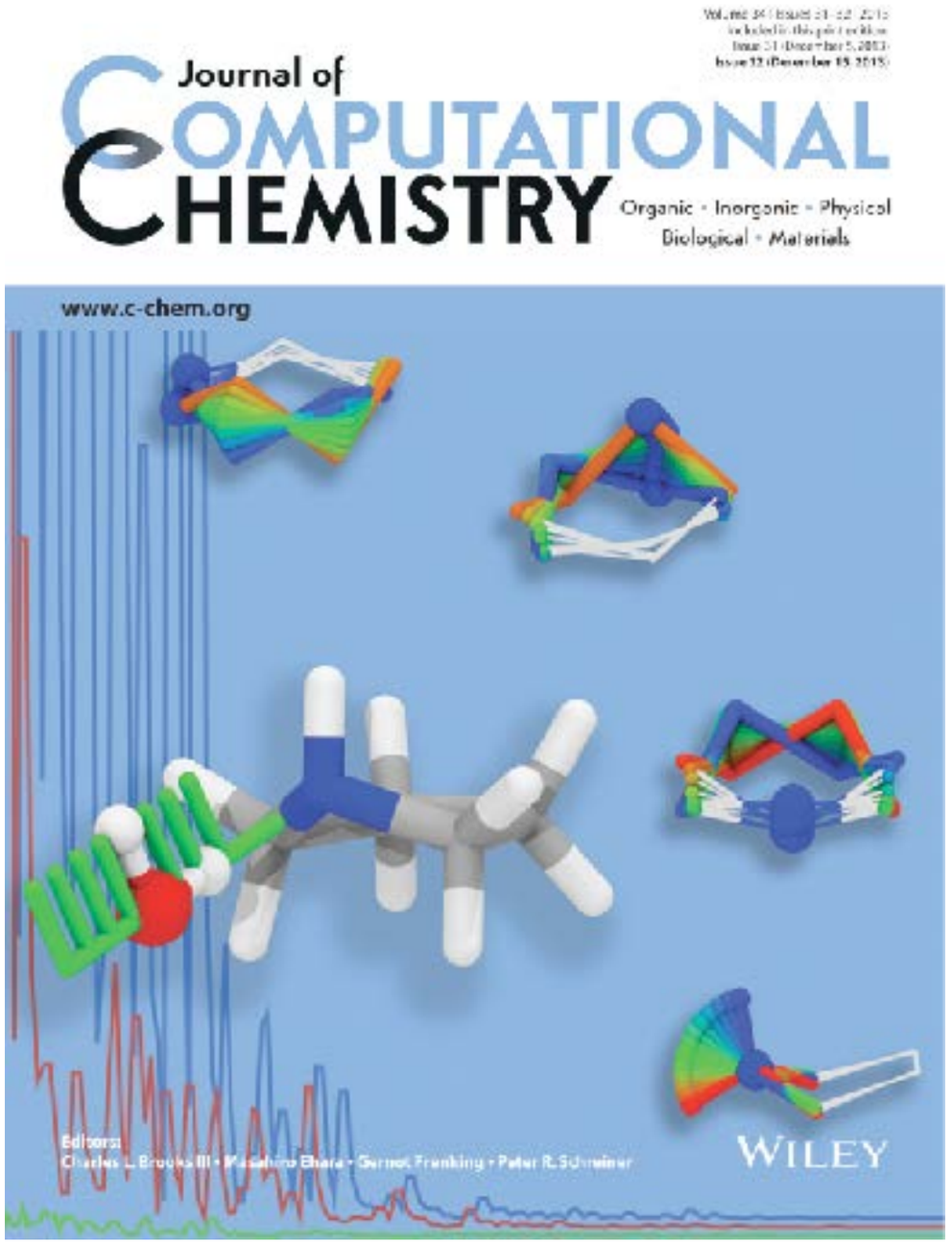




MacKerell Jr., A. D. et al. *J. Phys. Chem. B* **1998**, *102*, 3586-3616

If parameters are missing from the force field

Option 1. Parametrize the missing terms following the philosophy of the force field

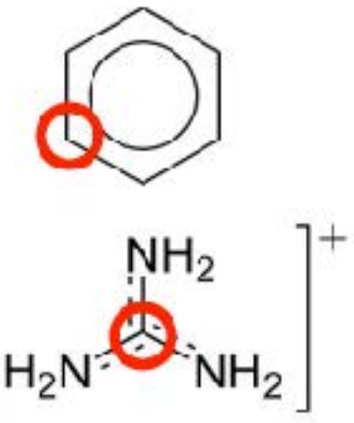


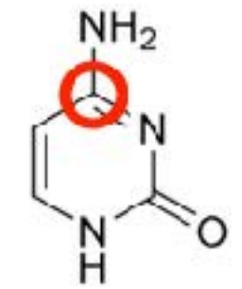
Mayne, C. G.; Saam, J.; Schulten, K.; Tajkhorshid, E.; Gumbart, J. C. *J. Comput. Chem.* **2013**, *34*, 2757-2770

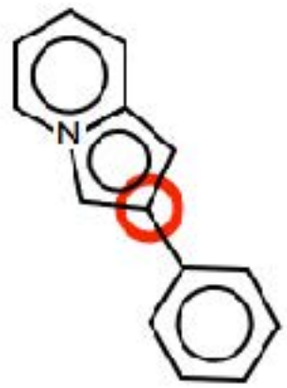
If parameters are missing from the force field

Option 2. Turn to a more comprehensive force field, e.g., OPLS

```
CA (len= 4):    (3.5500,0.0700) n= 571
                (3.5500,0.0500) n=   3
                (3.5000,0.0800) n=   7
                (3.5500,0.0760) n=  14
```







Jorgensen, W. L.; Tirado-Rives, J. *J. Am. Chem. Soc.* **1988**, *110*, 1657-1666

Kaminski, G. A.; Friesner, R. A.; Tirado-Rives, J.; Jorgensen, W. L. *J. Phys. Chem. B* **2001**, *105*, 6474-6487

If parameters are missing from the force field

Option 3. Resort to servers relying upon ad-hoc inferences and educated guesses of missing parameters

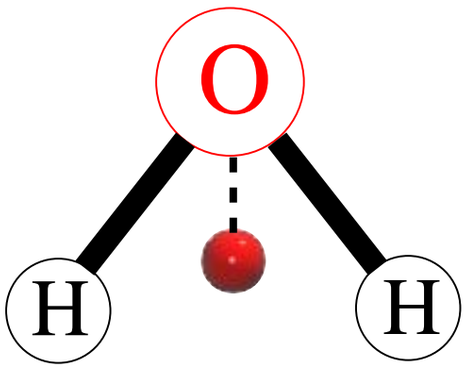
Vanommeslaeghe, K. et al. *J. Comput. Chem.* **2010**, *31*, 671-690

Vanommeslaeghe, K.; MacKerell, Jr, A. *J. Chem. Inf. Model.* **2012**, *52*, 3144-3154

Vanommeslaeghe, K.; Raman, E. P.; MacKerell, Jr, A. *J. Chem. Inf. Model.* **2012**, *52*, 3155-3168

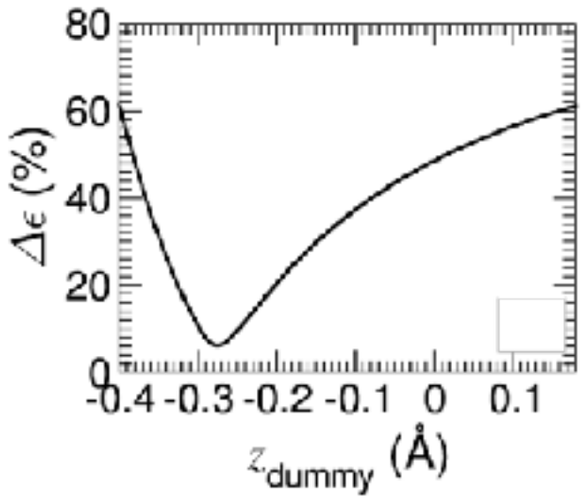
Water models

One of the commonest molecules — and one of the hardest to model.



Main culprit — the electrostatics. A simple three-point charge model yields an error of about 50% in the regeneration of the potential.

This error drops to less than 10% with a four-point charge model.



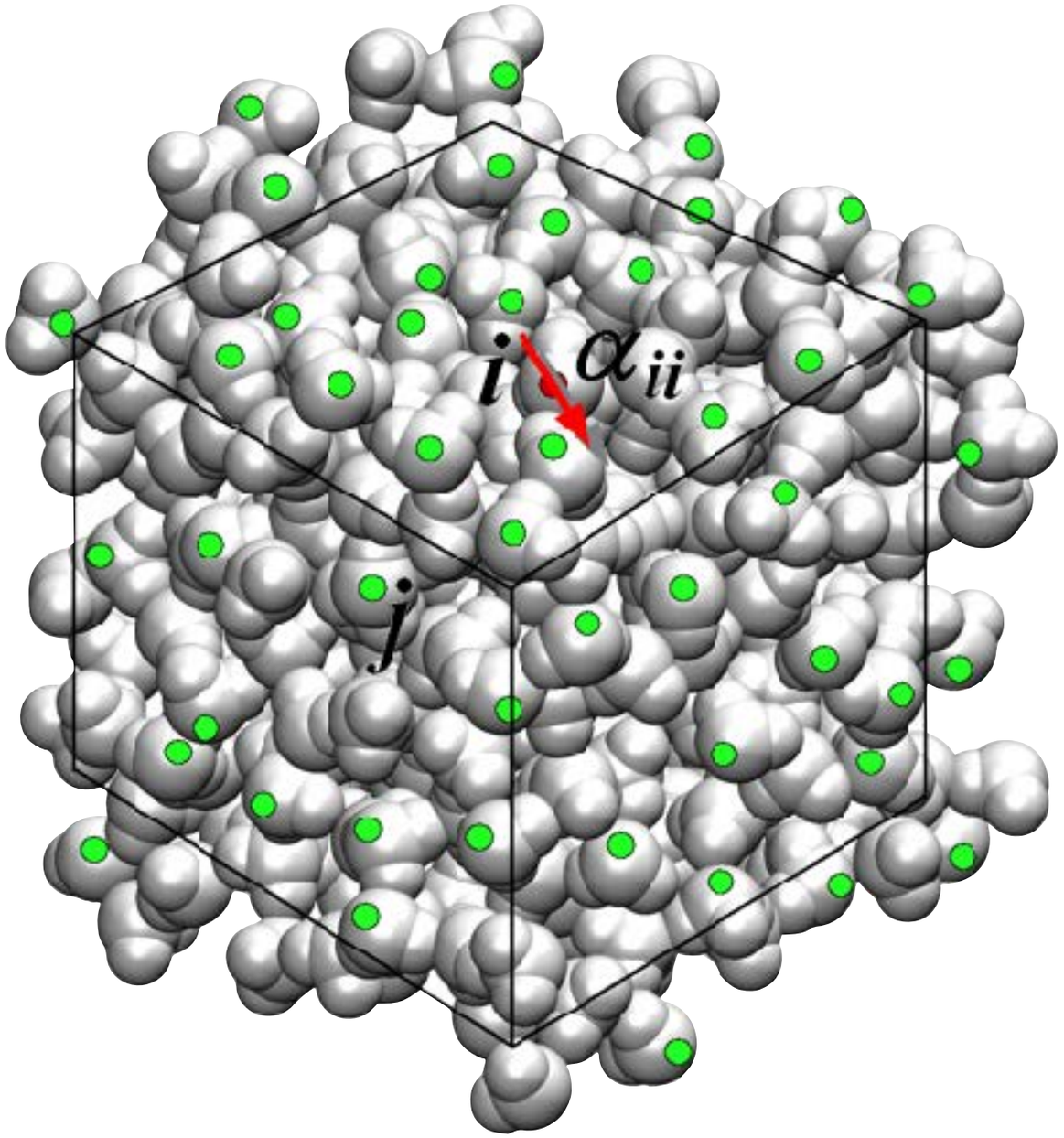
Problem — Most force fields were developed with three-point charge water models.

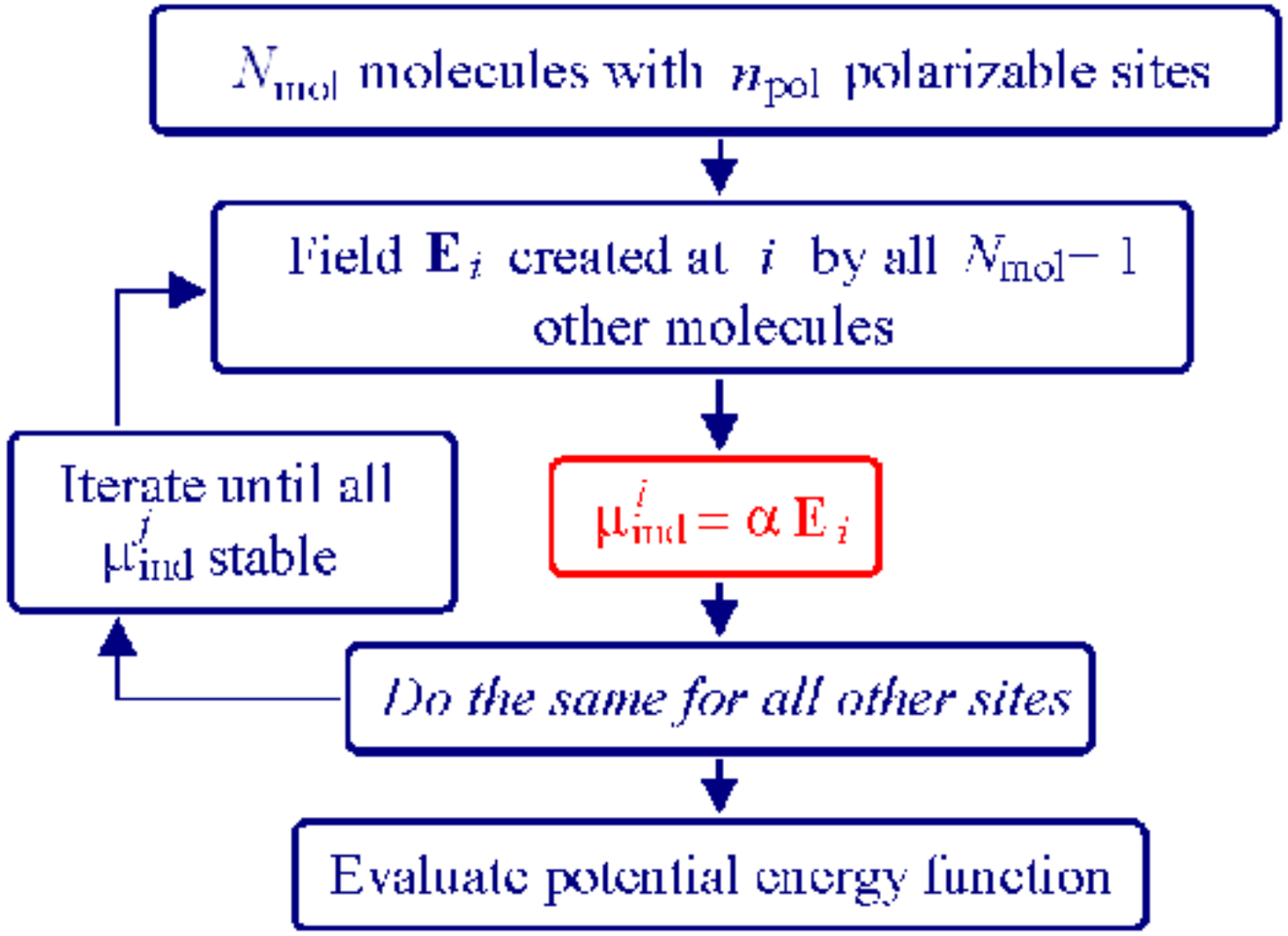
model	N	r_c (Å)	E_{pot} (kJ/mol)	ρ (g cm^{-3})	T (K)	D ($\times 10^{-9}$ m^2 s^{-1})
SPC/E[a] original	820	12.0	−47.2(0.18)	1.008	301(4.4)	2.7(0.12)
SPC/E[b] original	901	12.0	−45.4(0.03)	0.998	298.2(1.4)	2.8(0.06)
SPC[a] original	820	12.0	−42.2(0.16)	0.988	301(4.4)	4.2(0.08)
SPC[b] original	901	12.0	−40.5(0.03)	0.998	298.6(1.1)	4.2(0.08)
TIP3P[a] original	820	12.0	−40.8(0.16)	1.001	301(4.4)	5.4(0.14)
TIP3P[b] original	901	12.0	−39.0(0.02)	0.998	297.0(0.9)	5.6(0.08)
TIP3P[b] modified	901	12.0	−39.8(0.02)	0.998	299.2(1.0)	5.9(0.08)
SPC[b] refined	901	12.0	−40.3(0.03)	0.998	297.7(1.2)	4.2(0.10)
exptl			−41.5	0.997		2.3

Jorgensen, W. L. et al. *J. Chem. Phys.* **1983**, *79*, 926-935
Berendsen, H. J. C.; Grigera, J. R.; Straatsma, T. P. *J. Phys. Chem.* **1987**, *91*, 6269-6271
Archambault, F. et al. *J. Chem. Theor. Comput.* **2009**, *5*, 3022-3031

dynamic properties are more difficult to reproduce accurately

How to handle induction effects?

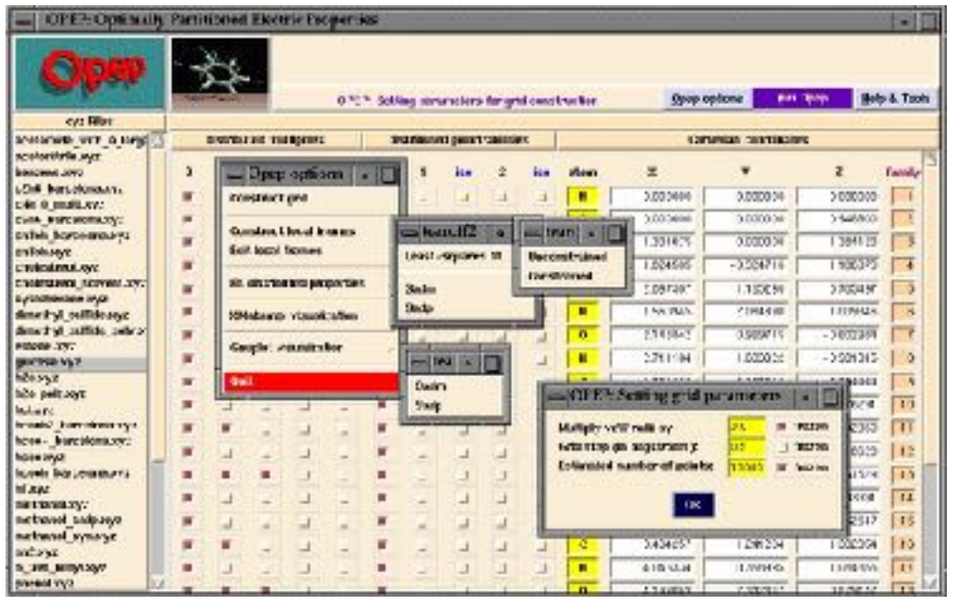


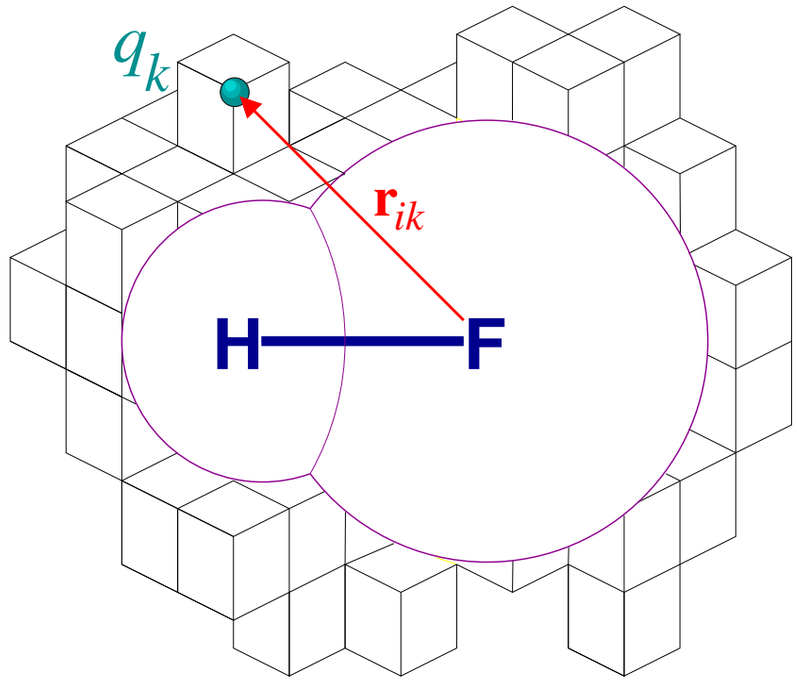


Ahlström, P.; Wallquist, A.; Engströms, S.; Jönsson, B. *Mol. Phys.* **1989**, *68*, 563-581

Wang, W.; Skeel, R. D. *J. Chem. Phys.* **2005**, *123*, 164107

How to handle induction effects?





Induction energy, $\mathscr{U}_{\mathrm{ind},k}$, resulting from the polarization of the molecule by a charge q_k, located at point $\mathbf{r}_k$,

$$\mathscr{U}_{\mathrm{ind},k} = \mathscr{E}_{\mathrm{total},k} - \mathscr{E}^0 - q_k \; V_k \qquad\qquad \forall \; k = 1, \ldots, N_p$$

Approximation of the induction energy, introducing $\boldsymbol{\alpha}$,

$$\tilde{\mathscr{U}}_{\mathrm{ind},k} = -\frac{1}{2} \sum_{i,j} \sum_{\ell=0}^{N_\ell(i)} \sum_{\kappa=-\ell}^{\ell} \sum_{\ell'=0}^{N_{\ell'}(j)} \sum_{\kappa'=-\ell'}^{\ell'} q_k \; T^{ki}_{\ell\kappa} \; \alpha^{ij}_{\ell\kappa,\ell'\kappa'} \; T^{jk}_{\ell'\kappa'} \; q_k$$

Chipot, C.; Ángyán, J. G. *New J. Chem.* **2005**, *29*, 411-420

How to handle induction effects?

The Drude oscillator

Induced dipole moment, $\mu = \frac{q_D^2 \mathbf{E}}{k_D}$

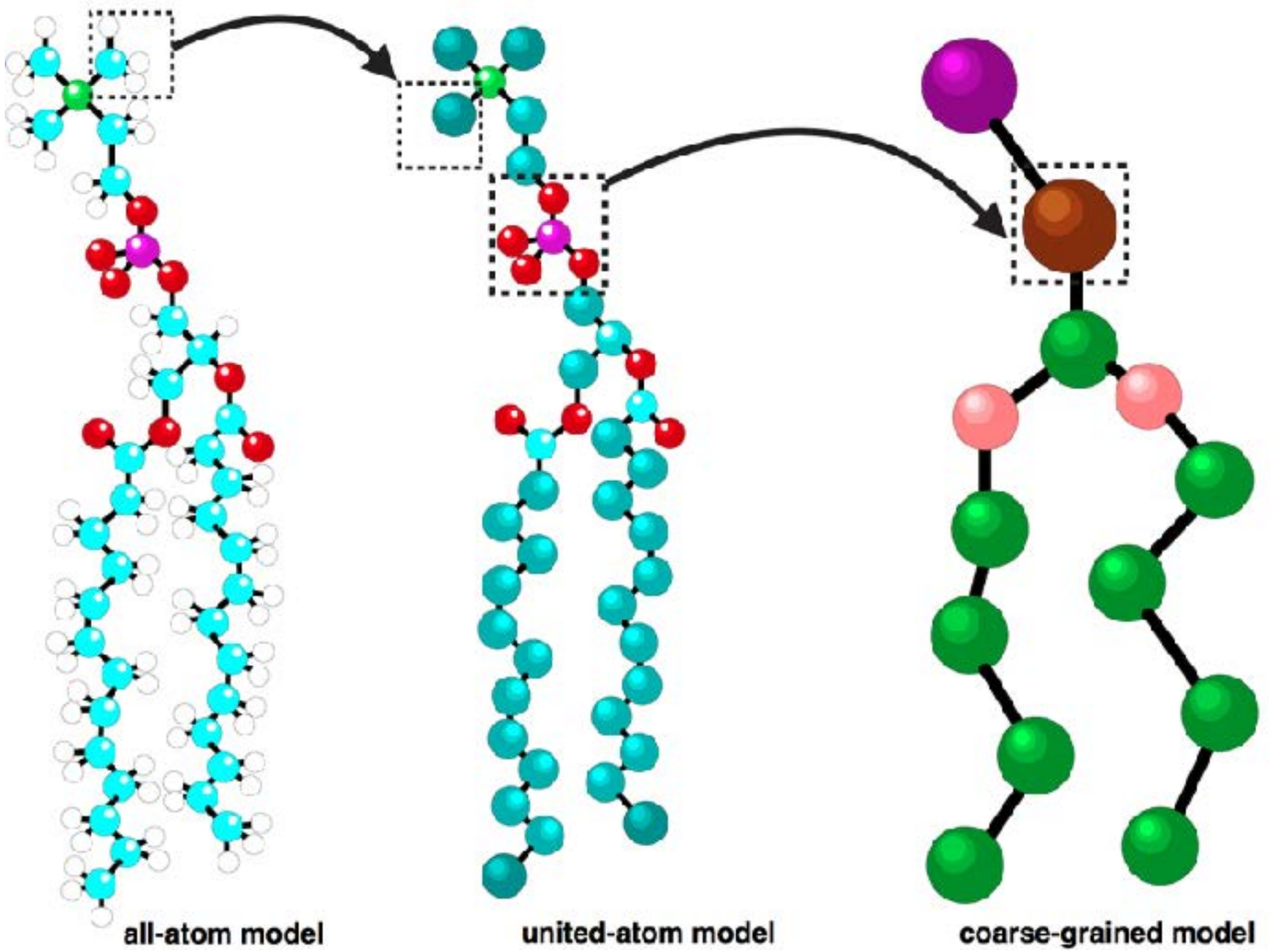
The primary computational cost of simulating classical Drude oscillators is the calculation of the local electrostatic field and the repositioning of the Drude particle at each step, which is done traditionally in a self-consistent fashion. This cost can be reduced by assigning a small mass to each Drude particle, applying a Lagrangian transformation and evolving the simulation in the generalized coordinates.

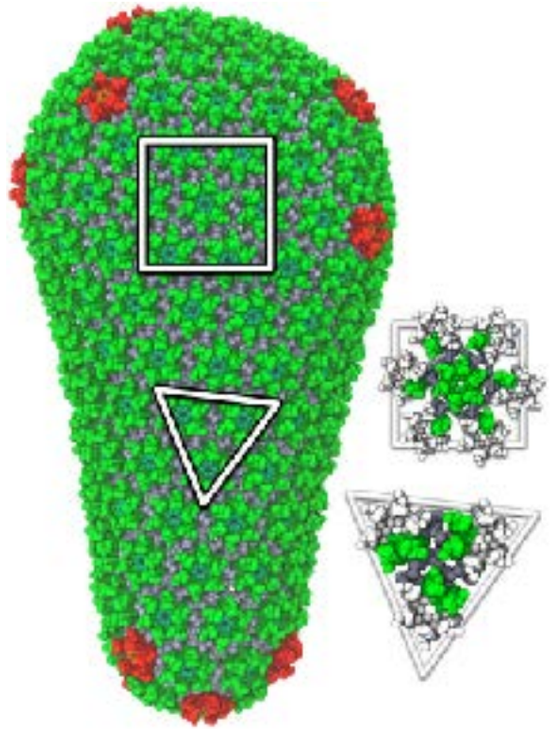
Main advantage: Simplicity of implementation, cost-effectiveness, charge-charge framework.

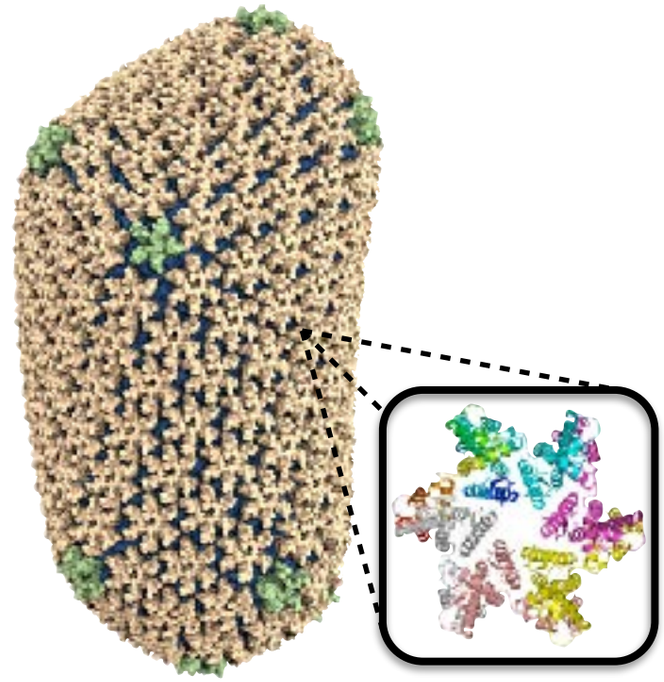
Drude, P. *Lehrbuch der Optik. 1. Ausgabe*. Verlag von S. Hirzel, **1900**

Huang, J.; Lopes, P. E. M.; Roux, B.; MacKerell, Jr, A. D. *J. Phys. Chem. Lett.* **2014**, *5*, 3144-3150

Towards a simpler representation



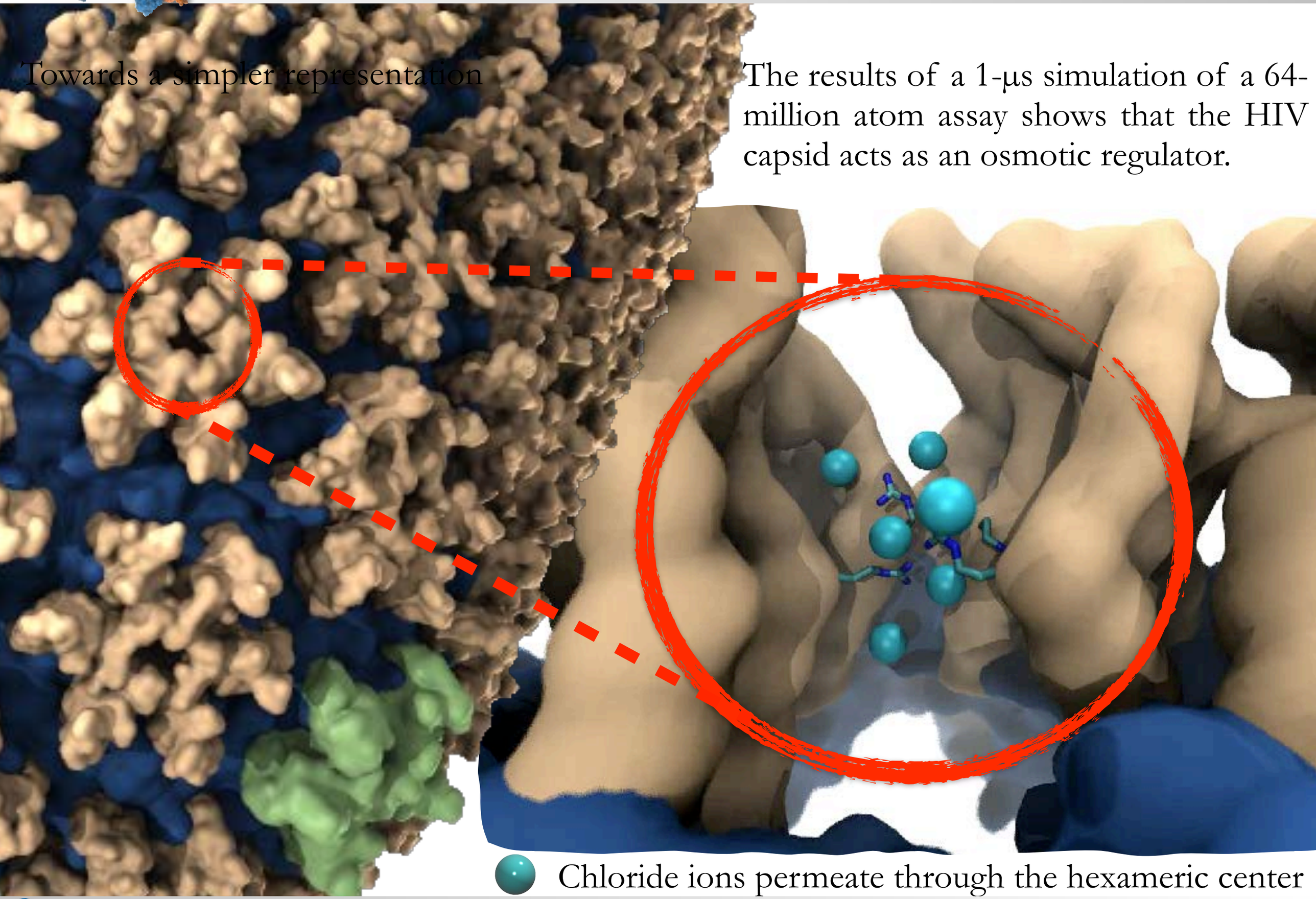




Marrink, S. J.; Risselada, H. J.; Yefimov, S.; Tieleman, D. P.; de Vries, A. H. *J. Phys. Chem. B* **2007**, *111*, 7812-7824

Towards a simpler representation

The results of a 1-μs simulation of a 64-million atom assay shows that the HIV capsid acts as an osmotic regulator.



Chloride ions permeate through the hexameric center

SUMMARY

If atom types and parameters are missing from a macromolecular force field, one ought to follow verbatim its philosophy to update it. A force field is a very fragile construct — its elementary bricks cannot be swapped without any precaution.

The vast majority of macromolecular force fields are pairwise additive, i.e., they do not account for through-space induction phenomena, nor of charge transfers.

To reduce the computational effort and access longer timescales, the atomic description can be coarse-grained. One should, however, not simplify a model until one understands fully the phenomena at play.

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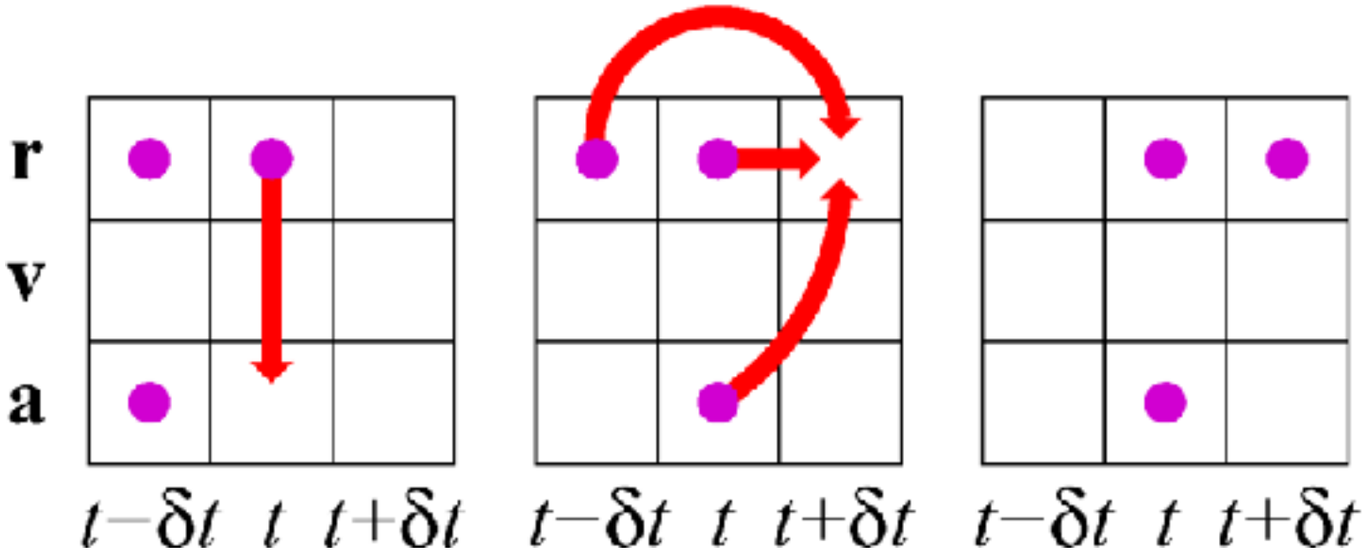
THE PROPAGATORS OF MOLECULAR DYNAMICS

Early experiments of propagating motion

The Verlet propagator



Taylor expansions at $t + \delta t$ and t - δt,

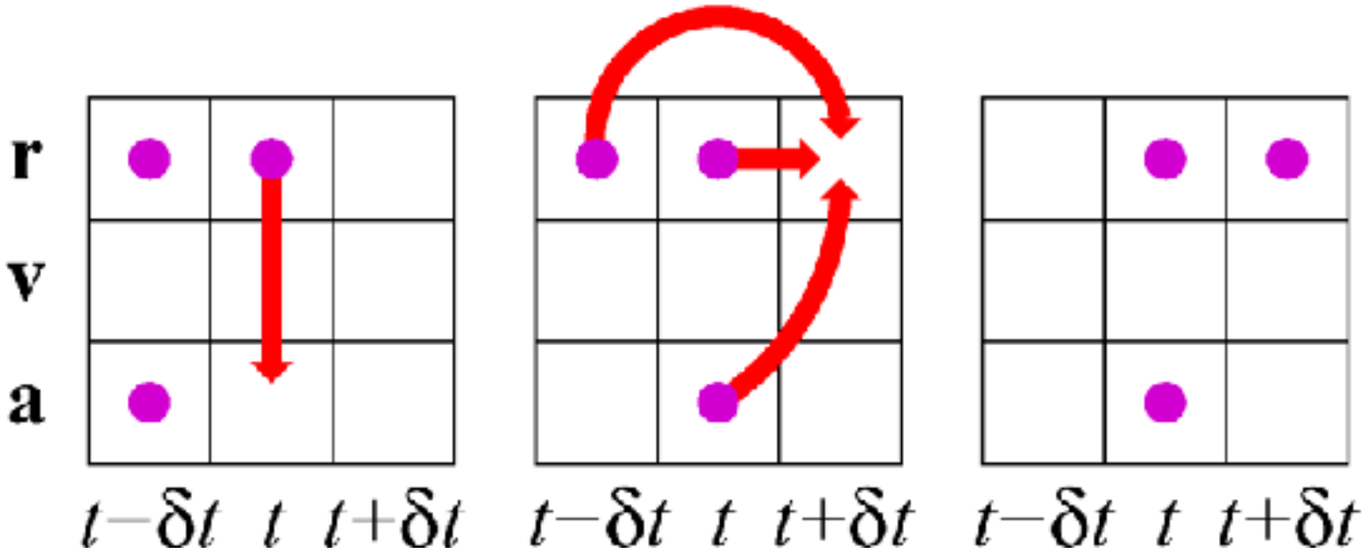
$$\mathbf{r}_i(t+\delta t) = \mathbf{r}_i(t) + \delta t\ \mathbf{v}_i(t) + \frac{\delta t^2}{2}\ \mathbf{a}_i(t) + \mathscr{O}(\delta t^3)$$

$$\mathbf{r}_i(t-\delta t) = \mathbf{r}_i(t) - \delta t\ \mathbf{v}_i(t) + \frac{\delta t^2}{2}\ \mathbf{a}_i(t) + \mathscr{O}(\delta t^3)$$

Verlet, L. *Phys. Rev.* **1967**, *159*, 98-103

Frenkel, D.; Smit, B. Understanding molecular simulations: From algorithms to applications, Academic Press, **2002**

The Verlet propagator



Taylor expansions at $t + \delta t$ and t - δt,

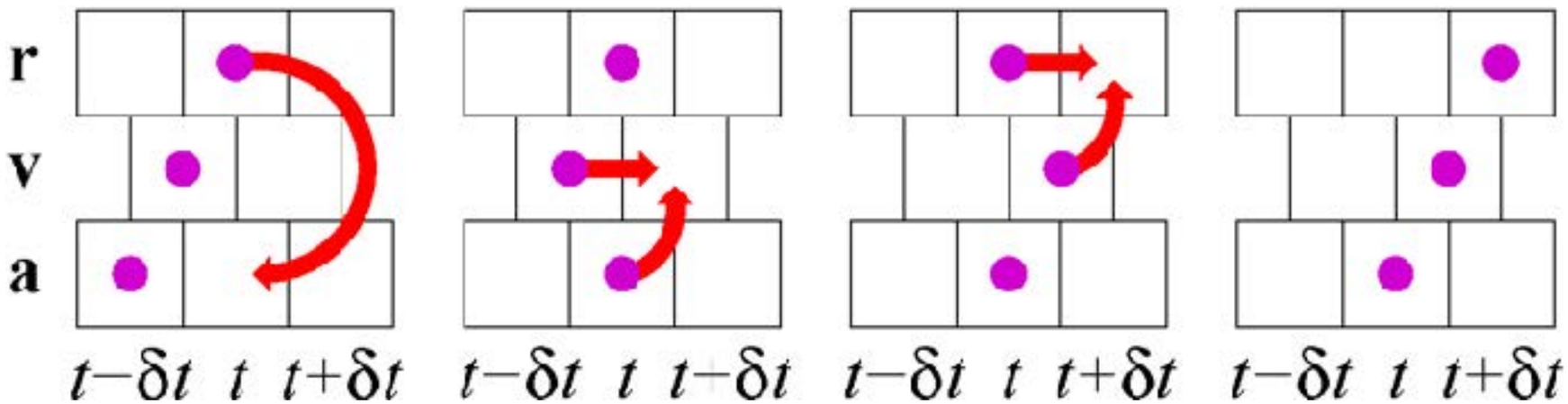
$$\mathbf{r}_i(t+\delta t) = 2\mathbf{r}_i(t) - \mathbf{r}_i(t-\delta t) + \mathbf{a}_i(t)\ \delta t^2 + \mathscr{O}(\delta t^4)$$

$$\mathbf{v}_i(t) = \frac{\mathbf{r}_i(t+\delta t) - \mathbf{r}_i(t-\delta t)}{2\ \delta t} + \mathscr{O}(\delta t^2)$$

Verlet, L. *Phys. Rev.* **1967**, *159*, 98-103

Frenkel, D.; Smit, B. Understanding molecular simulations: From algorithms to applications, Academic Press, **2002**

The leap-frog propagator



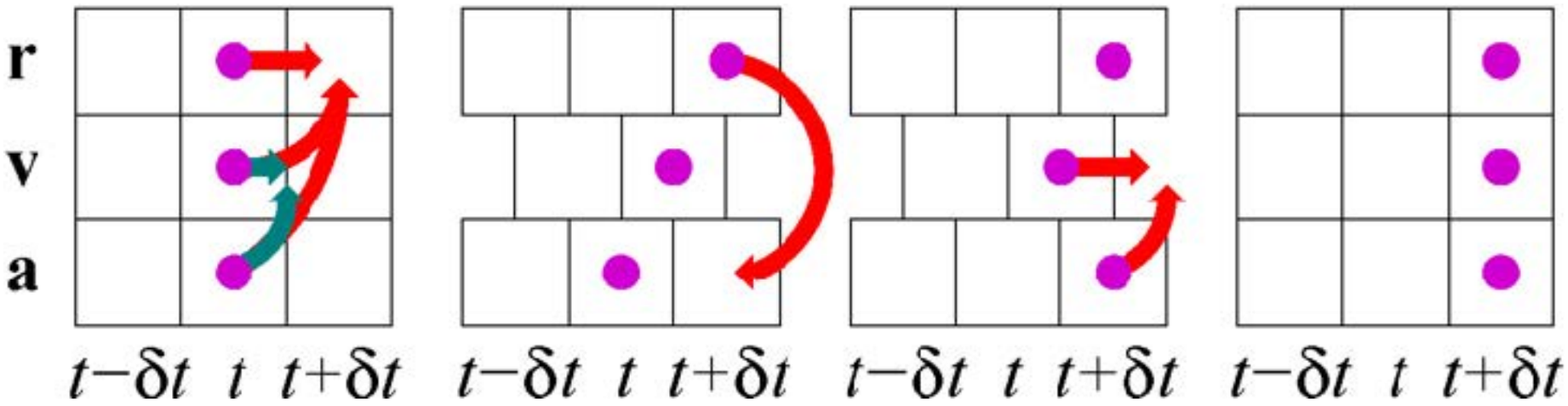
$$
\begin{cases}
\mathbf{r}_i(t+\delta t) = \mathbf{r}_i(t) + \mathbf{v}_i\left(t+\frac{\delta t}{2}\right)\ \delta t \\
\mathbf{v}_i\left(t+\frac{\delta t}{2}\right) = \mathbf{v}_i\left(t-\frac{\delta t}{2}\right) + \mathbf{a}_i(t)\ \delta t
\end{cases}
$$

$$
\mathbf{v}_i(t) = \frac{\mathbf{v}_i\left(t+\frac{\delta t}{2}\right) + \mathbf{v}_i\left(t-\frac{\delta t}{2}\right)}{2}
$$

Berendsen, H. J. C.; Postma, J. P. M.; Van Gunsteren, W. F.; DiNola, A.;Haak, J. R. *J. Chem. Phys.* **1984**, *81*, 3684-3690

Frenkel, D.; Smit, B. Understanding molecular simulations: From algorithms to applications, Academic Press, **2002**

The velocity Verlet propagator



$$\begin{cases} \mathbf{r}_i(t+\delta t) = \mathbf{r}_i(t) + \mathbf{v}_i(t)\ \delta t + \frac{1}{2}\ \mathbf{a}_i(t)\ \delta t^2 \\ \mathbf{v}_i(t+\delta t) = \mathbf{v}_i(t) + \frac{\mathbf{a}_i(t) + \mathbf{a}_i(t+\delta t)}{2}\ \delta t \end{cases}$$

$$\mathbf{v}_i\left(t + \frac{\delta t}{2}\right) = \mathbf{v}_i(t) + \frac{1}{2}\ \mathbf{a}_i(t)\ \delta t$$

$$\mathbf{v}_i(t+\delta t) = \mathbf{v}_i\left(t + \frac{\delta t}{2}\right) + \frac{1}{2}\ \mathbf{a}_i(t+\delta t)\ \delta t$$

This algorithm is time-reversible

Swope, W. C.; Andersen, H. C.; Berens, P. H.; Wilson, K. R. J. Chem. Phys. , 1982, 76, 637-649

Frenkel, D.; Smit, B. Understanding molecular simulations: From algorithms to applications, Academic Press, **2002**

The predictor-corrector algorithm

Stage 1: Estimate $\{\mathbf{r}_i(t+\delta t),\ \mathbf{v}_i(t+\delta t),\ \mathbf{a}_i(t+\delta t),\ \mathbf{b}_i(t+\delta t)\}$,

$$\begin{cases} \mathbf{r}_i(t+\delta t)^{\text{pred}} &= \mathbf{r}_i(t) + \mathbf{v}_i(t)\ \delta t + \frac{1}{2}\ \mathbf{a}_i(t)\ \delta t^2 + \frac{1}{6}\ \mathbf{b}_i(t)\ \delta t^3 \\ \mathbf{v}_i(t+\delta t)^{\text{pred}} &= \mathbf{v}_i(t) + \mathbf{a}_i(t)\ \delta t + \frac{1}{2}\ \mathbf{b}_i(t)\ \delta t^2 + \ldots \\ \mathbf{a}_i(t+\delta t)^{\text{pred}} &= \mathbf{a}_i(t) + \mathbf{b}_i(t)\ \delta t + \ldots \\ \mathbf{b}_i(t+\delta t)^{\text{pred}} &= \mathbf{b}_i(t) + \ldots \end{cases}$$

Stage 2: From the forces evaluated at $t+\delta t$, using $\{\mathbf{r}_i(t+\delta t)_{\text{pred}}\}$, correct the accelerations and supply an estimate of the prediction error,

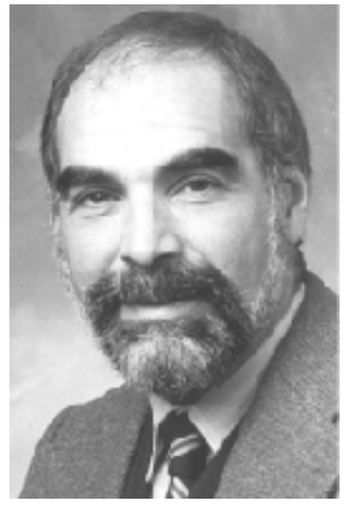
$$\begin{cases} \mathbf{r}_i(t+\delta t)^{\text{corr}} &= \mathbf{r}_i(t+\delta t)^{\text{pred}} + c_0\ \Delta\mathbf{a}(t+\delta t) \\ \mathbf{v}_i(t+\delta t)^{\text{corr}} &= \mathbf{v}_i(t+\delta t)^{\text{pred}} + c_1\ \Delta\mathbf{a}(t+\delta t) \\ \mathbf{a}_i(t+\delta t)^{\text{corr}} &= \mathbf{a}_i(t+\delta t)^{\text{pred}} + c_2\ \Delta\mathbf{a}(t+\delta t) \\ \mathbf{b}_i(t+\delta t)^{\text{corr}} &= \mathbf{b}_i(t+\delta t)^{\text{pred}} + c_3\ \Delta\mathbf{a}(t+\delta t) \end{cases}$$

Frenkel, D.; Smit, B. Understanding molecular simulations: From algorithms to applications, Academic Press, **2002**

Multiple time-step propagators

The Liouville equation of motion,

$$\frac{\partial \varrho_{NVT}(\mathbf{x}, \mathbf{p}_x, t)}{\partial t} = -i\mathscr{L}\, \varrho_{NVT}(\mathbf{x}, \mathbf{p}_x, t)$$



$$\mathbf{\Gamma}(t) = \mathrm{e}^{i\mathscr{L}t}\ \mathbf{\Gamma}(0)$$

Trotter factorization,

$$\mathrm{e}^{i\mathscr{L}\Delta t} = \mathrm{e}^{i\mathscr{L}_1 \frac{\Delta t}{2}} \left[\mathrm{e}^{i\mathscr{L}_2 \frac{\Delta t}{2k}}\ \mathrm{e}^{i\mathscr{L}_3 \frac{\Delta t}{k}}\ \mathrm{e}^{i\mathscr{L}_2 \frac{\Delta t}{2k}} \right]^k \mathrm{e}^{i\mathscr{L}_1 \frac{\Delta t}{2}}$$

```
timestep              2
nonBondedFreq         1
fullElectFrequency    2
```

Separation of the short- and long-range contributions,

$$\mathrm{e}^{i\mathscr{H}\Delta t} = \mathrm{e}^{i\mathscr{V}_{\mathrm{long}}(\mathbf{x})\frac{\Delta t}{2}} \left\{ \mathrm{e}^{i\mathscr{V}_{\mathrm{short}}(\mathbf{x})\frac{\Delta t}{2}} \left[\mathrm{e}^{i\mathscr{V}_{\mathrm{valence}}(\mathbf{x})\frac{\Delta t}{2}}\ \mathrm{e}^{i\mathscr{T}(\mathbf{p}_x)\frac{\Delta t}{2}}\ \mathrm{e}^{i\mathscr{V}_{\mathrm{valence}}(\mathbf{x})\frac{\Delta t}{2}} \right]^2 \mathrm{e}^{i\mathscr{V}_{\mathrm{short}}(\mathbf{x})\frac{\Delta t}{2}} \right\}^2 \mathrm{e}^{i\mathscr{V}_{\mathrm{long}}(\mathbf{x})\frac{\Delta t}{2}}$$

Δt

Δt / 2

Δt / 4

Tuckerman, M. E.; Berne, B. J.; Martyna, G. J. *J. Phys. Chem. B* **1992**, *97*, 1990-2001

Izaguirre, J. A.; Reich, S.; Skeel, R. D. *J. Chem. Phys.* **1999**, *110*, 9853-9864

SUMMARY

Integration of the equations of motion generally relies upon a Taylor expansion of the positions — possibly the velocities, at $t + \delta t$ and $t - \delta t$.

While in some algorithms knowledge of the velocities is not mandatory, the latter are required for the determination of the kinetic energy.

The cost of the simulation can be appreciably reduced, turning to a multiple-time step integrator, which exploits the fact different degrees of freedom relax over different time-scales and, thus, can be updated at different frequencies.

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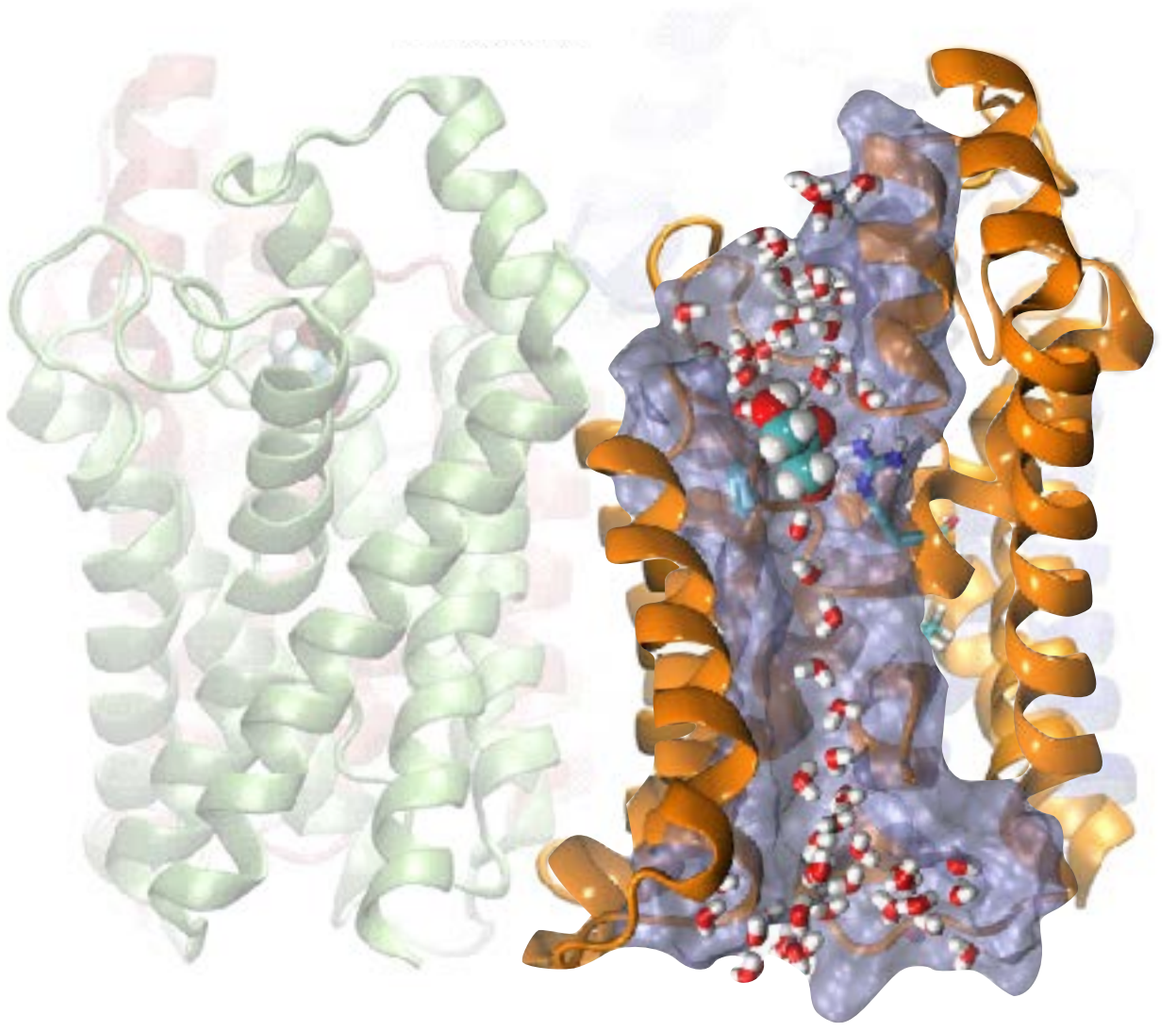
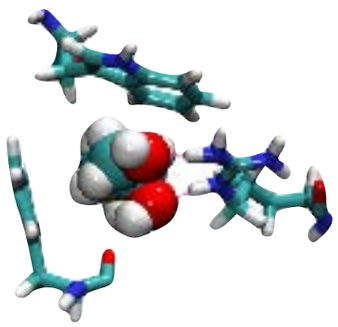
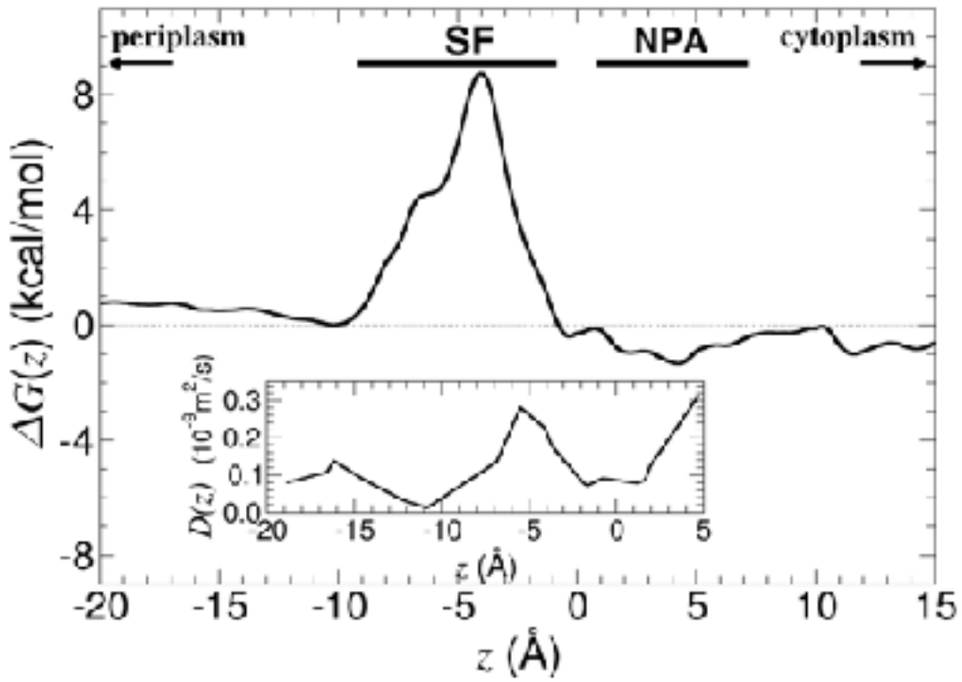
The concept of biased molecular dynamics simulation



To push back the limitation of brute-force molecular dynamics and access timescales not amenable to conventional simulation times — due to significant free-energy barriers.



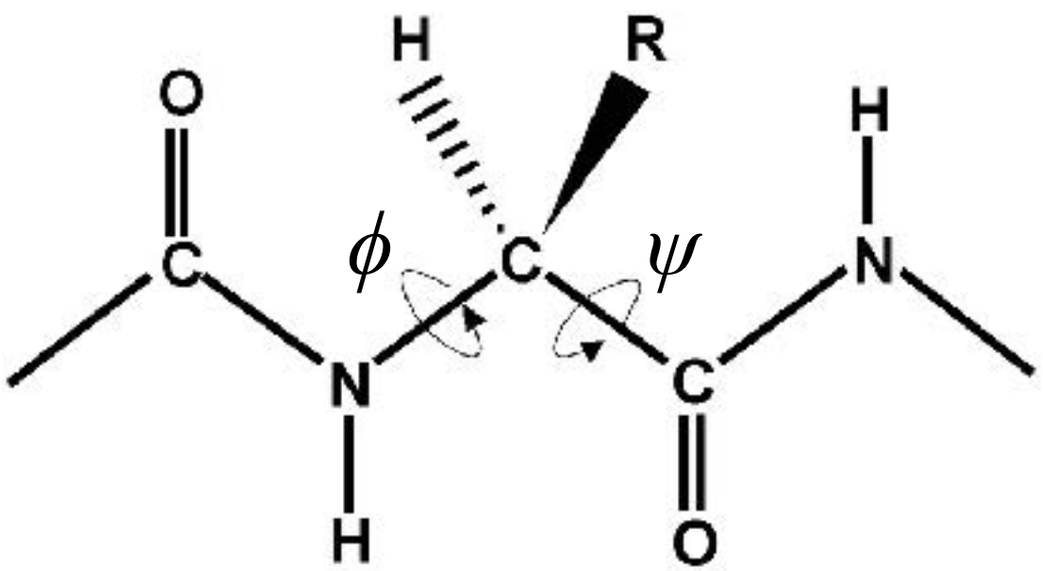


Adding additional forces to the conservative forces arising from the force field will result in preferential sampling of slow degrees of freedom ordinarily poorly explored in standard simulations.

Chipot, C.; Pohorille, A. *Free energy calculations. Theory and applications in chemistry and biology*. Springer Verlag, **2007**

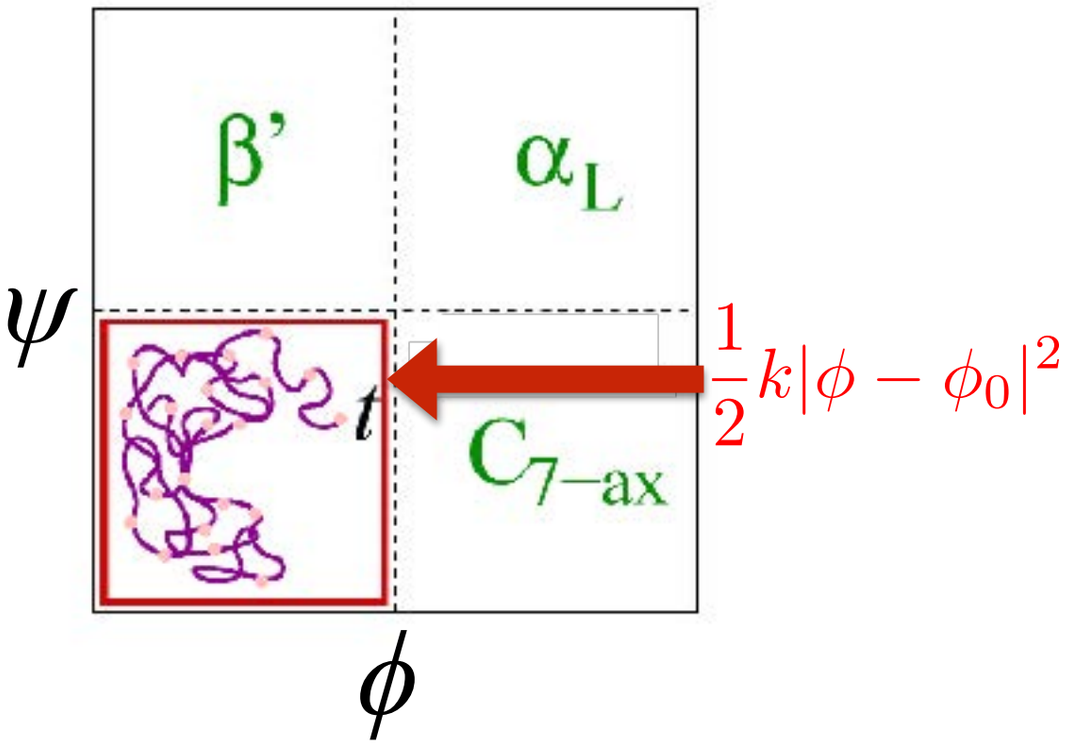
Hénin, J.; Tajkhorshid, E.; Schulten, K.; Chipot, C. *Biophys. J.* **2008**, *94*, 832-839

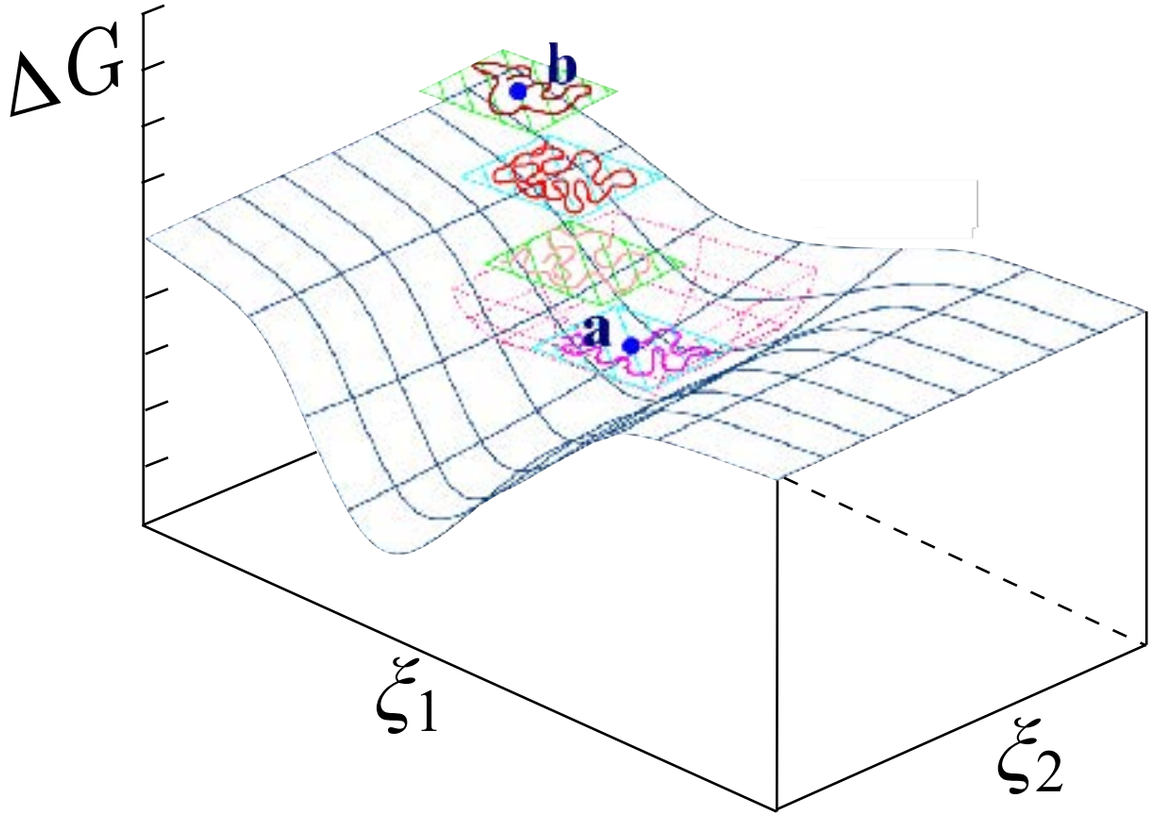
Role of geometrical restraints



Basic idea: Reduce the volume of configurational space to be sampled by means of geometrical, harmonic restraints.

Application: Staging in geometrical free-energy calculations.

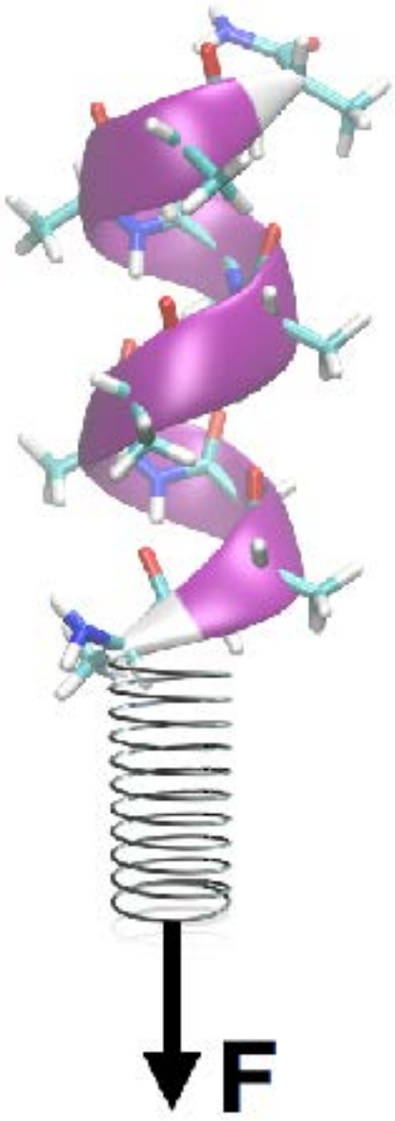




Valleau, J. P.; Card, D. N. *J. Chem. Phys.* **1972**, *57*, 5457-5462

Role of geometrical restraints

Application: Steered molecular dynamics. The external force is exerted onto the system to force it to drift along the desired direction of Cartesian space.



In constant-force SMD simulations, a constant force on the order of 10^{-12} to 10^{-9} N, is exerted onto a subset of atoms, in addition to the conservative forces of the potential energy function.

Constant-velocity SMD simulations mimic the action of a mobile cantilever acting on a substrate in AFM experiments.

In AFM, the spring constant of the cantilever is 10^{-3} Nm^{-1}, translating to large thermal fluctuations in the position of the attached substrate. SMD utilizes spring constants 10^2 stiffer, giving sharper spatial resolution and more detailed information about the interactions at play.

Until recently, the time scales explored by SMD were substantially shorter than those of AFM experiments, by a factor of 10^3-10^6.

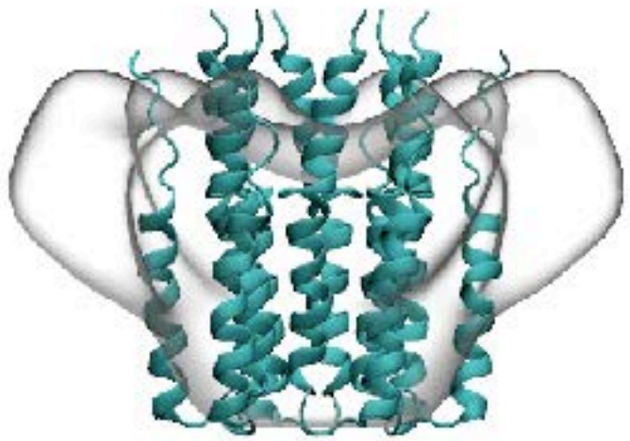
Izrailev, S. et al. *Computational molecular dynamics: Challenges, methods, ideas* Deuflhard, P. et al. (Ed.), Springer Verlag, **1998**, *4*, 39-65

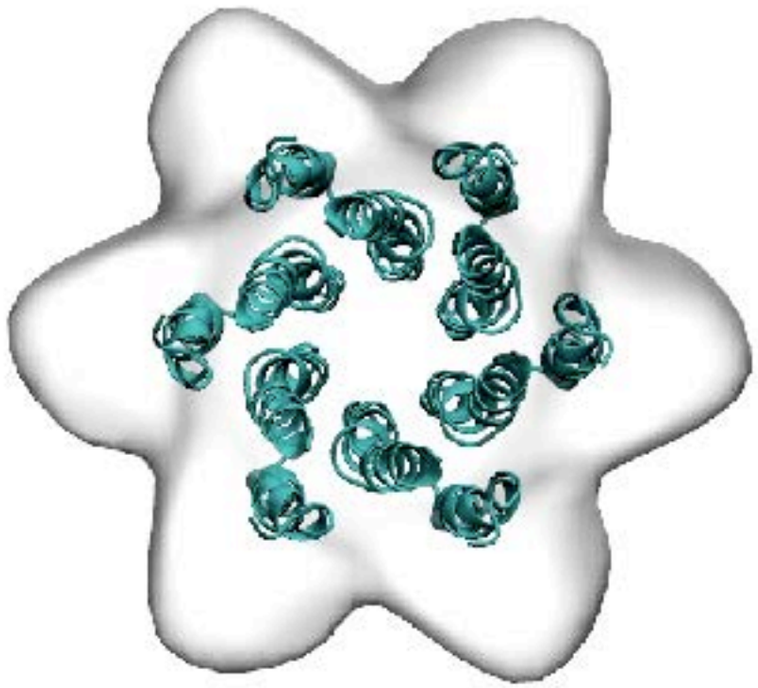
Rico, F.; Gonzalez, L.; Casuso, I.; Puig-Vidal, M.; Scheuring, S. *Science*, **2013**, *342*, 741-743

Role of geometrical restraints

Application: Molecular dynamics flexible fitting

Basic idea: Fit atomic structures into density maps. The method consists of adding external forces proportional to the gradient of the density map into a molecular dynamics simulation of the atomic structure.





Combination of high-resolution atomic structures with low-resolution cryo-electron microscopy maps results in atomic models representing the conformational state captured by cryo-EM.

Trabuco, L. G.; Villa, E.; Mitra, K.; Frank, J.; Schulten, K. *Structure* **2008**, *16*, 673-683
Trabuco, L. G.; Villa, E.; Schreiner, E.; Harrison, C. B.; Schulten, K. *Methods* **2009**, *49*, 174-180

Role of holonomic constraints

Eliminate the hard degrees of freedom of the system, that correspond to high frequencies of vibration. In other words, constraints ≠ restraints.

Application: Increase δt

$$\chi_{ij}(t) = |\mathbf{r}_j(t) - \mathbf{r}_i(t)|^2 - d_{ij}^2$$

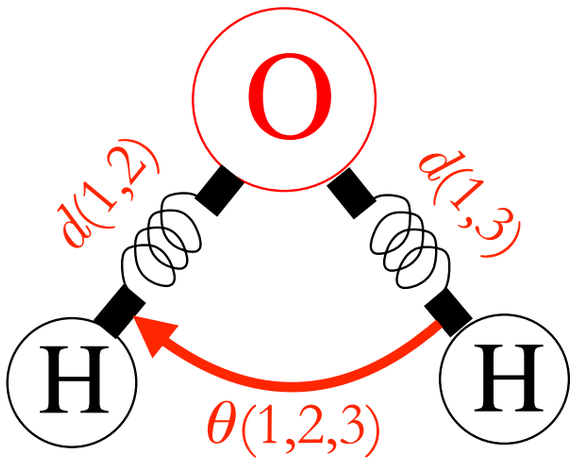
$$m_i \frac{\mathrm{d}^2\mathbf{r}_i(t)}{\mathrm{d}t^2} = \mathbf{f}_i + \mathbf{g}_i$$

Constraint force, $\mathbf{g}_i = -\sum_j \lambda_{ij}(t)\ \nabla_i\chi_{ij}(t) = -2\sum_j \lambda_{ij}(t)\ \mathbf{r}_{ij}(t)$

$$\mathbf{r}_i(t+\delta t) = \mathbf{r}_i(t) + \delta t\ \mathbf{v}_i(t) + \frac{\delta t^2}{2m_i}\ [\mathbf{f}_i(t) + \mathbf{g}_i(t)]$$

Frenkel, D.; Smit, B. Understanding molecular simulations: From algorithms to applications, Academic Press, **2002**

Role of holonomic constraints



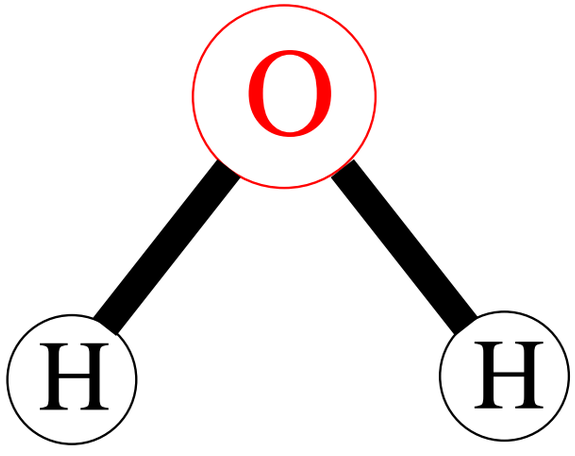
$d(1,2)$ and $d(1,3)$ are fixed. $\theta(1,2,3)$ may vary through the intramolecular potential.

Equations of motion,

$$\begin{cases} m_1\,\mathbf{a}_1 = \mathbf{f}_1 + \mathbf{g}_1 \\ m_2\,\mathbf{a}_2 = \mathbf{f}_2 + \mathbf{g}_2 \\ m_3\,\mathbf{a}_3 = \mathbf{f}_3 + \mathbf{g}_3 \end{cases}$$

Frenkel, D.; Smit, B. Understanding molecular simulations: From algorithms to applications, Academic Press, **2002**

Role of holonomic constraints



$d(1,2)$ and $d(1,3)$ are fixed. $\theta(1,2,3)$ may vary through the intramolecular potential.

Equations of motion,

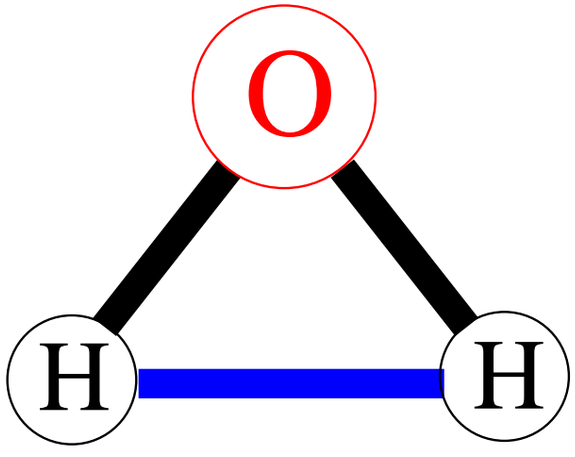
$$\begin{cases} m_1\ \mathbf{a}_1 &= \mathbf{f}_1 + \mathbf{g}_1 \\ m_2\ \mathbf{a}_2 &= \mathbf{f}_2 + \mathbf{g}_2 \\ m_3\ \mathbf{a}_3 &= \mathbf{f}_3 + \mathbf{g}_3 \end{cases}$$

Constraints to be satisfied,

$$\begin{cases} \chi_{12} &= r_{12}^2(t) - d_{12} = 0 \\ \chi_{13} &= r_{13}^2(t) - d_{13} = 0 \end{cases}$$

Frenkel, D.; Smit, B. Understanding molecular simulations: From algorithms to applications, Academic Press, **2002**

Role of holonomic constraints



$d(1,2)$ and $d(1,3)$ are fixed. $\theta(1,2,3)$ may vary through the intramolecular potential.

Equations of motion,

$$\begin{cases} m_1\ \mathbf{a}_1 &= \mathbf{f}_1 + \mathbf{g}_1 \\ m_2\ \mathbf{a}_2 &= \mathbf{f}_2 + \mathbf{g}_2 \\ m_3\ \mathbf{a}_3 &= \mathbf{f}_3 + \mathbf{g}_3 \end{cases}$$

Constraints to be satisfied,

$$\begin{cases} \chi_{12} &= r_{12}^2(t) - d_{12} = 0 \\ \chi_{13} &= r_{13}^2(t) - d_{13} = 0 \end{cases}$$

Introduction of the Lagrange multipliers, $\mathbf{g}_a = \frac{1}{2}\ \lambda_{12}\ \boldsymbol{\nabla}_{(r_a)}\ \chi 12 + \frac{1}{2}\ \lambda_{13}\ \boldsymbol{\nabla}_{(r_a)}\ \chi 23$

The set of constraints ought to be satisfied at *every* time step, $m_a\ \mathbf{a}_a = \mathbf{f}_a + \mathbf{g}_a \simeq \mathbf{f}_a + \mathbf{g}_a^{(r)}$

In the Verlet propagator,

$$\mathbf{r}_a(t+\delta t) = \mathbf{r}'(t+\delta t) + \frac{\delta t^2}{m_a}\ \mathbf{g}_a^{(r)}(t)$$

Frenkel, D.; Smit, B. Understanding molecular simulations: From algorithms to applications, Academic Press, **2002**

Role of holonomic constraints

Introduction of $\mathbf{g}_a{}^{(r)}$ into the Verlet propagator,

$$\begin{cases} \mathbf{g}_1^{(r)} &= \lambda_{12}\ \mathbf{r}_{12} \\ \mathbf{g}_2^{(r)} &= \lambda_{23}\ \mathbf{r}_{23} - \lambda_{12}\ \mathbf{r}_{12} \\ \mathbf{g}_3^{(r)} &= -\lambda_{23}\ \mathbf{r}_{23} \end{cases}$$

$$\begin{cases} \mathbf{r}_{12}(t+\delta t) &= \mathbf{r}'_{12}(t+\delta t) + \left(\frac{1}{m_1}+\frac{1}{m_2}\right)\ \lambda_{12}\ \delta t^2\ \mathbf{r}_{12}(t) - \frac{1}{m_2}\ \lambda_{23}\ \delta t^2\ \mathbf{r}_{23}(t) \\ \mathbf{r}_{23}(t+\delta t) &= \mathbf{r}'_{23}(t+\delta t) + \frac{1}{m_2}\ \lambda_{12}\ \delta t^2\ \mathbf{r}_{12}(t) - \left(\frac{1}{m_2}+\frac{1}{m_3}\right)\ \lambda_{23}\ \delta t^2\ \mathbf{r}_{23}(t) \end{cases}$$

This is a quadratic system of two equations of unknowns, λ_{12} and λ_{13}.

It is possible to rigidify the water molecule *fully* by enforcing an additional constraint on the H—H distance.

Frenkel, D.; Smit, B. Understanding molecular simulations: From algorithms to applications, Academic Press, **2002**

The SHAKE algorithm

Cyclic computation of all constraints, in an iterative fashion until each constraint be satisfied.

Modification of the Verlet propagator: At each step, $\mathbf{g}$ is approximated in order to satisfy the set of constraints,

$$\begin{cases} \mathbf{r}_a(t+\delta t) = \mathbf{r}'_a(t+\delta t) + \frac{1}{2}\,\frac{\delta t}{m_a}\,\mathbf{g}_a^{(r)}(t) \\ \mathbf{v}_a\left(t+\frac{\delta t}{2}\right) = \mathbf{v}'_a\left(t+\frac{\delta t}{2}\right) + \frac{1}{2}\,\frac{\delta t}{m_a}\,\mathbf{g}_a^{(r)}(t) \end{cases}$$

Note: Constraint forces, $\mathbf{g}_a{}^{(r)}(t)$, are collinear with $\mathbf{r}_{ab}(t)$, and so are $\mathbf{g}_a{}^{(r)}(t+\delta t)$.

Next: $\mathbf{v}_a(t+\delta t) = \mathbf{v}'_a(t+\delta t) + \frac{1}{2}\,\frac{\delta t}{m_a}\,\mathbf{g}_a^{(r)}(t+\delta t)$

NAMD

```
rigidbonds              all
```

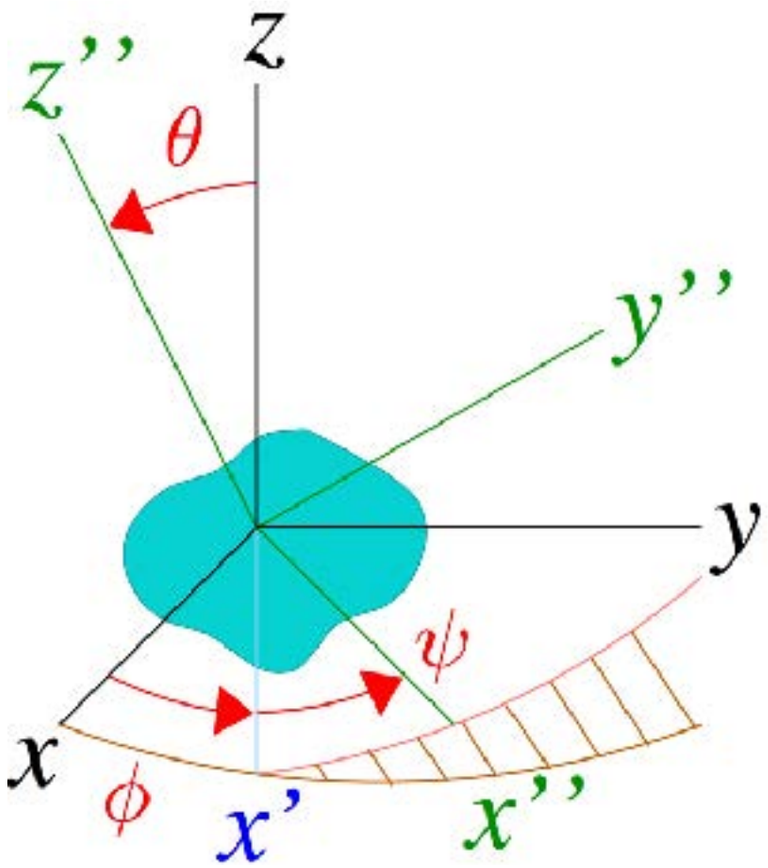
Note: Knowledge of $\mathbf{v}'_a(t+\delta t)$ requires the preliminary evaluation of $\mathbf{f}_a(t+\delta t)$.

The RATTLE algorithm — Iterative computation of the solutions to these equations.

Ryckaert, J.; Ciccotti, G.; Berendsen, H. J. C. *J. Comput. Phys.* **1977**, *23*, 327-341

Andersen, H. C. *J. Comput. Phys.* **1983**, *52*, 24-34

Rigid-body molecular dynamics



$\{\mathrm{e}^B\}$: Frame of reference of the rigid body.

$\{\mathrm{e}^S\}$: Absolute frame of reference: $\mathrm{e}^B = \mathrm{S} \,.\, \mathrm{e}^S$

$$\mathbf{S} = \begin{pmatrix} \cos\phi\ \cos\psi - \sin\phi\ \cos\theta\ \sin\psi & \sin\phi\ \cos\psi + \cos\phi\ \cos\theta\ \sin\psi & \sin\theta\ \sin\psi \\ -\cos\phi\ \sin\psi - \sin\phi\ \cos\theta\ \cos\psi & -\sin\phi\ \sin\psi + \cos\phi\ \cos\theta\ \cos\psi & \sin\theta\cos\psi \\ \sin\phi\ \sin\theta & -\cos\phi\ \sin\theta & \cos\theta \end{pmatrix}$$

$$\begin{cases} \boldsymbol{\tau}_i = \sum_a (\mathbf{r}_{ia} - \mathbf{r}_i) \times \mathbf{f}_{ia} & \text{torque} \\ \boldsymbol{\tau}^B = \mathbf{S}\,\boldsymbol{\tau}^S \\ \boldsymbol{\omega}^S = \mathbf{S}^{-1}\,\boldsymbol{\omega}^B & \text{angular velocity} \\ \dfrac{\mathrm{d}\mathbf{L}^B}{\mathrm{d}t} + \boldsymbol{\omega}^B \times \mathbf{L}^B = \boldsymbol{\tau}^B & \text{angular momentum} \end{cases}$$

$$\frac{\mathrm{d}\mathbf{e}^S}{\mathrm{d}t} = \frac{\mathrm{d}\mathbf{e}^B}{\mathrm{d}t} + \boldsymbol{\omega}^S \times \mathbf{e}^S = \boldsymbol{\omega}^S \times \mathbf{e}^S \quad \text{which depends upon } (\dot\phi, \dot\theta, \dot\psi), \text{ function of } 1/\sin\theta.$$

Allen, M. P.; Tildesley, D. J. Computer Simulation of Liquids, Clarendon Press, **1987**

Rigid-body molecular dynamics

Quaternions: Four scalar quantities satisfying $q_1 + q_2 + q_3 + q_4 = 1$

$$\begin{cases} q_0 = \cos\frac{\theta}{2}\cos\frac{\phi+\psi}{2} \\ q_1 = \sin\frac{\theta}{2}\cos\frac{\phi-\psi}{2} \\ q_2 = \sin\frac{\theta}{2}\sin\frac{\phi-\psi}{2} \\ q_3 = \cos\frac{\theta}{2}\sin\frac{\phi+\psi}{2} \end{cases} \qquad \mathbf{S} = \begin{pmatrix} q_0^2+q_1^2-q_1^2-q_3^2 & 2(q_1q_2+q_0q_3) & 2(q_1q_3-q_0q_2) \\ 2(q_1q_2-q_0q_3) & q_0^2-q_1^2+q_1^2-q_3^2 & 2(q_2q_3+q_0q_1) \\ 2(q_1q_3+q_0q_2) & 2(q_2q_3-q_0q_1) & q_0^2-q_1^2-q_1^2+q_3^2 \end{pmatrix}$$

For each rigid molecule, the quaternions satisfy,

$$\begin{pmatrix} \dot{q}_0 \\ \dot{q}_1 \\ \dot{q}_2 \\ \dot{q}_3 \end{pmatrix} = \frac{1}{2} \begin{pmatrix} q_0 & -q_1 & -q_2 & -q_3 \\ q_1 & q_0 & -q_3 & q_2 \\ q_2 & q_3 & q_0 & -q_1 \\ q_3 & -q_2 & q_1 & q_0 \end{pmatrix} \begin{pmatrix} 0 \\ \omega_x^B \\ \omega_y^B \\ \omega_z^B \end{pmatrix}$$

Application: Robust computation of root mean-square deviations.

Allen, M. P.; Tildesley, D. J. Computer Simulation of Liquids, Clarendon Press, **1987**

Often utilized interchangeably — erroneously so, *restraints* and *constraints* are two different concepts.

Geometric restraints are introduced in a molecular dynamics simulation to restrict sampling to regions of interest of configurational space.

Holonomic constraints are introduced to remove degrees of freedom — to freeze them in the equations of motion. Constrained molecular dynamics implies integrating modified equations of motion featuring constraint forces.

SYNOPSIS

1. Introduction
2. Periodic boundary conditions
3. Synopsis of a molecular dynamics simulation
4. The potential energy function
5. The propagators of molecular dynamics
6. Restraints versus constraints
7. In which ensemble should the simulation be performed?
8. Lattice sums: The Ewald–Kornfeld approach
9. Molecular dynamics on parallel architectures
10. Guidelines
11. Properties accessible from the trajectories

Thermodynamic ensembles and conserved properties

Ensemble	Free energy	Conserved Hamiltonian, $\mathscr{H}(\mathbf{x}, \mathbf{p}_x)$
$(N, V, \mathscr{E})$	—	U
(N, V, T)	$A = U - TS$	$\sum_i \frac{1}{2m_i} (p_{xi}^2 + p_{yi}^2 + p_{zi}^2) + \mathscr{V}(\mathbf{x})$
$(N, P_\perp, \mathscr{A}, T)$	$A = U - TS + P_\perp V$	$\sum_i \frac{1}{2m_i} (p_{xi}^2 + p_{yi}^2 + p_{zi}^2) + \mathscr{V}(\mathbf{x}) + P_\perp V$
$(N, P_\parallel, \mathscr{A}, T)$	$A = U - TS + P_\parallel V$	$\sum_i \frac{1}{2m_i} (p_{xi}^2 + p_{yi}^2 + p_{zi}^2) + \mathscr{V}(\mathbf{x}) + P_\parallel V$
(N, V, γ, T)	$A = U - TS - \gamma\mathscr{A}$	$\sum_i \frac{1}{2m_i} (p_{xi}^2 + p_{yi}^2 + p_{zi}^2) + \mathscr{V}(\mathbf{x}) - \gamma\mathscr{A}$
$(N, P_\perp, \gamma, T)$	$A = U - TS + P_\perp V - \gamma\mathscr{A}$	$\sum_i \frac{1}{2m_i} (p_{xi}^2 + p_{yi}^2 + p_{zi}^2) + \mathscr{V}(\mathbf{x}) + P_\perp V - \gamma\mathscr{A}$

Frenkel, D.; Smit, B. Understanding molecular simulations: From algorithms to applications, Academic Press, **2002**

Constant-temperature molecular dynamics

Velocity rescaling

Central idea: The velocities are rescaled periodically by a factor of $\sqrt{T/T_{\mathscr{T}}}$.

Strictly speaking, this algorithm yields *non-Newtonian* dynamics.

NAMD Scalable Molecular Dynamics

```
rescaleFreq              100
rescaleTemp              298.0
```

Constrained equations of motion

$$\begin{cases} \dot{\mathbf{x}}_i = \dfrac{\mathbf{p}_i}{m_i} \\ \\ \dot{\mathbf{p}}_i = \mathbf{f}_i - \xi(\mathbf{x};\mathbf{p}_x)\ \mathbf{p}_x \end{cases}$$

The friction coefficient guarantees that $\dot{T}_{\mathscr{T}} = 0$, and is chosen so that the perturbation of the chemical system is minimal,

$$\xi(\mathbf{x};\mathbf{p}_x) = \frac{\sum_i \mathbf{p}_i \cdot \mathbf{f}_i}{\sum_i |\mathbf{p}_i|^2}$$

Allen, M. P.; Tildesley, D. J. Computer Simulation of Liquids, Clarendon Press, **1987**

Constant-temperature molecular dynamics

Extended system

Central idea: Introduce an additional degree of freedom, s, thermostat of the system.

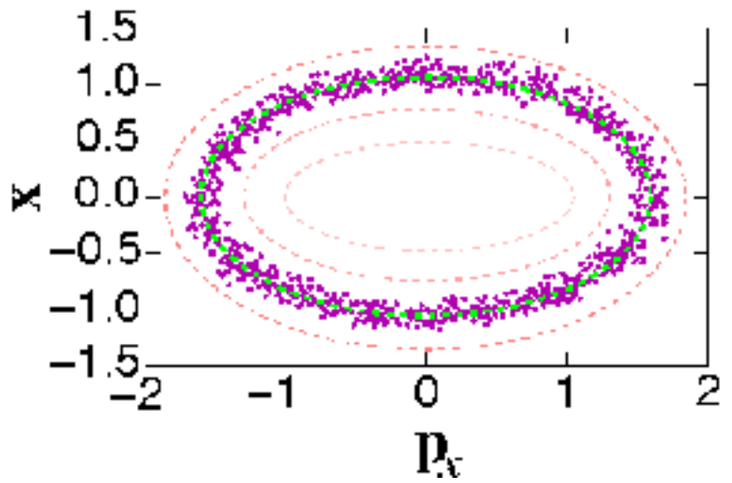
$$\begin{cases} \mathscr{V}_s = \dfrac{f+1}{\beta} \ln s \\ \mathscr{T}_s = \dfrac{1}{2} \mathscr{Q} \dot{s}^2 \end{cases}$$

Velocity of particle i: $\mathbf{v}_i = s\,\dot{\mathbf{r}}_i = \mathbf{p}_i / m_i s$

Extended Lagrangian: $\mathscr{L}_s(\mathbf{x};\mathbf{p}_x) = \mathscr{T}(\mathbf{p}_x) + \mathscr{T}_s(\mathbf{p}_x) - \mathscr{V}(\mathbf{x}) - \mathscr{V}_s(\mathbf{x})$

Poorly chaotic for a limited number of degrees of freedom

$$\begin{cases} \ddot{\mathbf{x}}_i = \dfrac{\mathbf{f}_i}{m_i s^2} - 2\,\dfrac{\dot{s}\dot{\mathbf{x}}}{s} \\ \mathscr{Q}\ddot{s} = \displaystyle\sum_i m_i \dot{x}_i^2 s - \frac{f+1}{\beta s} \end{cases}$$



Hoover, W. G. *Phys. Rev.* **1985**, *A31*, 1695-1697

Martyna, G. J.; Klein, M. L.; Tuckerman, M. E. *J. Chem. Phys.* **1992**, *97*, 2635-2645

Constant-temperature molecular dynamics

Extended system

Practical implementation:

$$\begin{cases} p' &= \dfrac{p}{s} \\ s' &= s \end{cases}$$

$$\xi = \frac{s' p'_s}{\mathscr{Q}}$$

$$\dot{\mathbf{x}}_i = \frac{\mathbf{p}_{x,i}}{m_i}$$

$$\dot{\mathbf{p}}_{x,i} = -\frac{\partial \mathscr{V}(\mathbf{x})}{\partial \mathbf{x}_i} - \xi \mathbf{p}_{x,i}$$

$$\dot{\xi} = \frac{\displaystyle\sum_i \frac{p_i^2}{m_i} - \frac{f+1}{\beta}}{\mathscr{Q}}$$

$$\frac{\dot{s}}{s} = \frac{\mathrm{d} \ln s}{\mathrm{d}t} = \xi$$

Hoover, W. G. *Phys. Rev.* **1985**, *A31*, 1695-1697

Frenkel, D.; Smit, B. Understanding molecular simulations: From algorithms to applications, Academic Press, **2002**

Constant-temperature molecular dynamics

Weak-coupling algorithm

Central idea: Let the instantaneous kinetic temperature, $T_{\mathscr{T}}(t)$, "relax" towards the desired, reference temperature, T.

$$\frac{\mathrm{d}T_{\mathscr{T}}(t)}{\mathrm{d}t} = \frac{T - T_{\mathscr{T}}(t)}{\tau_T}$$

$$\Delta\mathscr{T} = \frac{1}{2}\,(\chi^2 - 1)\; N\; k_B\; T_{\mathscr{T}}(t)$$

$$\chi = \left[1 + \frac{\delta t}{\tau_T}\left(\frac{T}{T_{\mathscr{T}}(t)} - 1\right)\right]^{1/2}$$

Strictly speaking, this algorithm does not yield a canonical distribution.

Berendsen, H. J. C.; Postma, J. P. M.; Van Gunsteren, W. F.; DiNola, A.; Haak, J. R. *J. Chem. Phys.* **1984**, *81*, 3684-3690

Morishita, T. *J. Chem. Phys.* **2000**, *113*, 2976-2982

Constant-temperature molecular dynamics

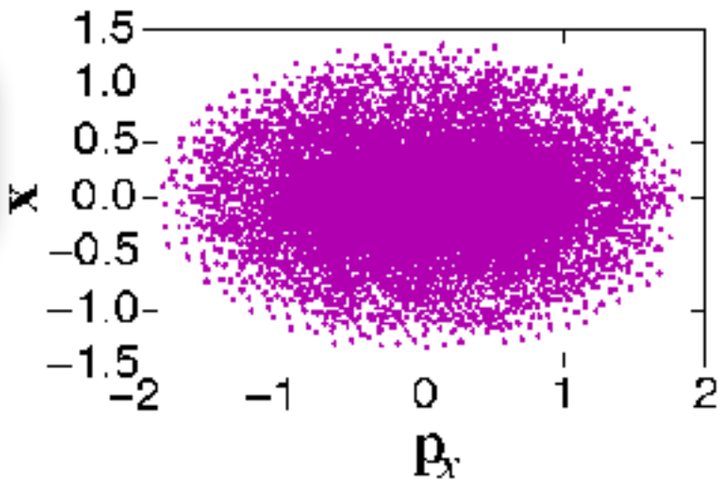
Langevin dynamics

Central idea: Add to the conservative forces a frictional force proportional to the velocity. The friction removes the kinetic energy from the system. A random force adds kinetic energy to the system.

$$m_i \frac{\mathrm{d}^2\mathbf{x}_i}{\mathrm{d}t^2} = -\frac{\mathrm{d}\mathscr{V}(\mathbf{x})}{\mathrm{d}x} - \gamma\, m_i \frac{\mathrm{d}\mathbf{x}_i}{\mathrm{d}t} + f(t)$$

Gaussian white noise of zero mean, $\langle f(t)\rangle = 0$, obeying the fluctuation-dissipation theorem

$$\langle f(t)\ f(t')\rangle = \frac{2\ m_i\ \gamma}{\beta}\ \delta(t-t')$$



which is precisely the condition to generate a canonical distribution.

Schlick, T. *Molecular modeling and simulation* Springer, **2002**

Constant-temperature molecular dynamics

Langevin dynamics

Central idea: Add to the conservative forces a frictional force proportional to the velocity. The friction removes the kinetic energy from the system. A random force adds kinetic energy to the system.

$$m_i \frac{\mathrm{d}^2\mathbf{x}_i}{\mathrm{d}t^2} = -\frac{\mathrm{d}\mathscr{V}(\mathbf{x})}{\mathrm{d}x} - \gamma\, m_i \frac{\mathrm{d}\mathbf{x}_i}{\mathrm{d}t} + f(t)$$

Gaussian white noise of zero mean, $\langle f(t)\rangle = 0$, obeying the fluctuation-dissipation theorem

$$\langle f(t)\ f(t')\rangle = \frac{2\ m_i\ \gamma}{\beta}\ \delta(t-t')$$

which is precisely the condition to generate a canonical distribution.

What should I use for the friction?

NAMD Scalable Molecular Dynamics

```
langevin                on
langevintemp            298.0
langevindamping         1.0
```

Schlick, T. *Molecular modeling and simulation* Springer, **2002**

Constant-temperature molecular dynamics

The Lowe-Andersen algorithm

Central idea: Couple the chemical system to a heat bath via stochastic forces that modify the kinetic energy of the atoms or molecules.

The time between collisions — or the number of collisions over a short-time interval, is decided randomly, based on the Poisson distribution, $P(t) = \nu \ \exp(-\nu t)$.

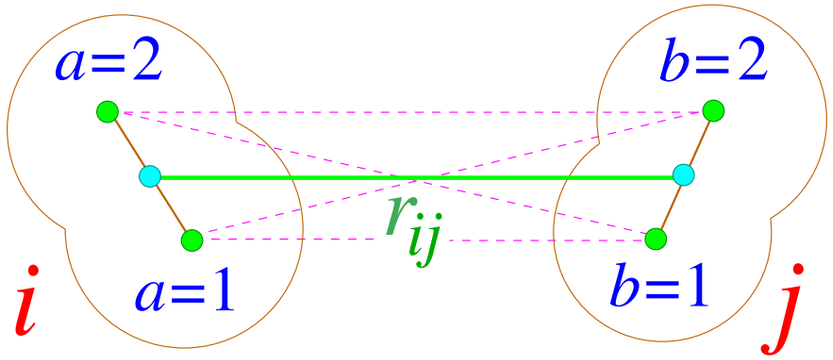
Between collisions the system evolves at constant energy. During a collision event, the new momentum of the particles is chosen randomly from a Boltzmann distribution at a given temperature. The stochastic collision frequency can adopt any value, albeit there is an optimum choice,

$$\nu = \frac{2a\kappa V^{1/3}}{3k_{\mathrm{B}}N}$$

Andersen, H. C. *J. Chem. Phys.* **1980**, *72*, 2384-2393

Instantaneous pressure and the virial theorem

Pair interactions: $$\sum_i \mathbf{x}_i \cdot \mathbf{f}_i = \sum_{i<j} \mathbf{x}_i \cdot \mathbf{f}_{ij} = \frac{1}{2} \sum_i \sum_{j \neq i} \mathbf{r}_i \cdot \mathbf{f}_{ij} + \mathbf{x}_j \cdot \mathbf{f}_{ji}$$



Third law of Newton, $\mathbf{f}_{ij} = -\mathbf{f}_{ji}$

$$\sum_i \mathbf{x}_i \cdot \mathbf{f}_i = \frac{1}{2} \sum_i \sum_{j \neq i} \mathbf{f}_{ij} \cdot (\mathbf{x}_i - \mathbf{x}_j) = \sum_{i<j} \mathbf{f}_{ij} \cdot \mathbf{x}_{ij}$$

Internal virial: $$\mathscr{W} = \frac{1}{3} \sum_i \mathbf{x}_i \cdot \mathbf{f}_i^{\text{intermolecular}} = -\frac{1}{3} \sum_i \mathbf{x}_i \cdot \boldsymbol{\nabla}_{(\boldsymbol{r_i})} \mathscr{V}(\mathbf{x})$$

The external pressure arises from external forces,

$$\frac{1}{3} \langle \sum_i \mathbf{x}_i \cdot \mathbf{f}_i^{\text{external}} \rangle = -PV = -\left(\frac{N}{\beta} + \langle \mathscr{W} \rangle \right)$$

Instantaneous pressure,

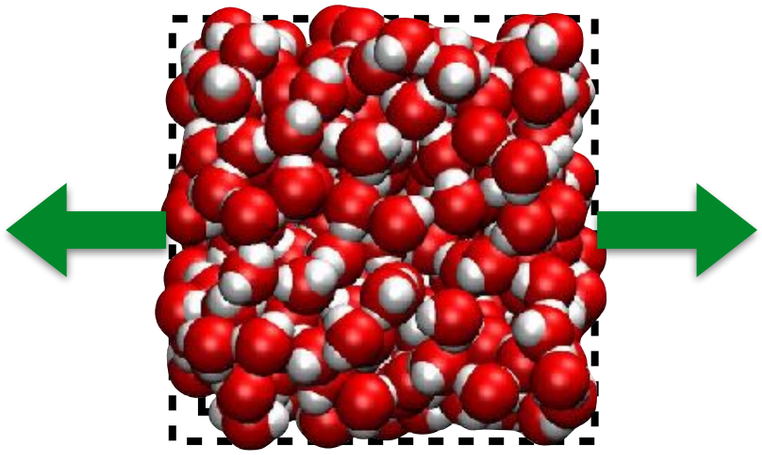
$$P_{\mathscr{P}} = \frac{\rho}{\beta} + \frac{\mathscr{W}}{V} = \frac{1}{V} \left(\frac{N}{\beta} - \frac{1}{3} \sum_i \mathbf{x}_i \cdot \mathbf{f}_i \right)$$

Constant-pressure molecular dynamics

Extended system

Central idea: Couple the system to an external, additional variable, V, that could be related to the motion of a piston.

$$\begin{cases} \mathscr{V}_V = \dfrac{1}{2}\, m_P\, \dot{V}^2 \\ \\ \mathscr{T}_V = P\, V \end{cases}$$



Rescale: $\mathbf{s} = \mathbf{x}/V^{1/3}$ and $\dot{\mathbf{s}} = \mathbf{v}/V^{1/3}$

Extended Lagrangian, $\mathscr{L}_V(\mathbf{x};\mathbf{p}_x) = \mathscr{T}(\mathbf{p}_x) + \mathscr{T}_V(\mathbf{p}_x) - \mathscr{V}(\mathbf{x}) - \mathscr{V}_V(\mathbf{x})$

Add a frictional term and a stochastic force to eliminate possible resonances between the piston and the chemical system.

$$\begin{cases} \ddot{\mathbf{s}}_i = \dfrac{\mathbf{f}_i}{m_i V^{1/3}} - \dfrac{2}{3}\,\dfrac{\dot{\mathbf{s}}_i \dot{V}}{V} \\ \\ \ddot{V} = \dfrac{P_{\mathscr{P}} - P}{m_P} - \gamma \dot{V} + R(t) \end{cases}$$

Andersen, H. C. *J. Chem. Phys.* **1980**, *72*, 2384-2393

Feller, S. E.; Zhang, Y. H.; Pastor, R. W.; Brooks, B. R. *J. Chem. Phys.* **1995**, *103*, 4613-4621

Constant-pressure molecular dynamics

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NAMD Scalable Molecular Dynamics

```
langevinpiston            on
langevinpistontarget       1
langevinpistonperiod     100
langevinpistondecay      100
langevinpistontemp       298
```

Rescale: $\mathbf{s} = \mathbf{x}/V^{1/3}$ and $\dot{\mathbf{s}} = \mathbf{v}/V^{1/3}$

Extended Lagrangian, $\mathscr{L}_V(\mathbf{x};\mathbf{p}_x) = \mathscr{T}(\mathbf{p}_x) + \mathscr{T}_V(\mathbf{p}_x) - \mathscr{V}(\mathbf{x}) - \mathscr{V}_V(\mathbf{x})$

Add a frictional term and a stochastic force to eliminate possible resonances between the piston and the chemical system.

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Andersen, H. C. *J. Chem. Phys.* **1980**, *72*, 2384-2393

Feller, S. E.; Zhang, Y. H.; Pastor, R. W.; Brooks, B. R. *J. Chem. Phys.* **1995**, *103*, 4613-4621

Constant-pressure molecular dynamics

The weak -coupling algorithm

Central idea: The instantaneous pressure, $P_{\mathscr{P}}(t)$, relaxes towards the reference value, P.

$$\frac{\mathrm{d}P_{\mathscr{P}}(t)}{\mathrm{d}t} = \frac{P - P_{\mathscr{P}}(t)}{\tau_P}$$

The atomic coordinates and the dimensions of the simulation cell are rescaled by a factor ς.

Change in the volume, $\Delta V = (\varsigma^3 - 1)\ V$, and variation of the pressure:

$$\Delta P = \frac{\Delta V}{\beta_{\mathscr{T}}\ V}$$

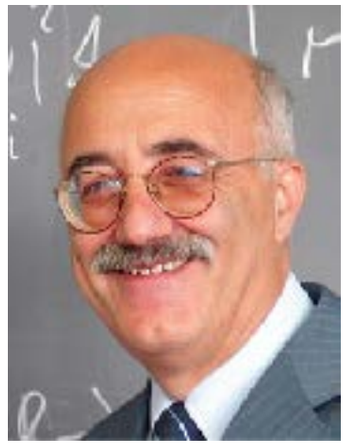
$$\varsigma = \left[1 - \beta_{\mathscr{T}}\ \delta t\ \frac{P - P_{\mathscr{P}}(t)}{\tau_P}\right]^{1/3}$$

Strictly speaking, this algorithm does not yield an isobaric distribution.

Berendsen, H. J. C.; Postma, J. P. M.; Van Gunsteren, W. F.; DiNola, A.; Haak, J. R. *J. Chem. Phys.* **1984**, *81*, 3684-3690

Constant-pressure molecular dynamics

Modifying the shape of the cell



Metric transform: $\mathbf{r} = \mathbf{H}\ \mathbf{s}$, where $\mathbf{H} \equiv (\mathbf{h}_1; \mathbf{h}_2; \mathbf{h}_3)$

Volume of the cell: $V = \|\mathbf{H}\| = \mathbf{h}_1 \cdot \mathbf{h}_2 \times \mathbf{h}_3$

Extended Lagrangian:
$$\begin{cases} \mathscr{V}_V = P\ V \\ \mathscr{T}_V = \dfrac{1}{2}\ Q \sum_\alpha \sum_\beta \|\dot{\mathbf{H}}_{\alpha\beta}\|^2 \end{cases}$$

$$m\frac{\mathrm{d}^2\mathbf{s}}{\mathrm{d}t^2} = \frac{1}{\mathbf{H}}\ \mathbf{f} - \frac{m}{\mathbf{G}}\ \dot{\mathbf{G}}\ \frac{\mathrm{d}\mathbf{s}}{\mathrm{d}t} \qquad \text{where} \qquad \mathbf{G} = \mathbf{H}^{\mathrm{T}}\ \mathbf{H}$$

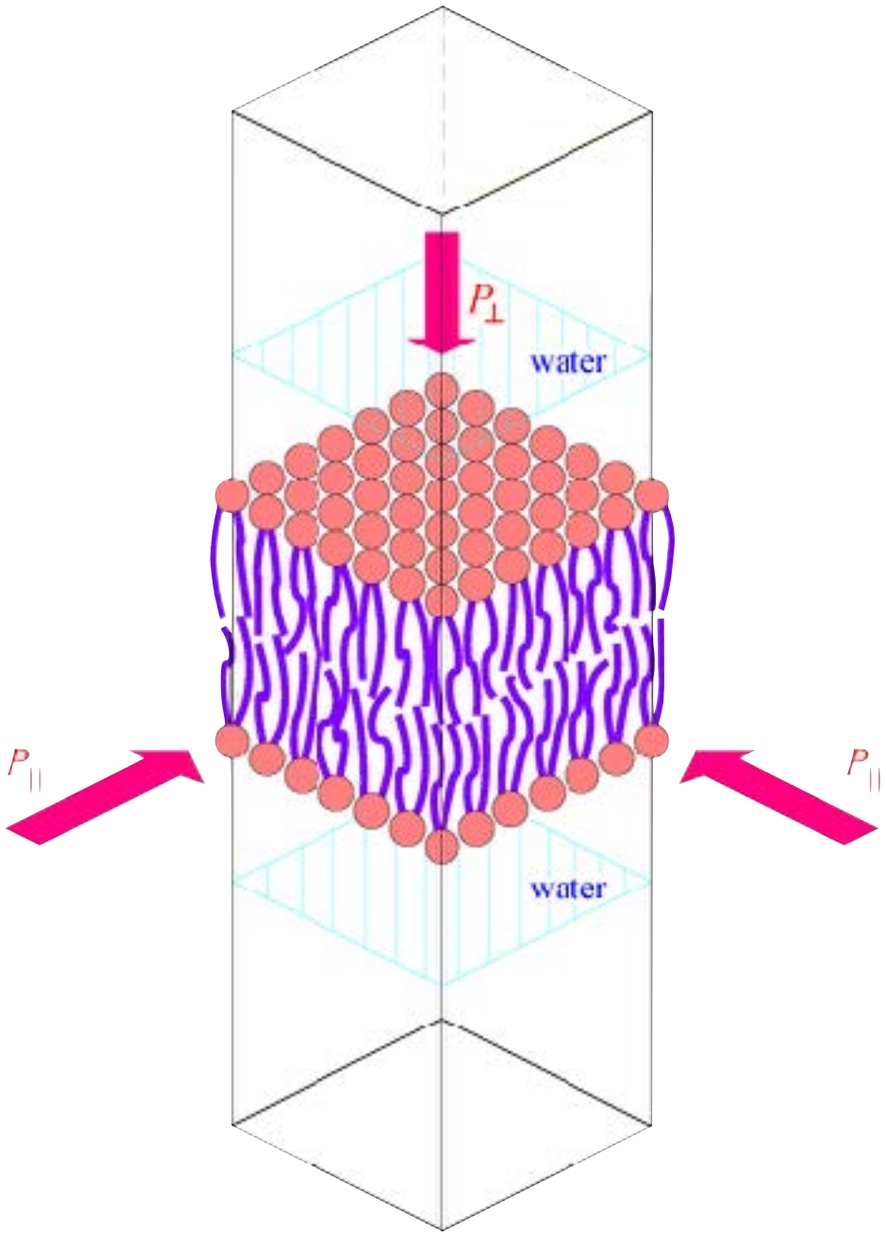
$$Q\ \ddot{\mathbf{G}} = (\mathbf{P}_{\mathscr{P}} - \mathbf{1}P)\ V\ \left(\frac{1}{\mathbf{H}}\right)^{\mathrm{T}}$$

$$P_{\mathscr{P}}^{\alpha\beta} = \frac{1}{V}\left[\sum_i m_i \left(\mathbf{H}\ \frac{\mathrm{d}\mathbf{s}_i}{\mathrm{d}t}\right)^{\mathrm{T}}_\alpha \left(\mathbf{H}\ \frac{\mathrm{d}\mathbf{s}_i}{\mathrm{d}t}\right)^{\mathrm{T}}_\beta + \sum_i \sum_{j>i} (\mathbf{H}\ \mathbf{s}_{ij})_\alpha\ (\mathbf{f}_{ij})_\beta\right]$$

Parrinello, M.; Rahman, A. *J. Chem. Phys.* **1982**, *76*, 2662-2666

Constant-pressure molecular dynamics

How to handle anisotropic chemical systems?



Berger, O.; Edholm, O.; Jähnig, F. *Biophys. J.* **1997**, *72*, 2002-2013

Historically, two conflicting approaches for handling the pressure:

A membrane is a self-assembled system. Consequently, $\gamma = 0$, because:

$$\gamma = \int_{z_1}^{z_2} \mathrm{d}z \ \left[P_\perp(z) - P_{||}(z)\right]$$

Since only a small patch of the "real" membrane is simulated, a component of the capillary wave and bending motion spectra is missing. γ is, therefore, finite.

More accurate force fields reconcile the two views.

Feller, S. E.; Pastor, R. W. *Biophys. J.* **1996**, *71*, 1350-1355

Feller, S. E.; Pastor, R. W. *Biophys. J.* **1999**, *111*, 1281-1287

Klauda, J. B.et al. *J. Phys. Chem. B* **2010**, *114*, 7830-7843

Molecular dynamics simulations can be carried out in a variety of ensembles.

The choice of the thermodynamic ensemble is dictated by the conditions in which the experiment was performed — and the nature of the molecular assembly.

Several algorithms are available to maintain the temperature and the pressure constant. Only a few of them supply the correct distribution.

The parameters of the thermostat and of the barostat have a direct impact on the behavior of the simulation and the convergence properties thereof.

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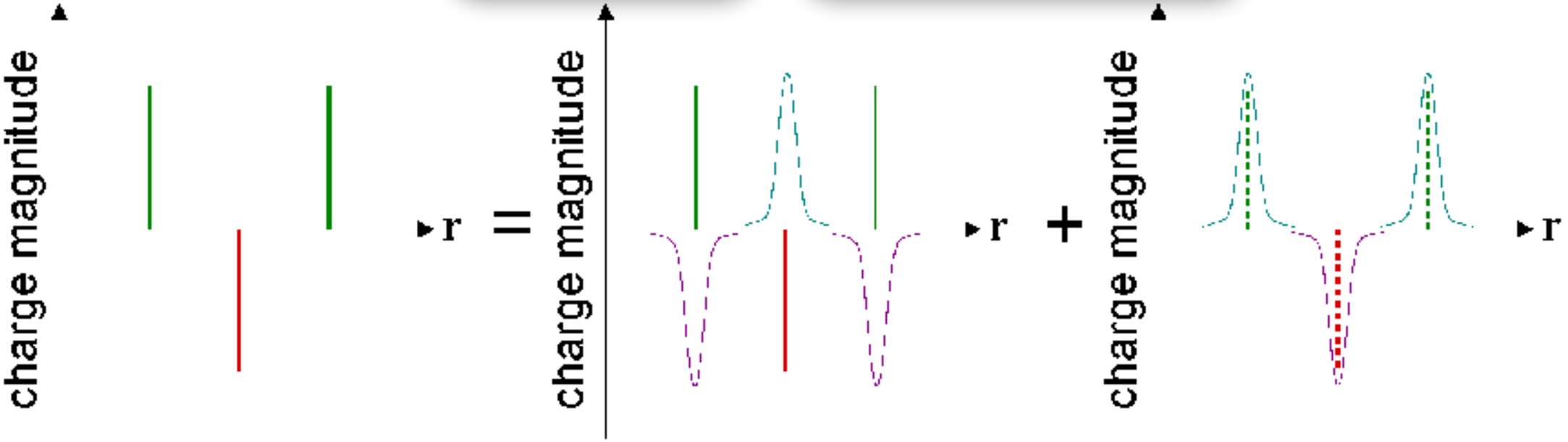
Why should we turn to lattice sums?

Central idea: For an electrically neutral system, replace the conditionally convergent,

$$\mathscr{V}_{\text{Coulomb}}(\mathbf{r}) = \sum_{i<j} \frac{q_i q_j}{4\pi\epsilon_0\epsilon_1 r_{ij}}$$

by,

$$\sum_{\mathbf{n}} \frac{1}{|\mathbf{n}|}\mathscr{F}(\mathbf{n}) + \sum_{\mathbf{m}} \frac{1}{|\mathbf{m}|}[1-\mathscr{F}(\mathbf{m})]$$



Gaussian charge distribution, $\varrho_i(\mathbf{r}) = q_i\alpha^3 \dfrac{\exp(-\alpha^2 r^2)}{\sqrt{\pi^3}}$

Ewald, P. *Ann. Phys.* **1921**, *64*, 253-287

Why should we turn to lattice sums?

$$\sum_{\mathbf{n}} \frac{1}{|\mathbf{n}|}\mathscr{F}(\mathbf{n}) + \sum_{\mathbf{m}} \frac{1}{|\mathbf{m}|}[1-\mathscr{F}(\mathbf{m})]$$

The interactions of charges are screened by the charge distribution, limiting their contribution to a short-range term. Convergence of the sum of charges and their images in the direct space is fast.

In the reciprocal space, a Fourier transform is used for solving $\nabla^2 \mathscr{V}_i(\mathbf{r}) = -4\pi\varrho_i(\mathbf{r})$. The transform decreases rapidly and the sum converges equally so.

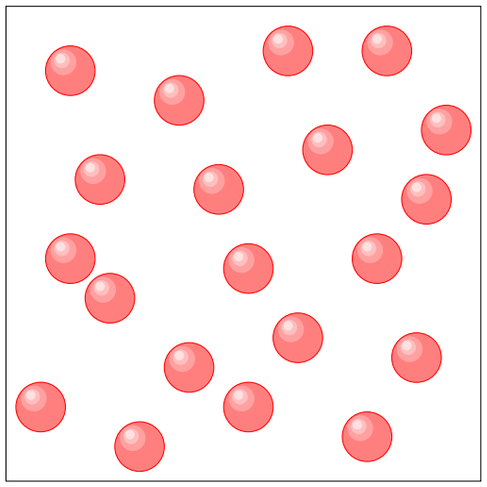
$$\mathscr{V}_{\text{Ewald}}(\mathbf{r}) = \frac{1}{2V\epsilon_0}\sum_{\mathbf{k}\neq\mathbf{0}} \frac{\exp(-k^2/4\alpha^2)}{k^2}\left[\sum_j q_j \exp(-i\mathbf{k}\cdot\mathbf{r}_j)\right]\left[\sum_j q_j \exp(i\mathbf{k}\cdot\mathbf{r}_j)\right]$$

$$+ \frac{1}{4\pi\epsilon_0}\sum_i\sum_{j>i}\frac{q_i q_j}{r_{ij}\,\operatorname{erfc}(\alpha r_{ij})} - \frac{\alpha}{4\pi^{3/2}\epsilon_0}\sum_i q_i^2$$

$$+ \frac{1}{4\pi\epsilon_0}\sum_i \sum_{j>i}^{j \text{ bound to } i} \frac{q_i q_j}{r_{ij}}$$

Ewald, P. *Ann. Phys.* **1921**, *64*, 253-287

Why should we turn to lattice sums?



(a)

Define a grid filling the simulation Cartesian space. Interpolate the charges on the grid and evaluate the charge distribution, $\varrho(\mathbf{r})$;

Fourier transform to obtain $\hat{\varrho}(\mathbf{k})$ and estimate of $\hat{\mathscr{V}}_{\text{long}}(\mathbf{k})$;
Inverse transform to get $\mathscr{V}_{\text{long}}(\mathbf{r})$;

Numerical evaluation of the forces from the potential;

Interpolation of the electric field towards the position of the particles.

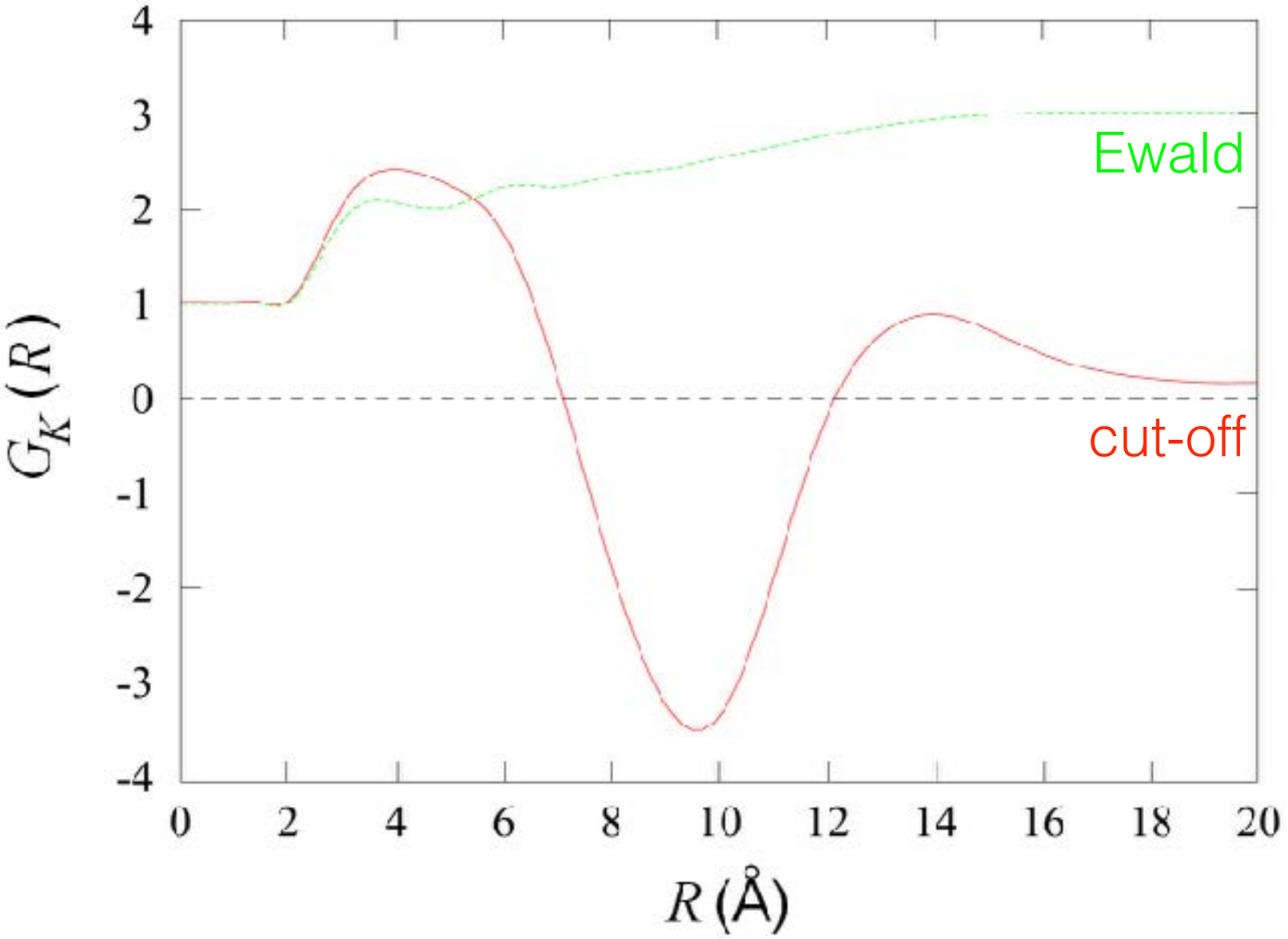
Analytical: $O(N^{3/2})$ at best
Discretized: $O(N \ln N)$

NAMD
Scalable Molecular Dynamics

```
PME                 yes
PMETolerance        10e-6
PMEInterpOrder      4
PMEGridSpacing      1
```

Toukmaji, A. Y. & Board Jr., J. A. *Comput. Phys. Comm.* **1996**, *95*, 73-92

Why should we turn to lattice sums?

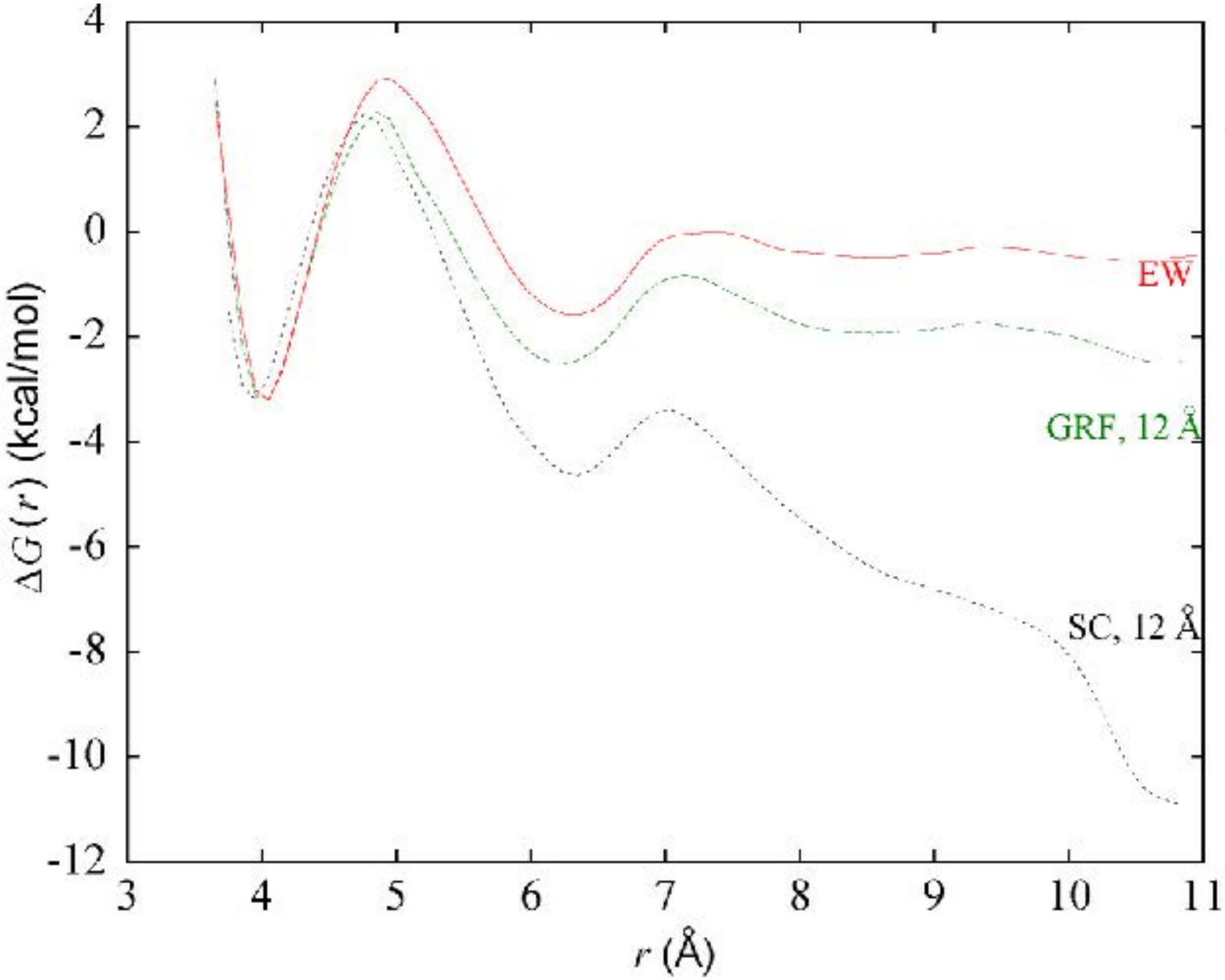


$$G_K(R) = \frac{\left\langle \sum_{i,j;r_{ij}<R} \boldsymbol{\mu}_i \cdot \boldsymbol{\mu}_j \right\rangle}{N\mu^2}$$

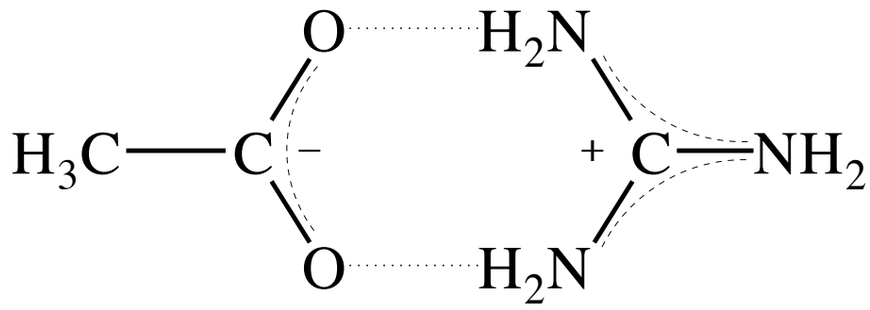
Access to dielectric permittivity.

Barker, J. A.;Watts, R. O. *Mol. Phys.* **1973**, *26*, 789-792

Why should we turn to lattice sums?



$$\Delta G(r) = -\frac{1}{\beta} \ln \frac{\int \mathrm{d}\mathbf{x}\ \delta(r'(\mathbf{x}) - r)\ \mathrm{e}^{-\beta \mathscr{V}(\mathbf{x})}}{\int \mathrm{d}\mathbf{x}\ \mathrm{e}^{-\beta \mathscr{V}(\mathbf{x})}}$$



Rozanska, X.; Chipot, C. *J. Chem. Phys.* **2000**, *112*, 9691-9694

SUMMARY

Long-range electrostatics cannot be properly handled by a mere spherical truncation.

Lattice-sum algorithms address the long-range nature of electrostatic interactions and the conditional convergence of the Coulomb sum by splitting the latter into a real-space and a Fourier-space contribution.

Contrary to traditional Ewald sum, particle-mesh approaches handle the Fourier-space part of the Coulomb sum on grids over which the position of the atoms is interpolated.

The usual N ln N cost of particle-mesh algorithms can be modulated by using a coarser discretization of space at the expense of accuracy.

Alternate schemes, e.g., the fast multipole method, are available, but have proven effective so far only for large arrays of particles.

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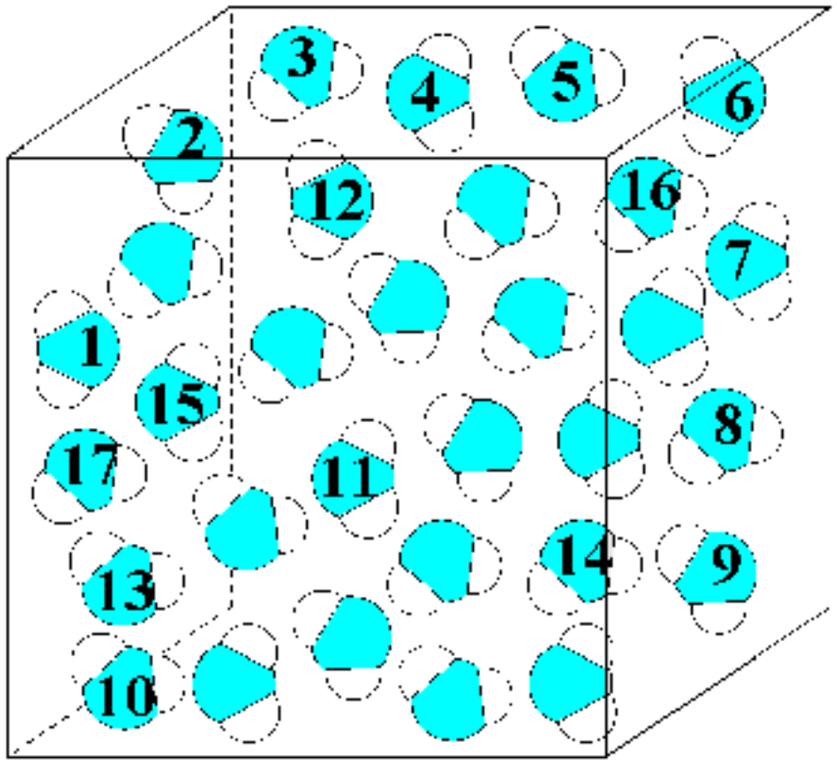
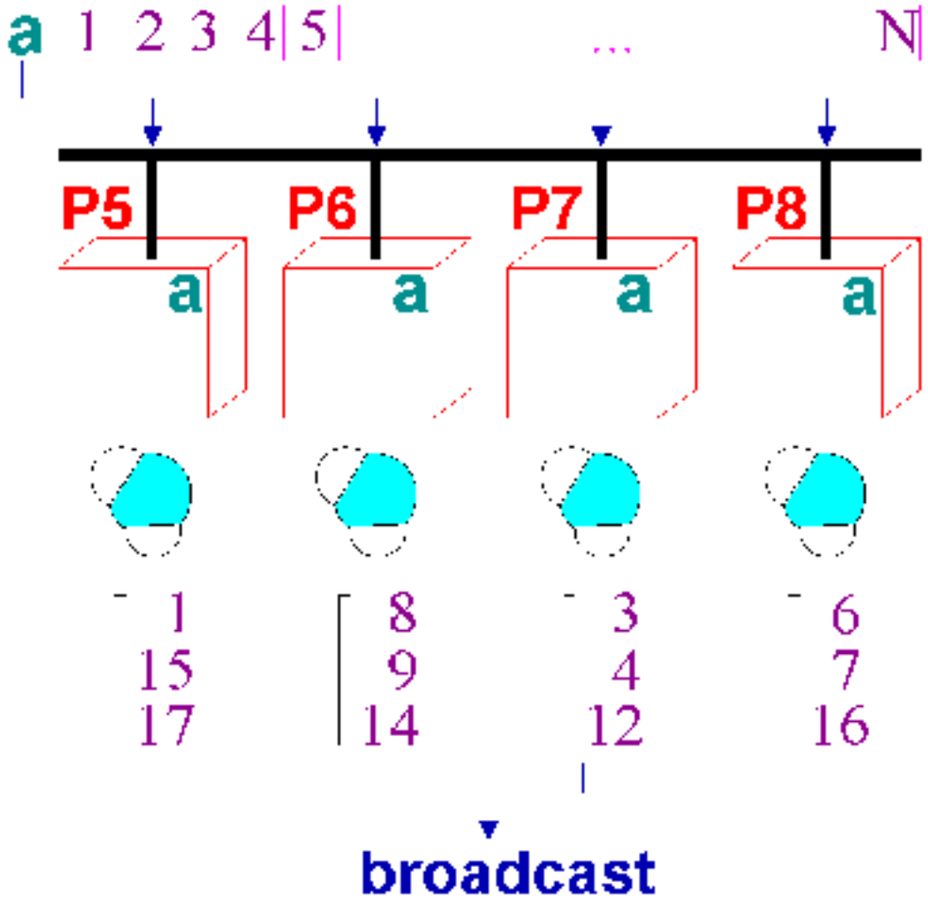
Data replication

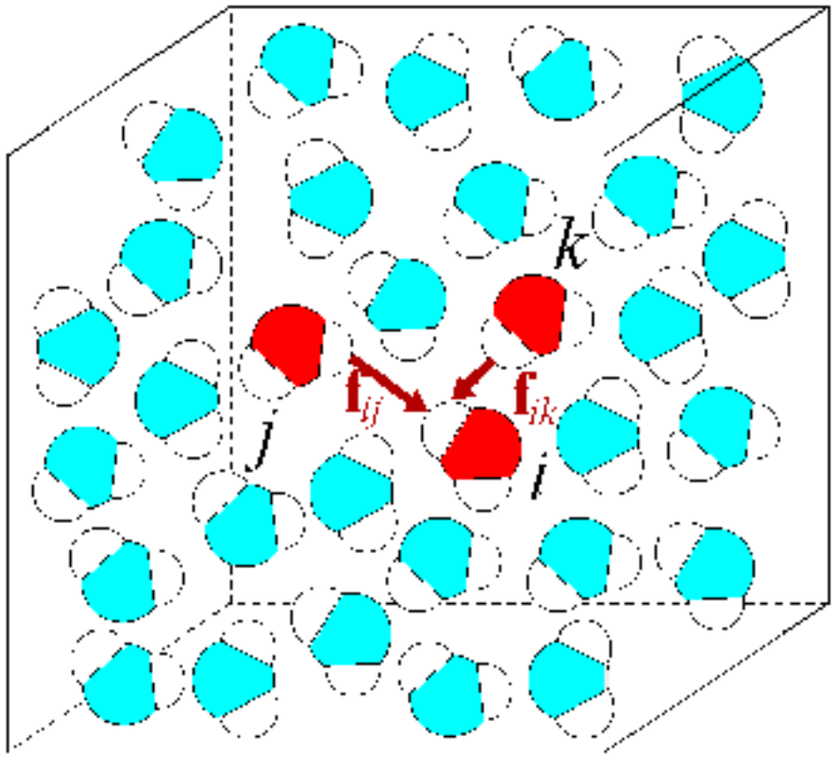


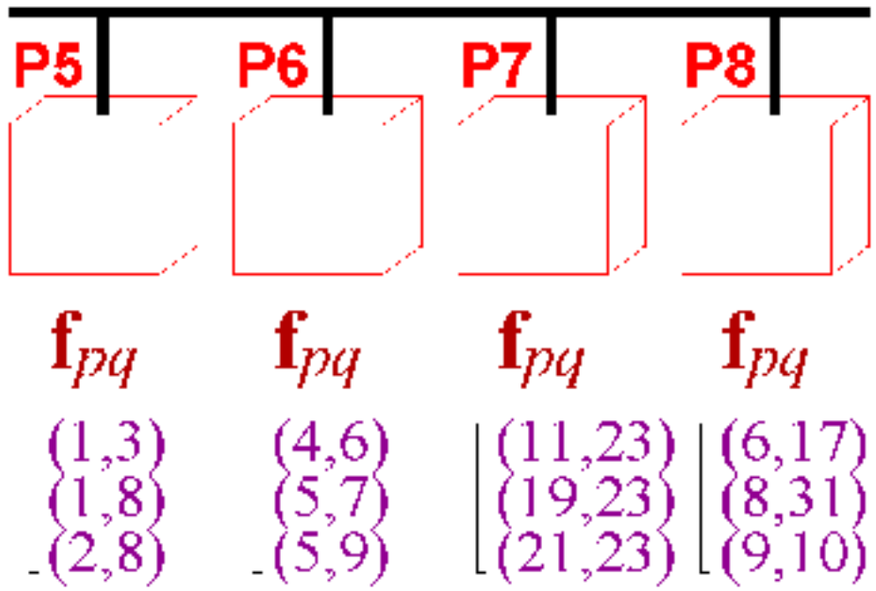


The particles are scattered onto the different processors.

Mertz, J. E.; Tobias, D. J.; Brooks III, C. L.; Singh, U. C. *J. Comput. Chem.* **1991**, *12*, 1270-1277

Force-loop splitting





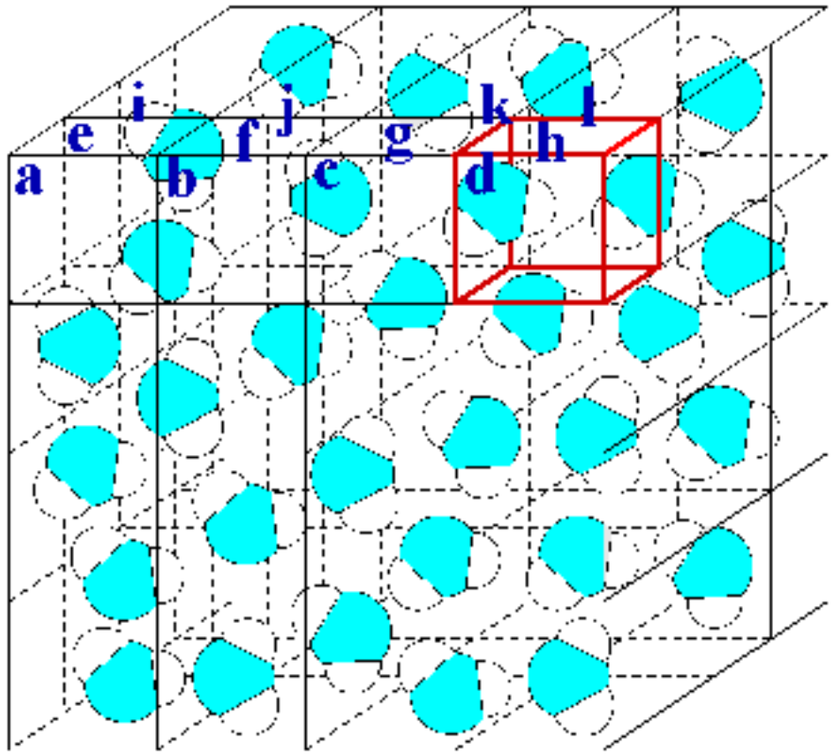
The intermolecular forces are scattered onto the different processors

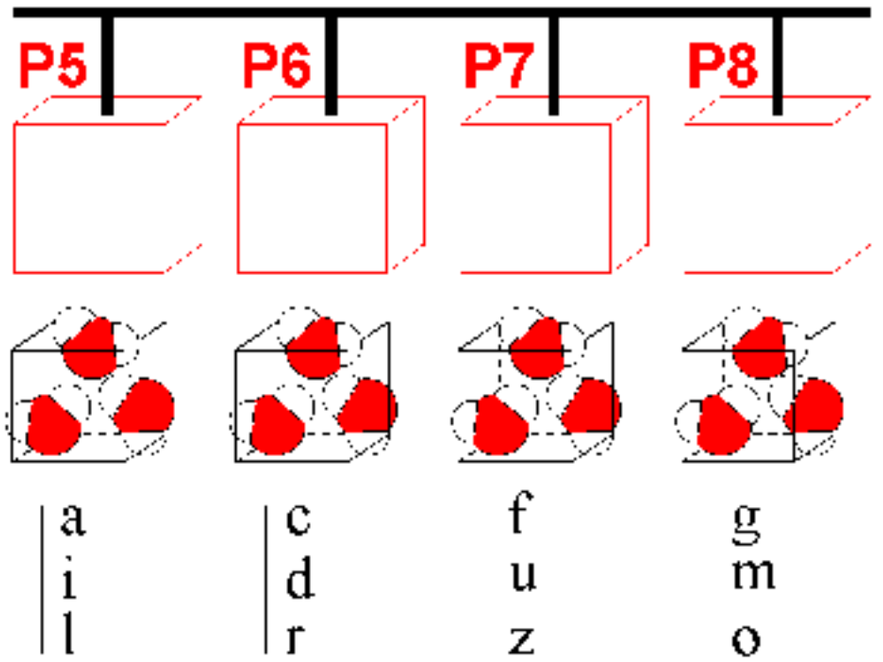
Super linear behavior for a small number of cores, but rapid collapse of performance.

Couturier, R.; Chipot, C. *Comp. Phys. Comm.* **2000**, *124*, 49-59

```
!$OMP  PARALLEL DO PRIVATE(i,k,j)
!$OMP+ SHARED(A,B,C)
      DO i=1,n
        k=A(i)
        DO j=1,k
          B(i)=k*B(i)+C(i)
        ENDDO
      ENDDO
!$OMP END PARALLEL DO
```

Spatial decomposition





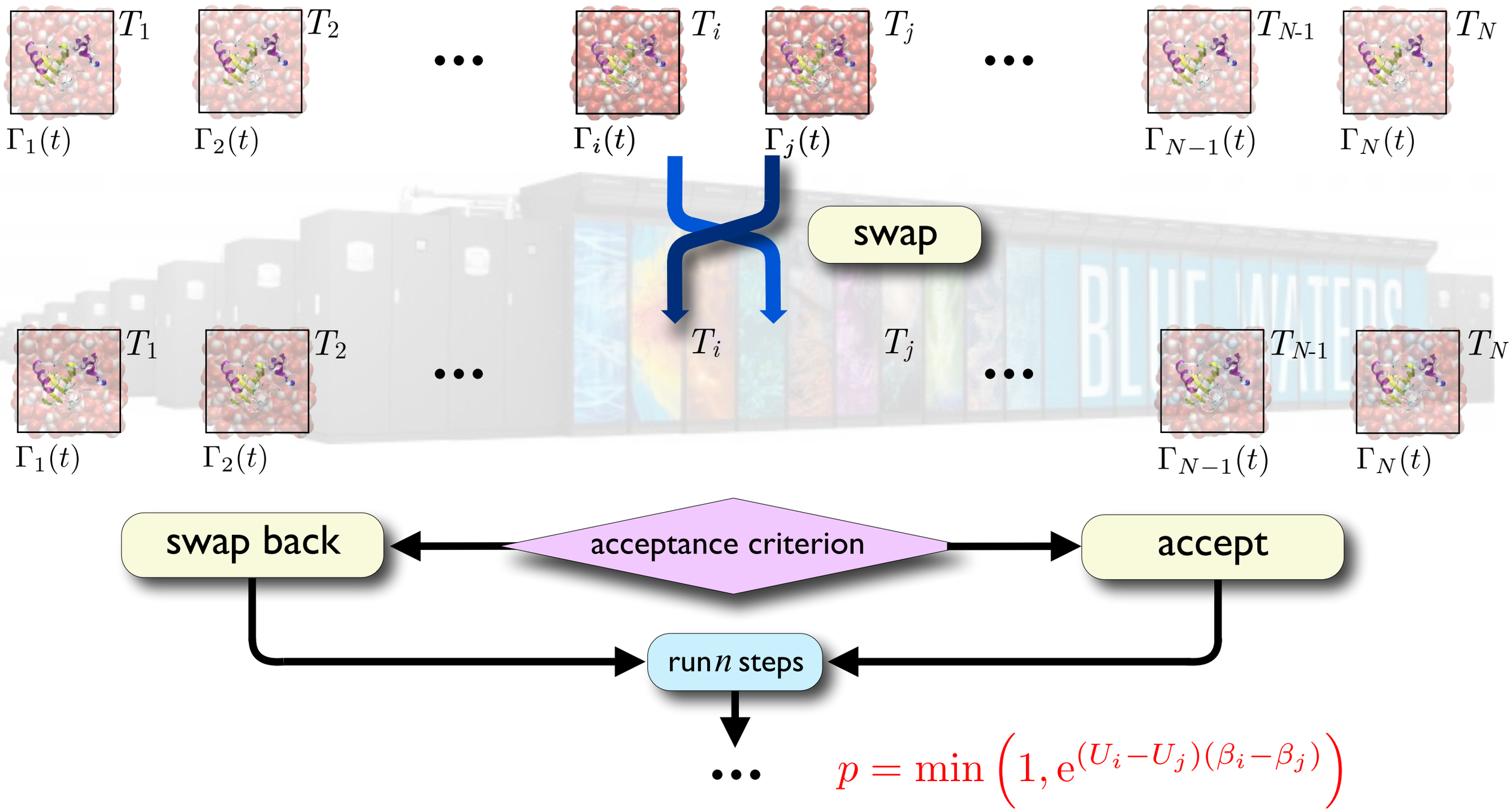
The simulation cell is broken into subcells, scattered onto the different processors, optimizing communication

Crucial role of load balancing for optimal performance.

Brown, D.; Clarke, J. H. R.; Okuda, M.; Yamazaki, T. *Comput. Phys. Comm.* **1993**, *74*, 67-80

Kalé, L. et al. *J. Comput. Phys.* **1999**, *151*, 283-312

Towards ergodic sampling — parallel tempering



Swendsen, R. H.; Wang, J. S. *Phys. Rev. Lett.* **1986**, *57*, 2607-2609

Sugita, Y.; Okamoto, Y. *Chem. Phys. Lett.* **1999**, *314*, 141-151

SUMMARY

Molecular dynamics is parallelizable in nature. Domain-decomposition strategies currently offer the best performance on multipurpose parallel computer architectures.

GPU acceleration offers a cost-effective alternative to conventional CPU-based machines. Further increase of the performance implies design of specific, dedicated processors.

Efficient parallelization on massively parallel architectures dilates the size scale more than it dilates the time scale.

Replica-exchange based algorithms enhance ergodic sampling by making high-temperature configurations available to low-temperature simulations.

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Appropriate questions that ought to be asked —

The results of the simulation are unexpected

A new phenomenon has been discovered

The results are simply erroneous

- The model used for this application is unadapted
- The force field is inadequate
- The simulation has not converged
- The program contains undocumented bugs
- The program has been misused

- Detailed description of the models?
- Detailed description of the force field?
- Time series?
- Checkup of the code?
- Detailed description of simulation setup?

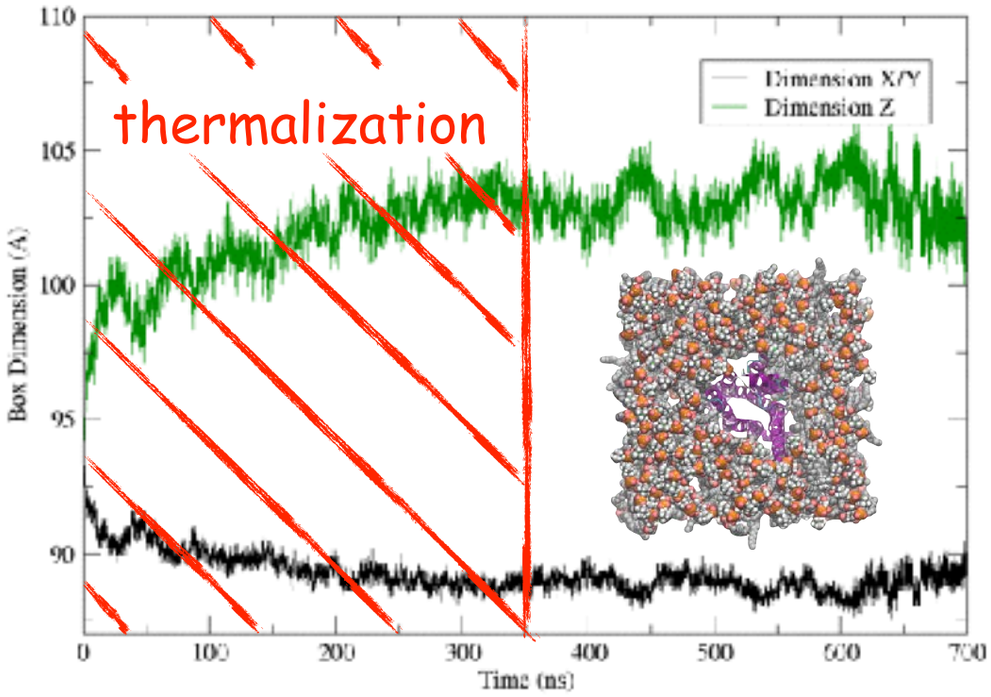
van Gunsteren, W. F.; Mark, A. E. *J. Chem. Phys.* **1998**, *108*, 6109-6116

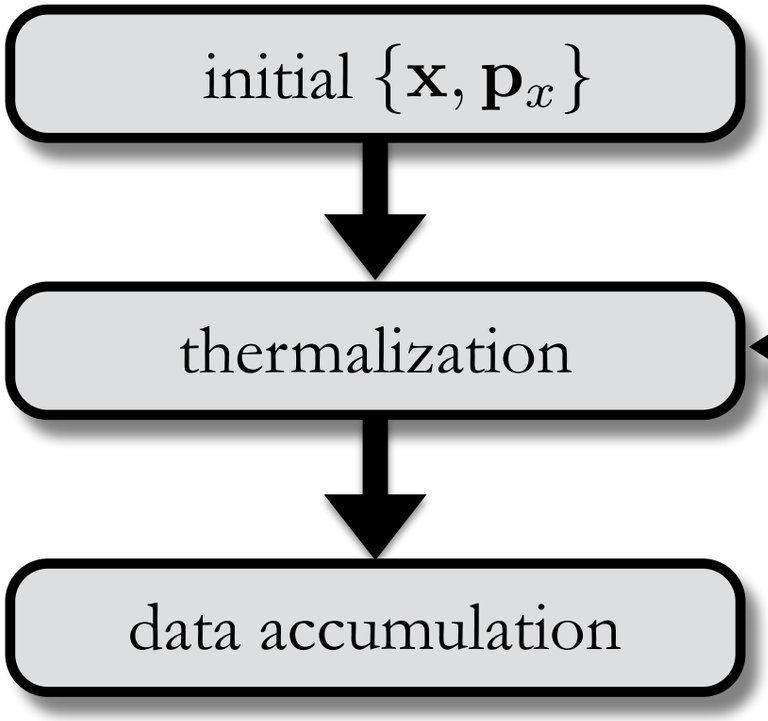
Appropriate questions that ought to be asked —

Why is it of paramount importance to thermalize the molecular assembly prior to accrue data for analysis?

First, because evolution of the temperature and the pressure ought to reflect the proper thermodynamic ensemble.

Second, because large fluctuations in the volume of the simulation cell may reflect suboptimal packing.





Poorly thermalized assays may result in artifactual observations due, for instance, to spurious conformational changes.

van Gunsteren, W. F.; Mark, A. E. *J. Chem. Phys.* **1998**, *108*, 6109-6116

Molecular dynamics simulations are a source of numerous errors of different nature.

Insufficient thermalization is at the origin of spurious behaviors, often difficult to discern.

Thermalization ought to be performed in a stepwise fashion, confining the position of the different components of the molecular assay prior to unrestrained sampling.

Other factors can impact the outcome of the simulation. A clear understanding of the different parameters at play and their respective effects is highly desirable.

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Radial distribution functions

The pair correlation function,

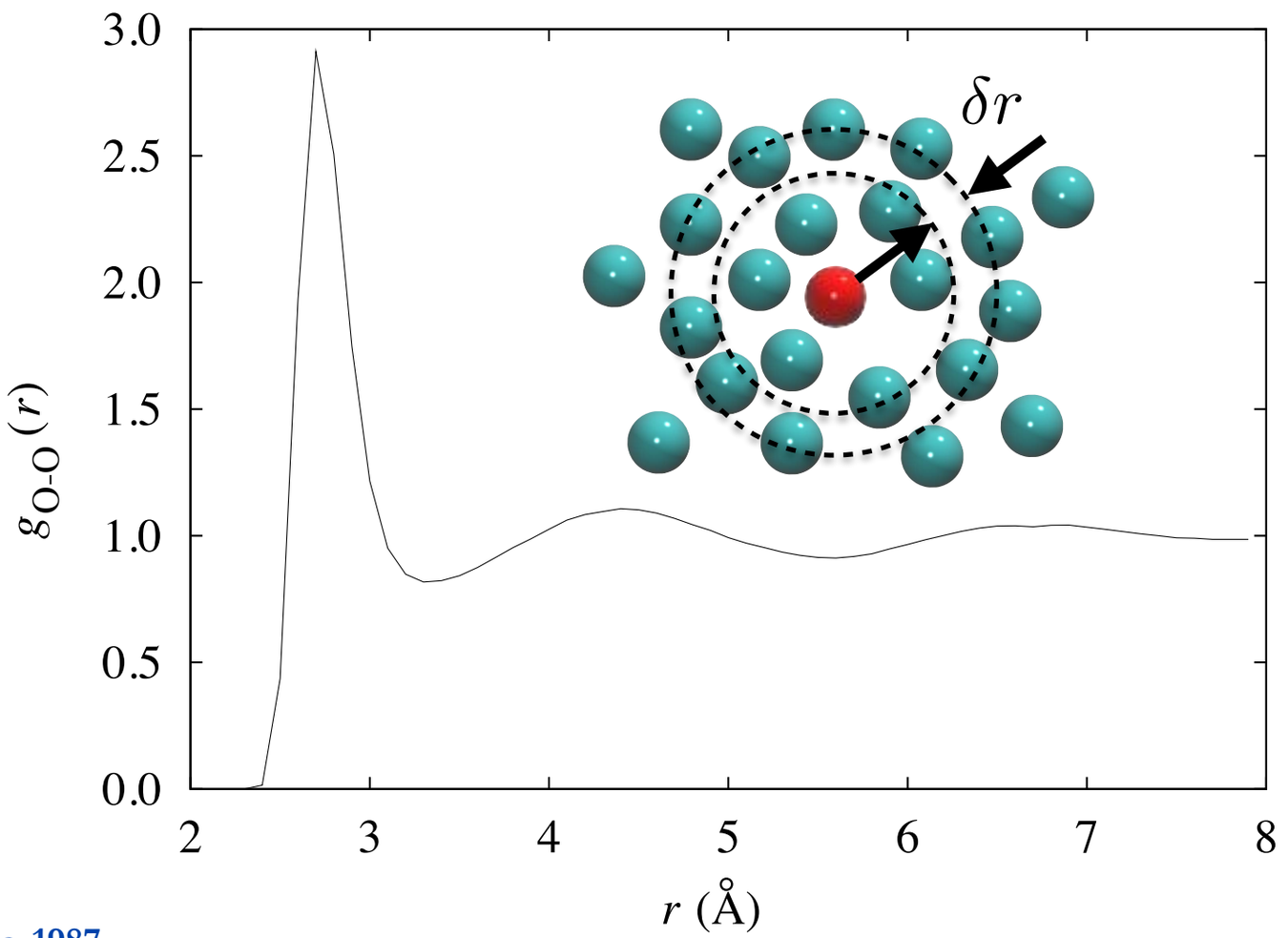
$$g(\mathbf{x}_1;\mathbf{x}_2) = \frac{N(N-1)}{\rho^2 \int \mathrm{e}^{-\beta\mathscr{V}(\mathbf{x}_1,\ldots,\mathbf{x}_N)}\,\mathrm{d}\mathbf{x}_1\ldots\mathrm{d}\mathbf{x}_N} \int \mathrm{e}^{-\beta\mathscr{V}(\mathbf{x}_1,\ldots,\mathbf{x}_N)}\,\mathrm{d}\mathbf{x}_3\ldots\mathrm{d}\mathbf{x}_N$$

can be restated as an ensemble average,

$$g(r) = \frac{V}{N^2}\left\langle \sum_i \sum_{j\neq i} \delta(\mathbf{x}-\mathbf{x}_{ij}) \right\rangle$$

which after normalization reads,

$$g_{ij}(r) = \frac{\langle n_j(r;r+\delta r)\rangle}{4\pi\rho_j r^2 \mathrm{d}r}$$



Chandler, D. *Introduction to modern statistical mechanics*, Oxford University Press, **1987**

Autocorrelation functions

Correlation coefficient of observable $\mathscr{B}$,

$$c_{\mathscr{B}\mathscr{B}'} = \frac{\langle \delta\mathscr{B}\ \delta\mathscr{B}' \rangle}{\sigma(\mathscr{B})\ \sigma(\mathscr{B}')}$$

with $\delta\mathscr{B} = \mathscr{B} - \langle \mathscr{B} \rangle$

$$c_{\mathscr{B}\mathscr{B}'}(t) = \frac{\langle \delta\mathscr{B}(t)\ \delta\mathscr{B}'(0) \rangle}{\sigma(\mathscr{B})\ \sigma(\mathscr{B}')}$$

$$c_{\mathscr{B}\mathscr{B}}(t) = \frac{\langle \delta\mathscr{B}(t)\ \delta\mathscr{B}(0) \rangle}{\langle \delta\mathscr{B}(0)\ \delta\mathscr{B}(0) \rangle}$$

Allen, M. P.; Tildesley, D. J. Computer Simulation of Liquids, Clarendon Press, **1987**

Diffusion coefficients

From autocorrelation functions,

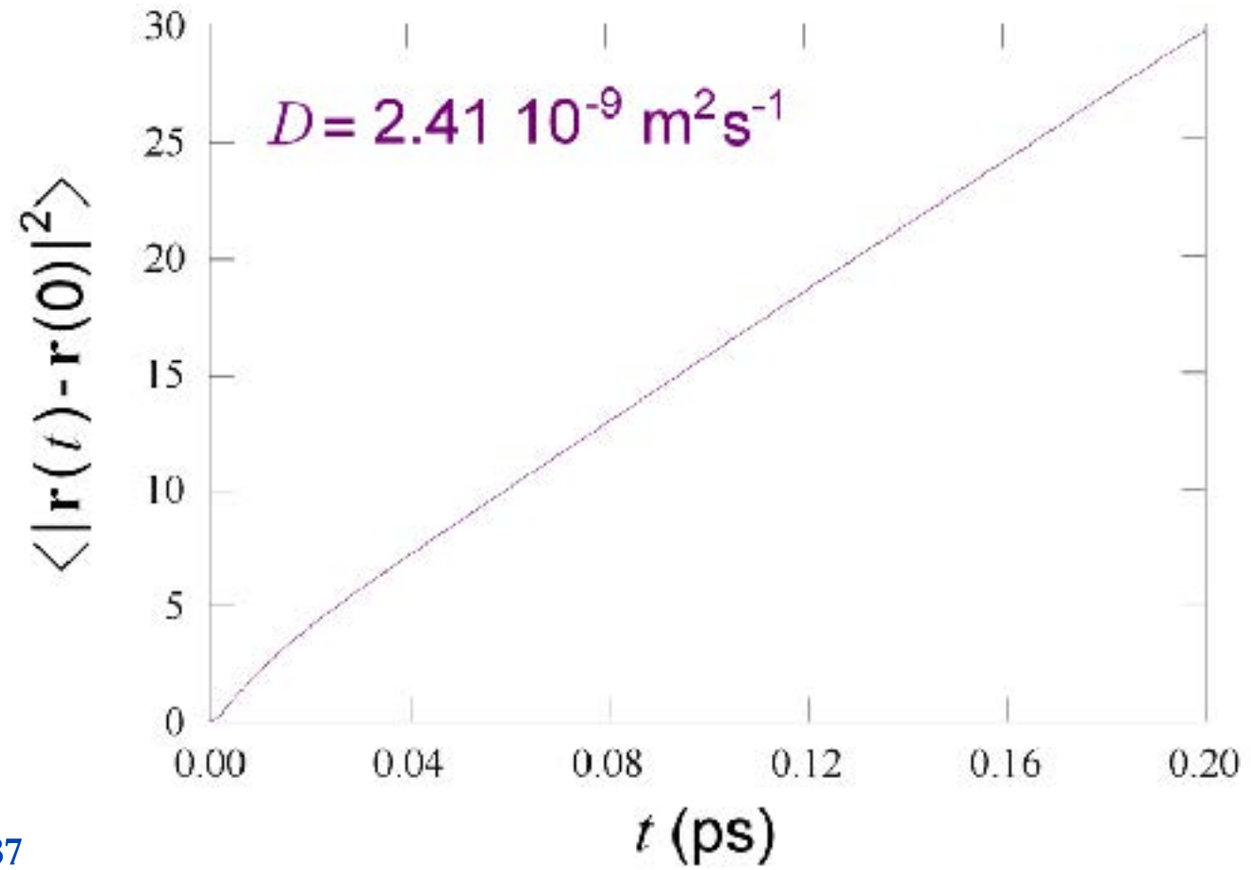
$$\gamma = \int_0^\infty \left\langle \dot{\mathscr{B}}(t)\dot{\mathscr{B}}(0)\right\rangle \mathrm{d}t$$

$$2t\gamma = \left\langle \left(\dot{\mathscr{B}}(t) - \dot{\mathscr{B}}(0)\right)^2 \right\rangle$$

$$D = \frac{1}{3}\int_0^\infty \langle \mathbf{v}(t)\cdot\mathbf{v}(0)\rangle$$

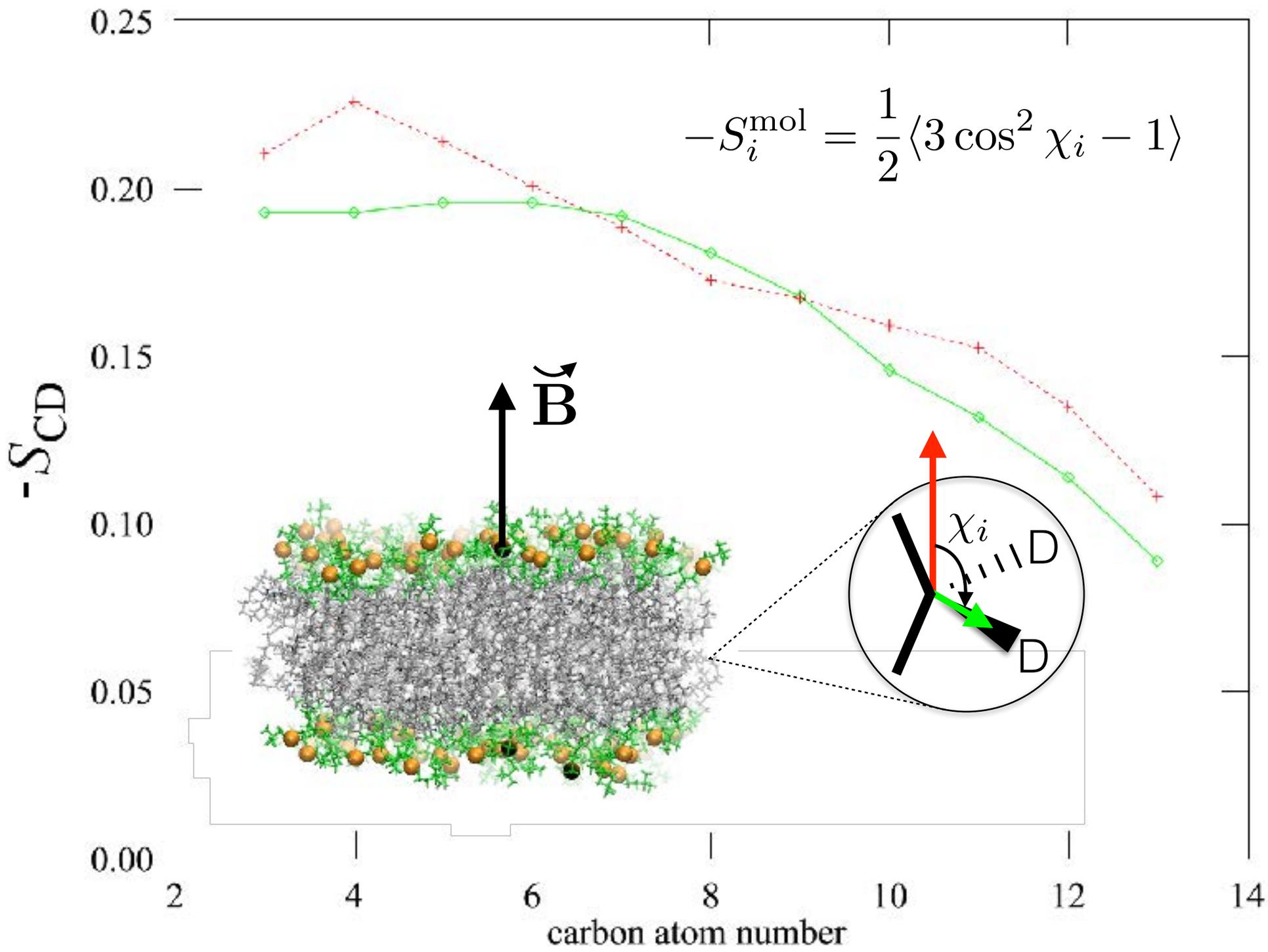
which, over long times, coincides with,

$$2tD = \frac{1}{3}\left\langle |\mathbf{r}(t) - \mathbf{r}(0)|^2 \right\rangle$$



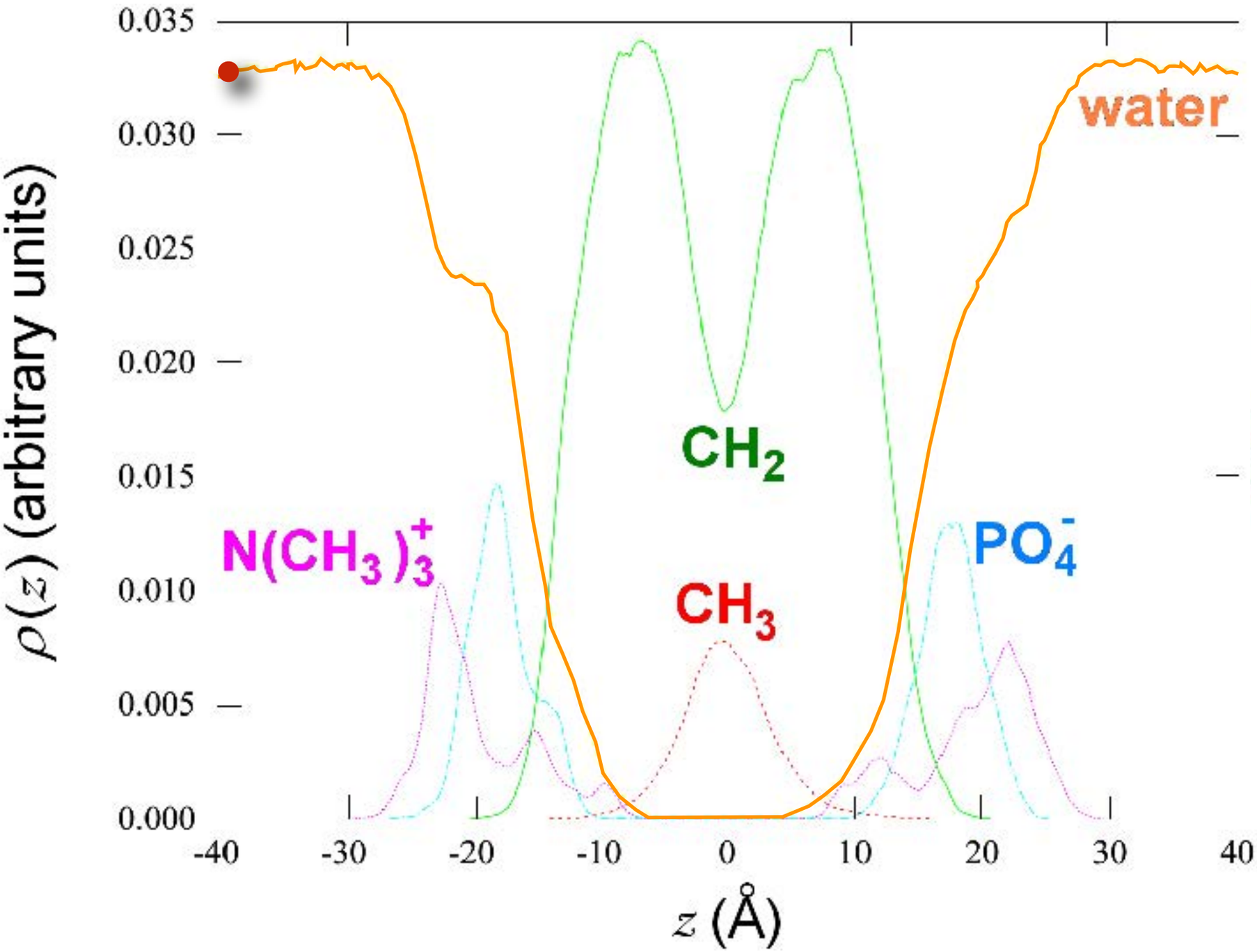
Allen, M. P.; Tildesley, D. J. Computer Simulation of Liquids, Clarendon Press, **1987**

Structural properties



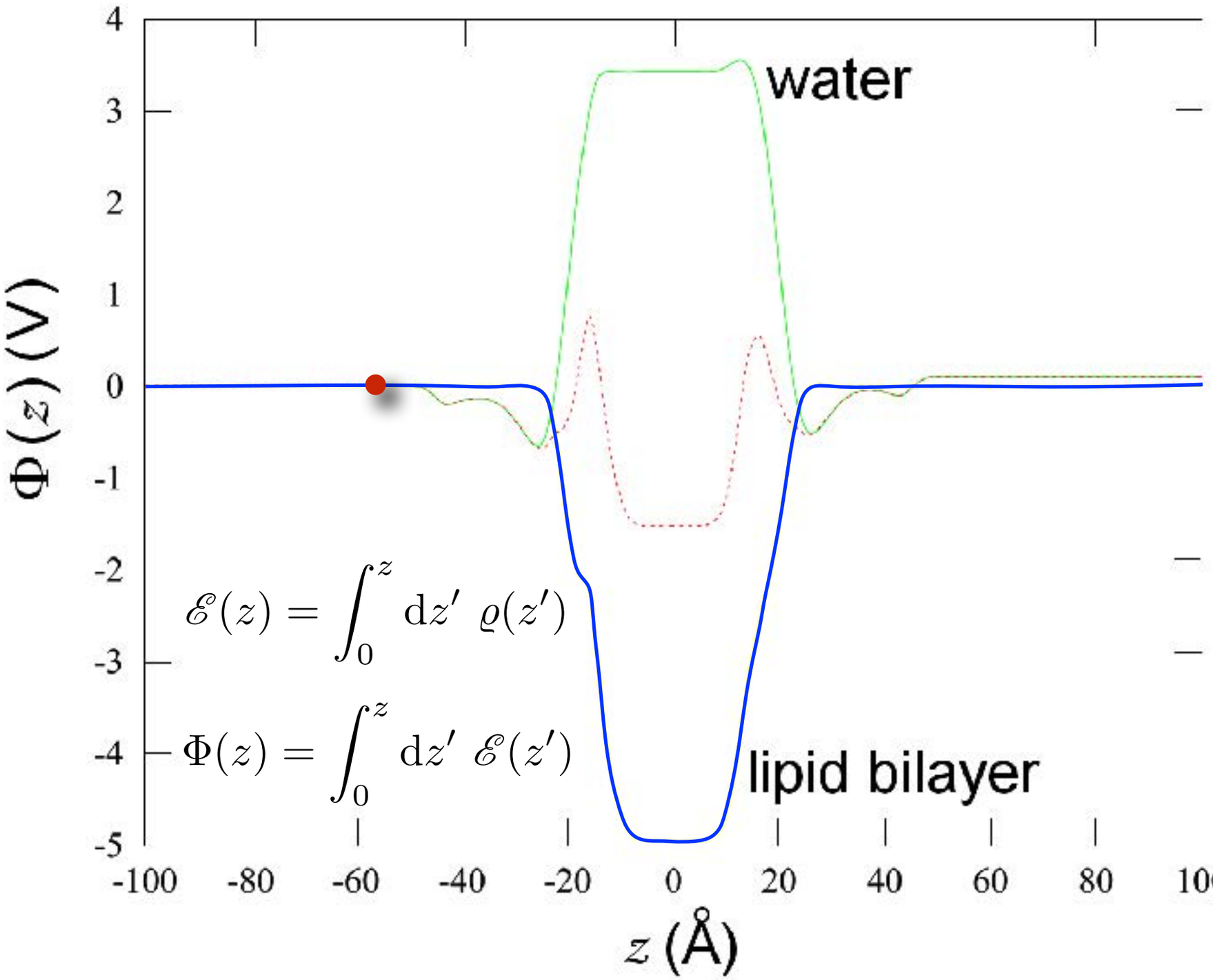
Douliez, J. P.; Léonard, A.; Dufourc, E. J. *Biophys. J.* **1995**, *68*, 1727-1739

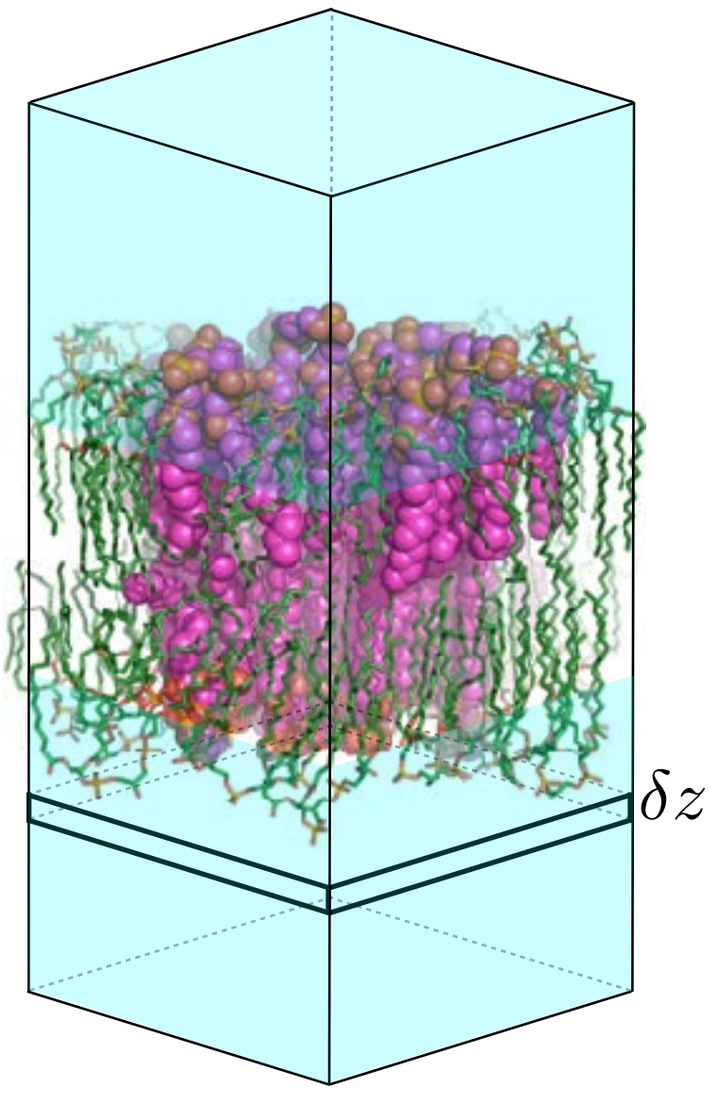
Structural properties



Chandler, D. *Introduction to modern statistical mechanics*, Oxford University Press, **1987**

Structural properties

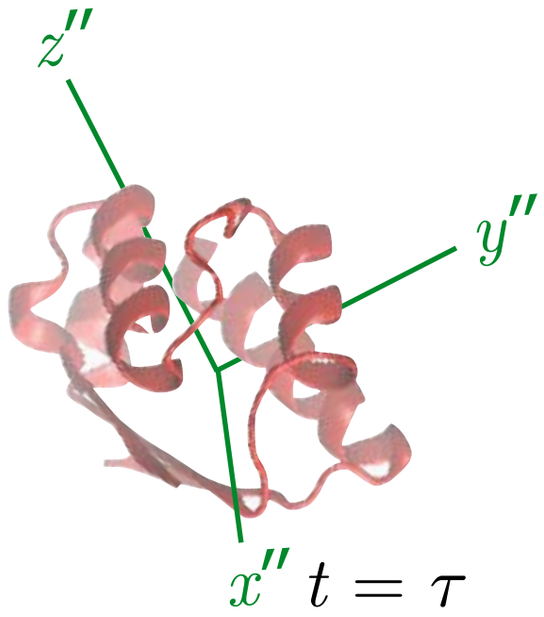


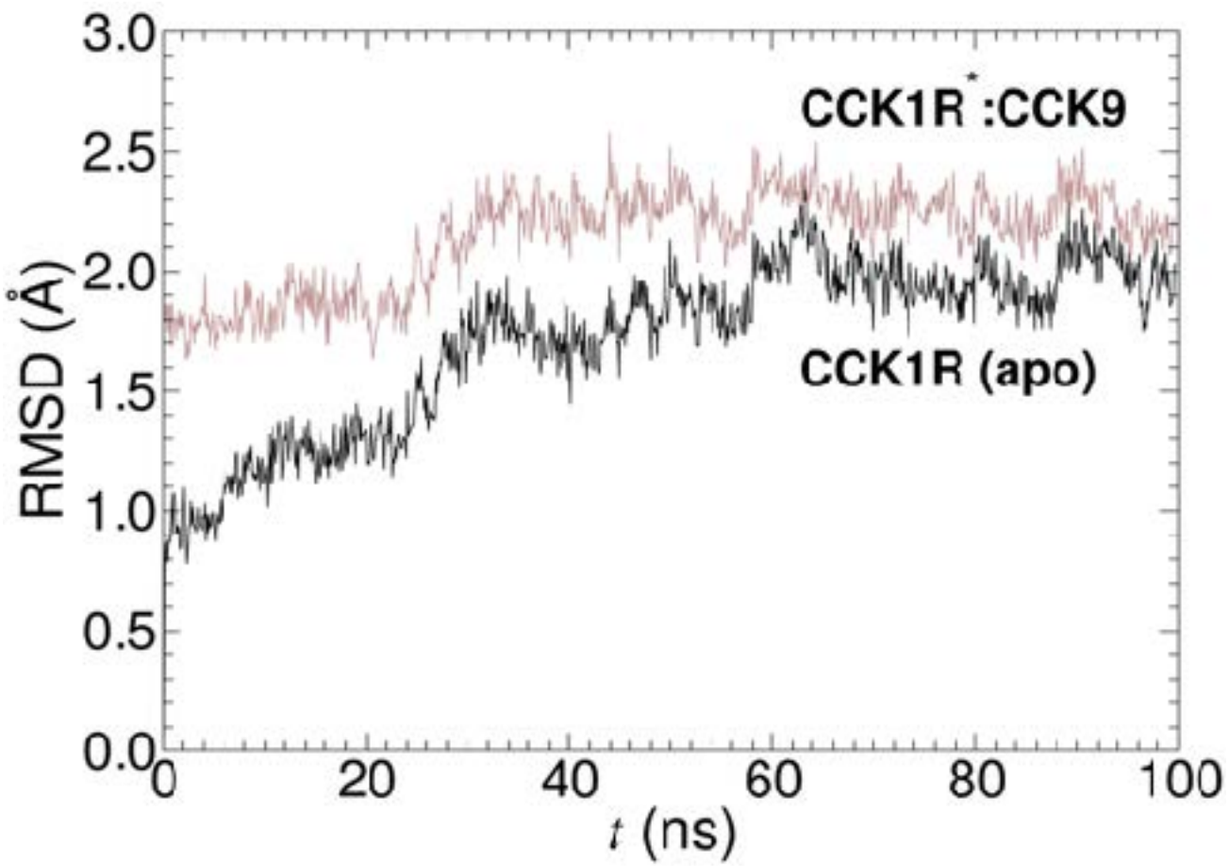


Chandler, D. *Introduction to modern statistical mechanics*, Oxford University Press, **1987**

Structural properties

Time series of the distance root mean-square deviation with *some* reference structure,





Find the optimal rotation, S, which minimizes,

$$\mathrm{RMSD}(\{\mathbf{x}_i(t)\},\{\mathbf{x}_i^{\mathrm{ref}}\}) = \left(\frac{1}{N}\sum_i \left|S[\mathbf{x}_i(t)-\mathbf{x}_{\mathrm{COM}}(t)]-(\mathbf{x}_i^{\mathrm{ref}}-\mathbf{x}_{\mathrm{COM}}^{\mathrm{ref}})\right|^2\right)^{1/2}$$

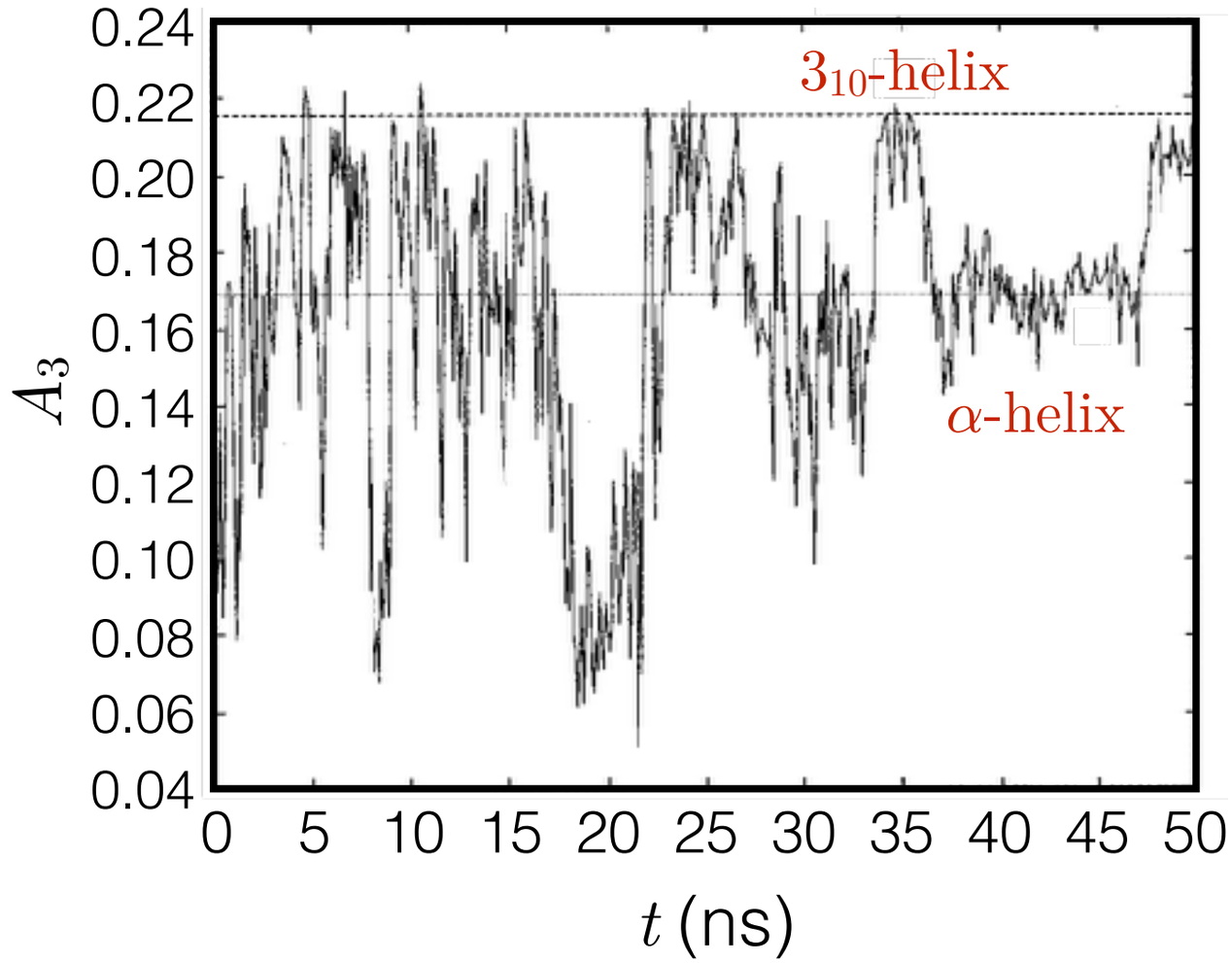
Leach, A. R. *Molecular modeling*. Longman, **1996**

Structural properties

Time series of the radius of gyration, $R_0^k = \sqrt{\frac{I^k}{M}}$

$$\mathbf{I} = \sum_i m_i \left[(\mathbf{r}_i \cdot \mathbf{r}_i)\mathbf{e} - \mathbf{r}_i \times \mathbf{r}_i \right]$$

Asymmetry, $A_3 = \dfrac{\sum_{i>j} \left\langle \left(R_0^{i2} - R_0^{j2} \right)^2 \right\rangle}{2 \left\langle \left(\sum_i R_0^{i2} \right)^2 \right\rangle}$



Simplified expressions —

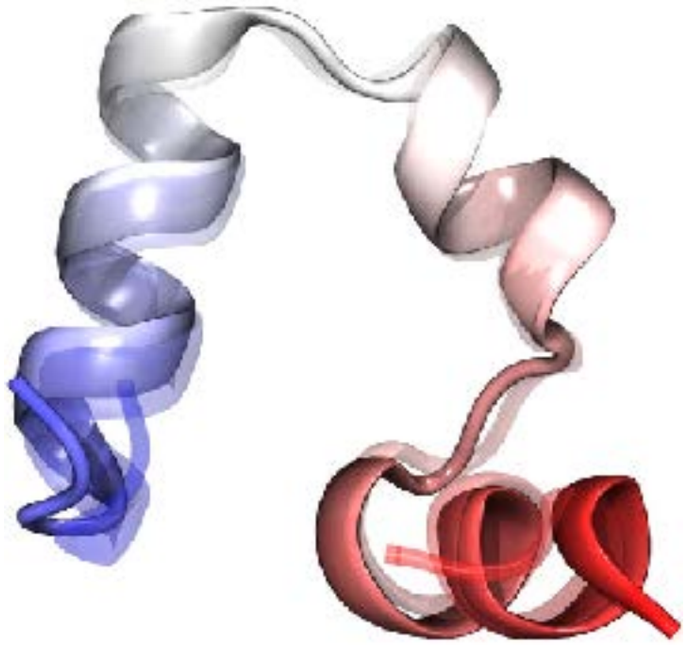
$$R_g^2 := \frac{1}{N} \sum_i (\mathbf{r}_i - \bar{\mathbf{r}})^2$$

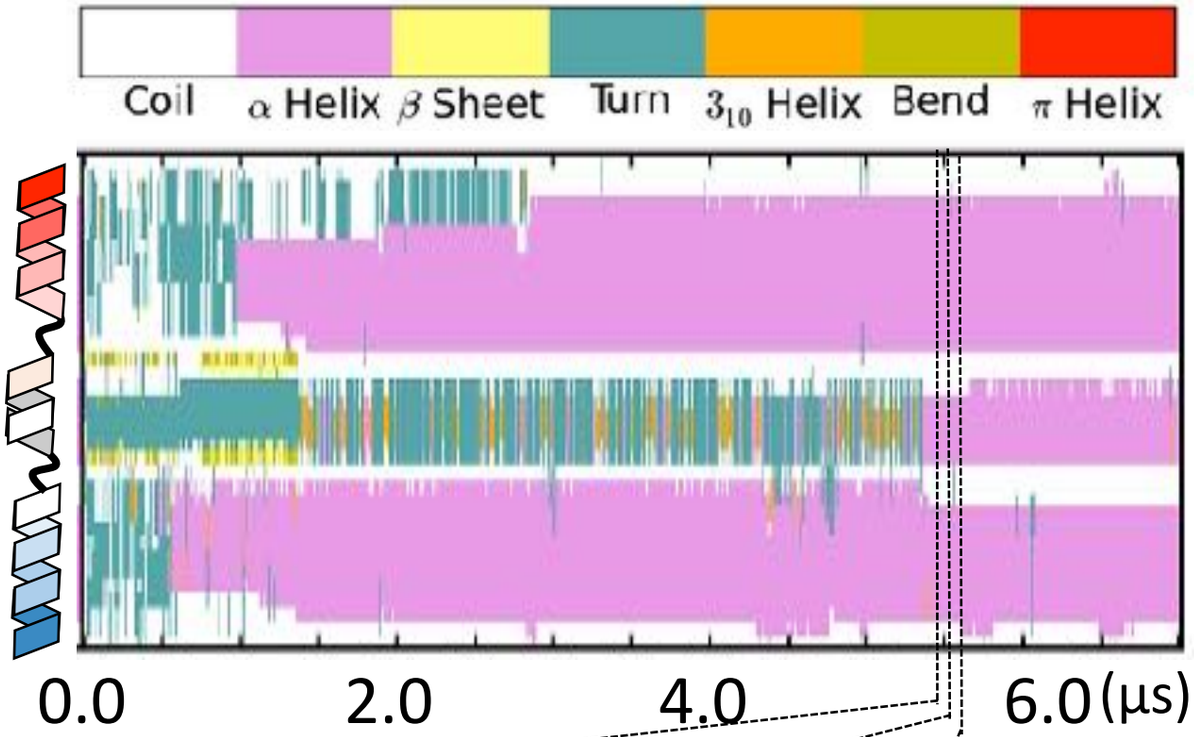
Goldstein, H. *Classical mechanics*. Addison-Wesley, **1980**

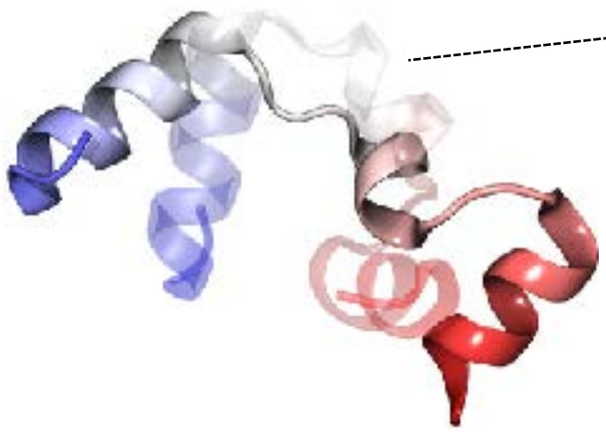
Rudnick, J.; Gaspari, G. *Science* **1987**, *237*, 384-389

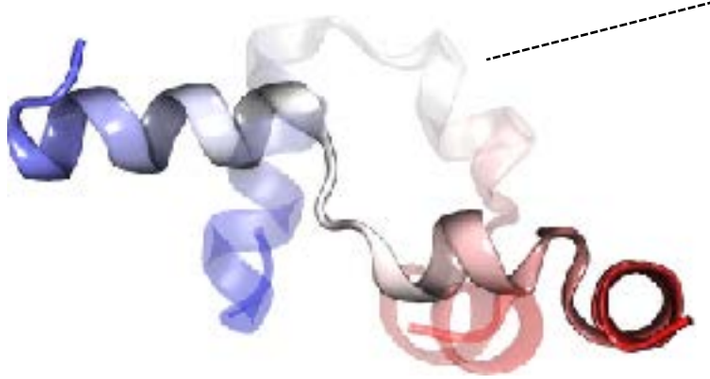
Structural properties

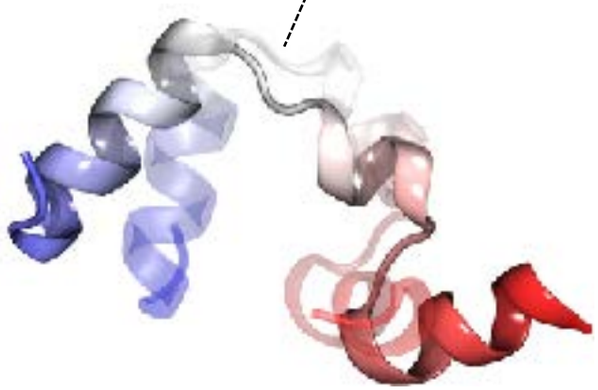
Folding dynamics of villin headpiece unveiled in molecular dynamics simulations exploring key folding transitions never seen hitherto.





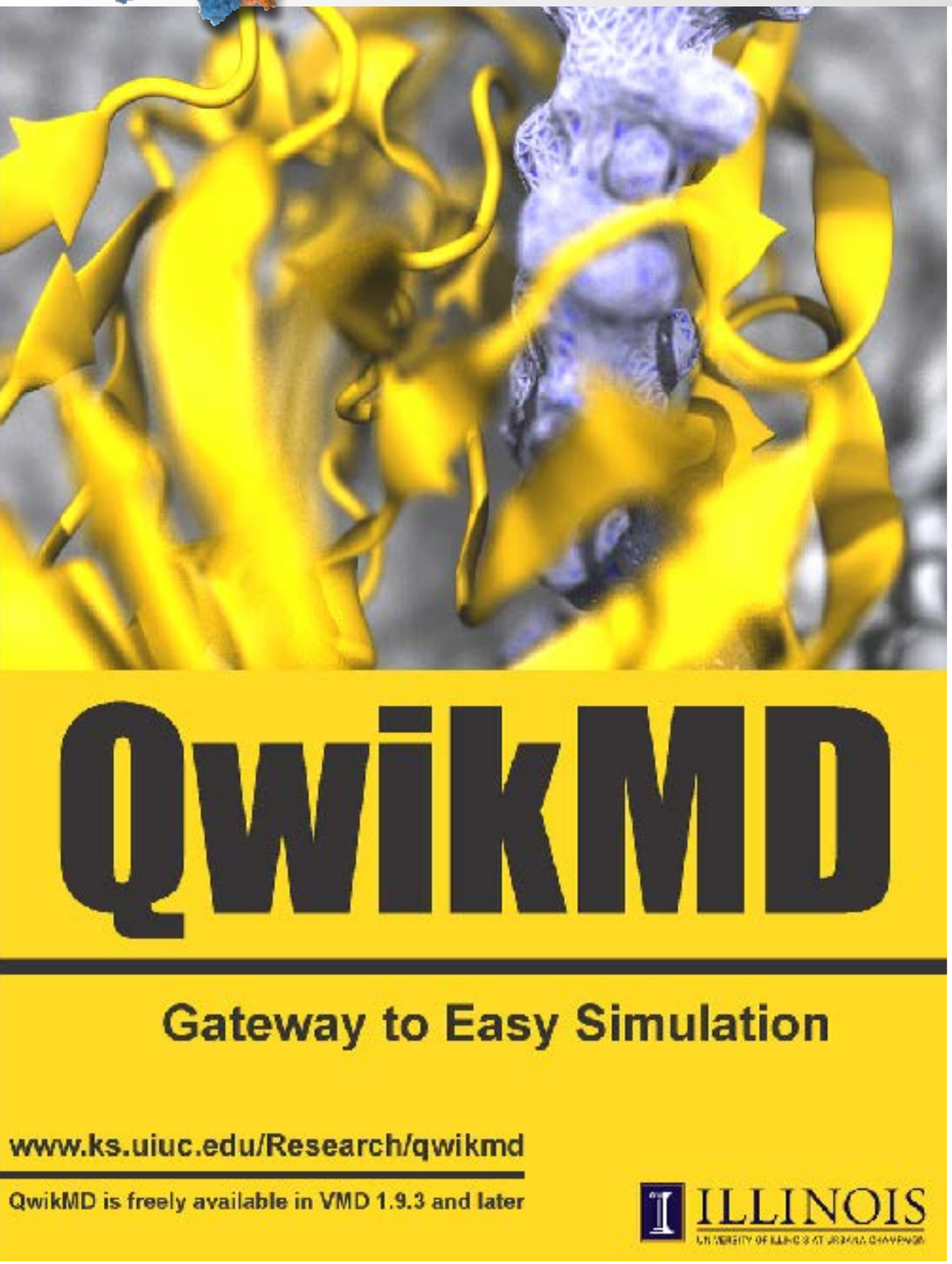


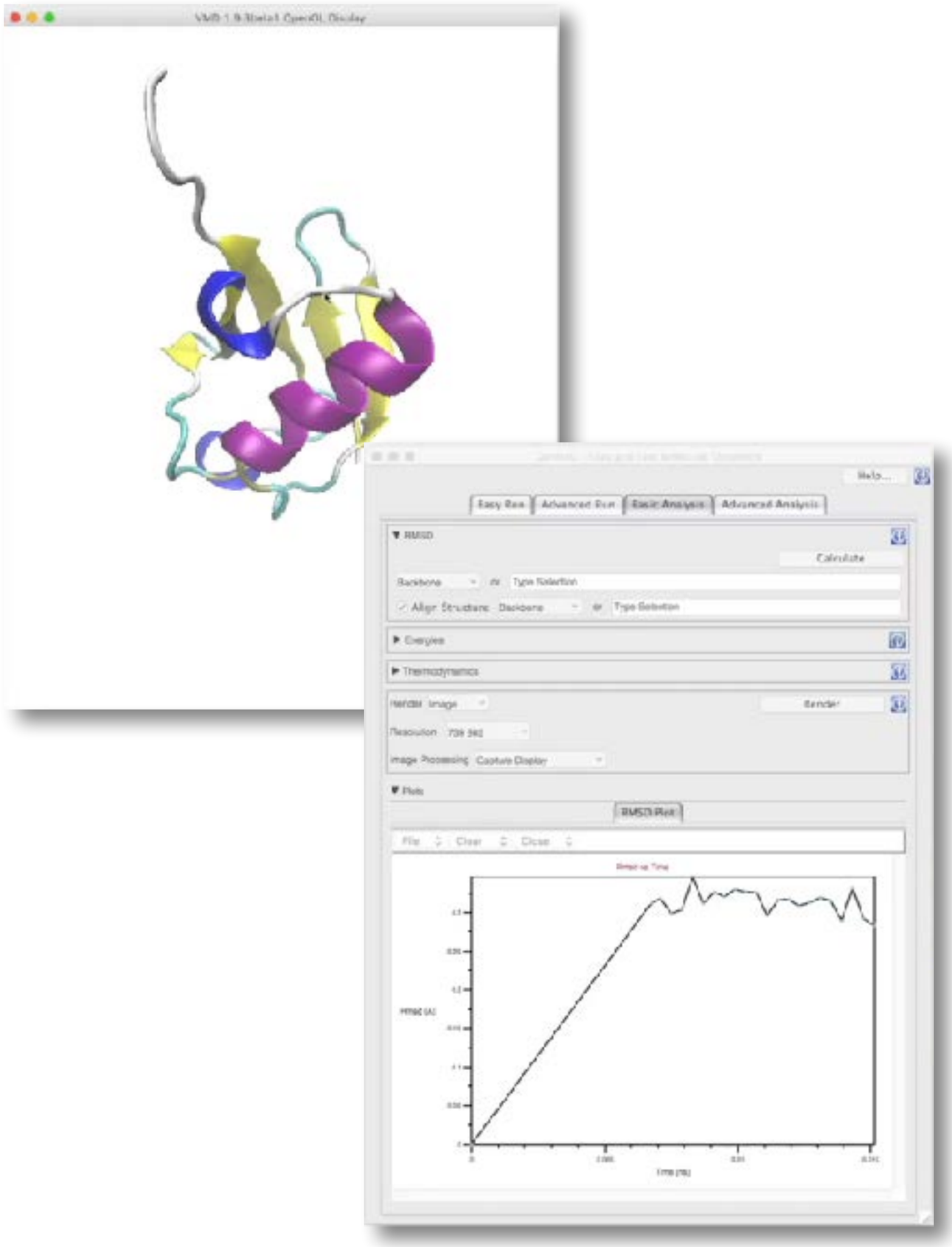




Freddolino, P. L.; L., F.; Gruebele, M.; Schulten, K. *Biophys. J.* **2008**, *94*, L75-L77

Freddolino, P. L.; Schulten, K. *Biophys. J.* **2009**, *97*, 2338-2347



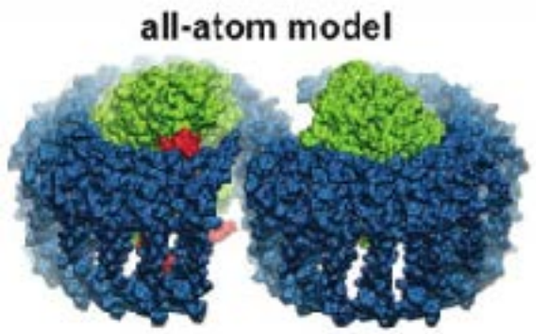


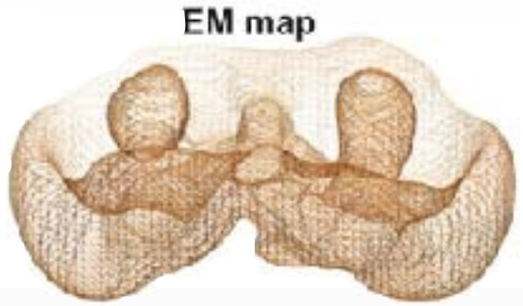
Ribeiro, J. V. et al. *Sci. Rep.* **2016**, *6*, 26536

Structure refinements

The shape of the chromatophore is determined by LH1-RC

The curvature of LH1-RC was inferred by MDFF

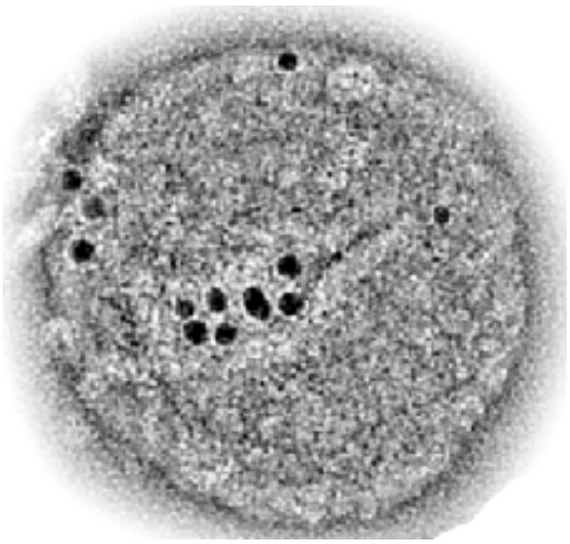


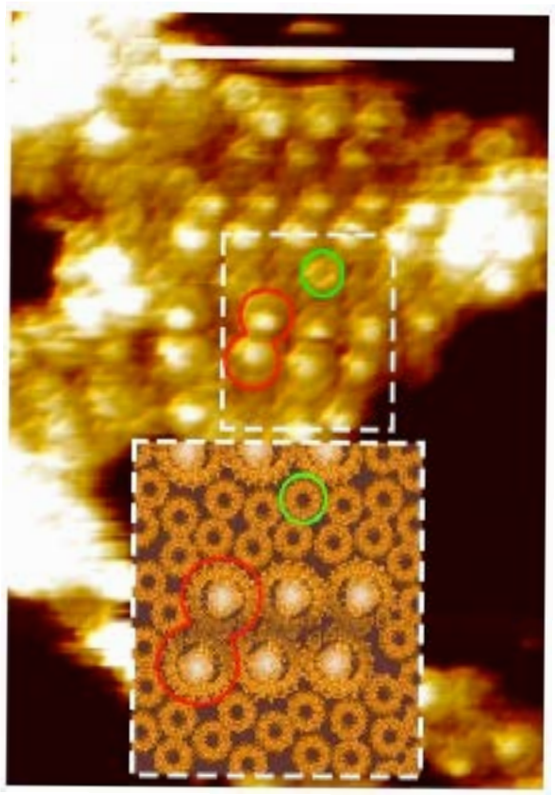


The radius of curvature consistent with experiment;
The membrane curvature exhibits both anisotropy and twist.

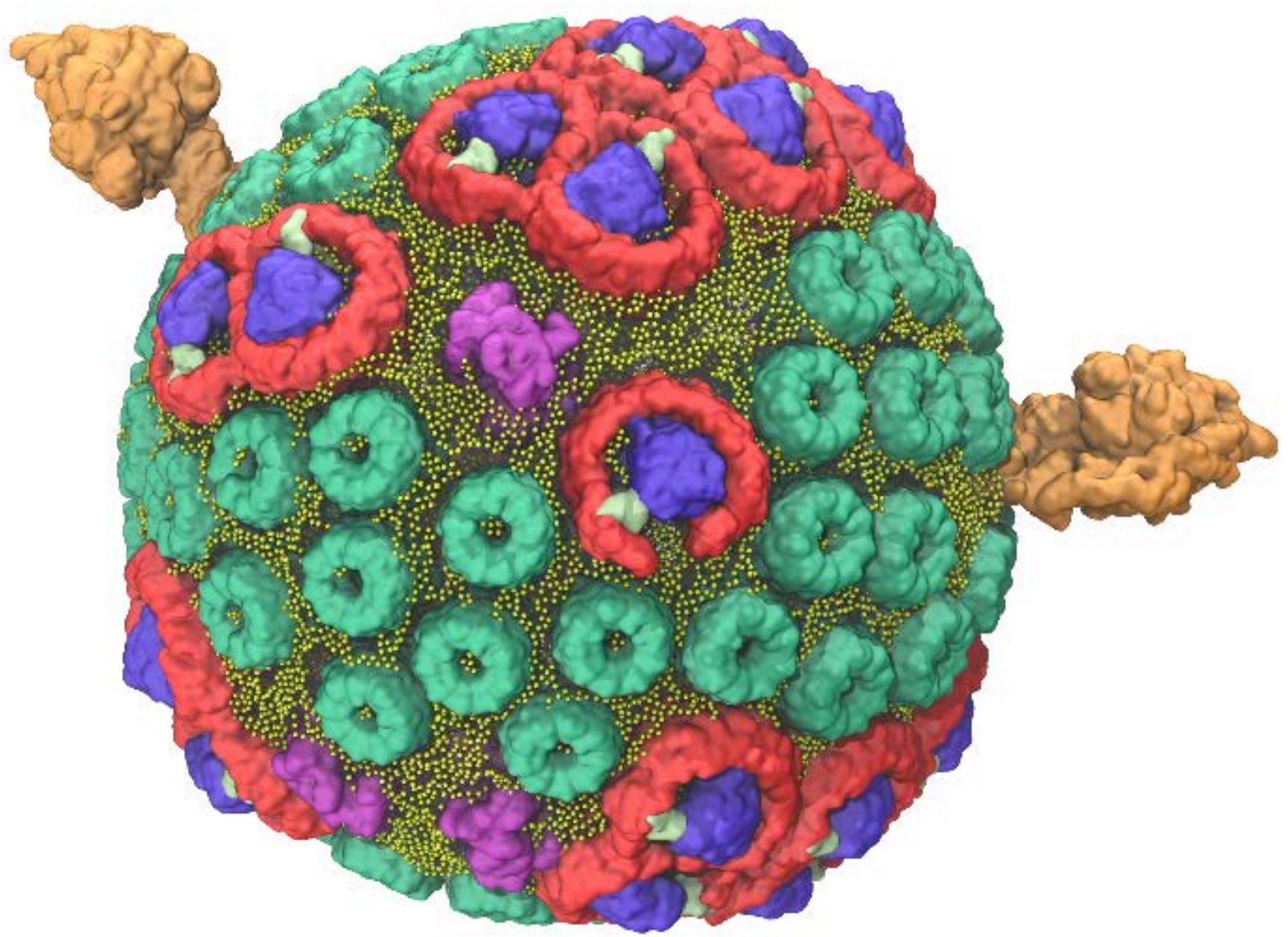
Sener,M. et al. *Chem. Phys.*, **2009**, *357*, 188-197

Structure refinements





Structure determined from experimental data through modeling and simulation.

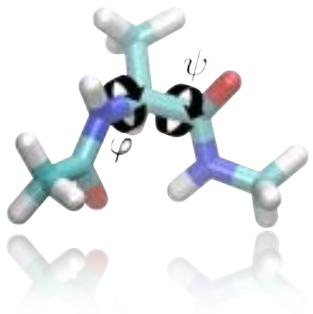


Sener, M. K.; Olsen, J. D.; Hunter, C. N.; Schulten, K. *Proc. Natl. Acad. Sci. U. S. A.* **2007**, *104*, 15723-15728

Cartron, M. L. et al. *Biochim. Biophys. Acta* **2014**, *1837*, 1769-1780

Free energies and other thermodynamic properties

(1) Methods based on histograms



$$\Delta A(\xi) = -\frac{1}{\beta} \ln P(\xi) + \Delta A_0$$

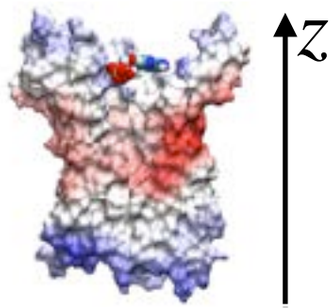
(2) Non-equilibrium work simulations

$$\exp(-\beta \Delta A) = \langle \exp(-\beta w) \rangle$$

(3) Perturbation theory

$$\exp(-\beta \Delta A) = \langle \exp(-\beta \Delta U) \rangle_0$$

(4) Integration of the gradient



$$\frac{\mathrm{d}A(\xi)}{\mathrm{d}\xi} = \left\langle \frac{\partial U}{\partial \xi} - \frac{1}{\beta} \frac{\partial \ln |J|}{\partial \xi} \right\rangle_\xi$$

Torrie, G. M.; Valleau, J. P. *Chem. Phys. Lett.* **1974**, *28*, 578-581
Widom, B. *J. Chem. Phys.* **1963**, *39*, 2808-2812
Israelewitz, B.; Gao, M.; Schulten, K. *Curr. Opin. Struct. Biol.* **2001**, *11*, 224-230
Jarzynski, C. *Phys. Rev. Lett.* **1997**, *78*, 2690-2693
Zwanzig, R. W. *J. Chem. Phys.* **1954**, *22*, 1420-1426
Pohorille, A.; Jarzynski, C.; Chipot, C. *J. Phys. Chem. B* **2010**, *114*, 10235-10253
Kirkwood, J. G. *J. Chem. Phys.* **1935**, *3*, 300-313
Carter, E. et al. *Chem. Phys. Lett.* **1989**, *156*, 472-477

SUMMARY

A variety of properties, structural, thermodynamic or dynamic, can be inferred from molecular dynamics simulations.

Because analysis of these properties is ordinarily performed post facto, it is recommended to store configurations as frequently as possible.

Convergence of the calculation of these properties may vary appreciably — a free energy versus a diffusivity.

Many properties can be readily compared to experiment. Accurate reproduction of the latter is subservient to the reliability of the force field and finite-length effects. Estimation of the associated error is strongly recommended.

CONCLUDING REMARKS

The computational microscope — In recent years, molecular dynamics simulations have become an important tool to complement experiment, offering unprecedented resolution and access to valuable dynamic information.

The inherent parallelizable nature of molecular dynamics makes it an ideal candidate for harnessing the constantly growing capacity of novel computer architectures, dilating both the size- and timescale tackled by simulations.

Molecular dynamics rests on the equations of classical mechanics and the use of empirical potential energy functions, the construction of which relies on stringent assumptions and approximations.

As macromolecular force fields become more sophisticated — and, thus, less tractable, accounting for induction and charge-transfer phenomena, one must choose between longer simulations with a more approximate description and shorter, more accurate simulations.