NSF Summer School on Theoretical and Computational Biophysics

Force Evaluation, Integrators, and Propagators.

Robert D. Skeel

Department of Computer Science and Beckman Institute

University of Illinois at Urbana-Champaign

http://bionum.cs.uiuc.edu/2003lecture.pdf

http://bionum.cs.uiuc.edu/2003notes.pdf

Initial remarks

- mathematical explanations will be avoided.
- equations will be presented but not be discussed in detail.
- lecture will conclude with brief demonstration of use of *Mathematica* notebooks.

Simulation methodologies

Uncontrolled approximations—modeling

- predetermined models,
- computed models, e.g., PMF + diffusion coeff.

Controlled approximations—algorithms

- sampling protocols,
- integrators/propagators,
- minimizers,
- fast force evaluation methods.

Good references

- T. Schlick, *Molecular Modeling and Simulation: An Interdisciplinary Guide*, 2002, http://monod.biomath.nyu.edu/index/book.html
- M. P. Allen and D. J. Tildesley, *Computer Simulation of Liquids*, 1987,
- A. R. Leach, *Molecular Modelling: Principles and Applications*, 1996,
- D. Frenkel and B. Smit, *Understanding Molecular Simulation: From Algorithms to Applications*, 1996.
- For others see Appendix C of the first.

Outline

I. Models and aims
   - classical atomistic model
   - aims
   - enhanced models—polarizable forces
   - reduced models

II. Fast force evaluation

III. Numerical integrators for long-time kinetics

IV. Propagators for thermodynamics

Equations of motion

Atomic positions $\vec{r}_i$ obey

$$m_i \frac{\mathrm{d}^2}{\mathrm{d}t^2} \vec{r}_i(t) = -\nabla_i U(\vec{r}_1(t), \vec{r}_2(t), \ldots, \vec{r}_N(t)), \quad i = 1, 2, \ldots, N,$$

where

- m_i are masses,
- the potential energy $U(\vec{r}_1, \vec{r}_2, \ldots, \vec{r}_N)$ is a sum of
  - $\mathcal{O}(N)$ potentials for bonded forces,
  - $\mathcal{O}(N^2)$ potentials for nonbonded forces.

Concise notation

x collection of positions $\vec{r}_i$,

M diagonal matrix of masses,

v collection of velocities,

$p = Mv$ collection of momenta,

$F(x) = -\nabla U(x)$ collection of forces.

Equations are a Hamiltonian system,

$$\frac{\mathrm{d}}{\mathrm{d}t}x(t) = M^{-1}p(t), \quad \frac{\mathrm{d}}{\mathrm{d}t}p(t) = F(x(t)),$$

with Hamiltonian $H(x,p) = \frac{1}{2}p^{\mathsf{T}}M^{-1}p + U(x)$.

Periodic electrostatics

A periodic box of dimensions $L \times L \times L$ replicated infinitely far in all directions.

$$U^{\mathsf{el}}(x) = \frac{1}{2} \sum_{\vec{n}} \sum_{i=1}^{N} \sum_{j=1}^{N}{}' \frac{q_i q_j}{\varepsilon_0 |\vec{r}_j - \vec{r}_i + \vec{n}|}$$

where q_i are partial charges,
ε_0 is the dielectric constant, and
$\vec{n}$ are lattice points obtained as integer multiples of L.
Primed sum omits excluded pairs (i, j) including $j = i$ for $\vec{n} = \vec{0}$.

This sum is not well defined.

Ewald sum

Imagine, instead, that the replicas merely fill a huge sphere, outside of which the dielectric coefficient is $\varepsilon_{\rm s}$.
In the limit of an infinite sphere

$$U^{\rm el}(x) = \frac{1}{2\varepsilon_0}\sum_{i,j} q_i q_j \sum_{\vec{n}}{}' \frac{\operatorname{erfc}(\beta\,|\vec{r}_j - \vec{r}_i + \vec{n}|)}{|\vec{r}_j - \vec{r}_i + \vec{n}|}$$

$$+ \frac{1}{2\pi\varepsilon_0 L^3}\sum_{\vec{m}\neq\vec{0}} \frac{\exp(-\pi^2|\vec{m}|^2/\beta^2)}{|\vec{m}|^2}\left|\sum_j q_j \exp(2\pi \mathrm{i}\vec{m}\cdot\vec{r}_j)\right|^2$$

$$- \frac{1}{2\varepsilon_0}\sum_{i,j}{}'' q_i q_j \frac{\operatorname{erf}(\beta\,|\vec{r}_j - \vec{r}_i|)}{|\vec{r}_j - \vec{r}_i|} + \frac{2\pi}{(\varepsilon_0 + 2\varepsilon_{\rm s})L^3}\left|\sum_i q_i \vec{r}_i\right|^2 .$$

The first three terms constitute the Ewald sum (1921).

Aims: kinetics

The equations of motion are *chaotic*. Exercise 1
To make sense of trajectories,
incorporate uncertainty stochastically
and ask only for averages:

To compute expectation of $A(\Gamma(t))$ where $\Gamma = \begin{bmatrix} x \\ p \end{bmatrix}$,

use

$$\frac{1}{N_{\mathrm{trials}}} \sum_{\nu=1}^{N_{\mathrm{trials}}} A(\Gamma_{(\nu)}(t)).$$

where the $\Gamma_{(\nu)}(0)$ are random with p.d.f. $\rho_0(\Gamma)$.

Aims: thermodynamics

Thermodynamics calculations (structure and energetics) can be expressed

$$\int A(\Gamma)\rho(\Gamma)\,\mathrm{d}\Gamma$$

for some given p.d.f. $\rho(\Gamma)$. For constant-T, constant-V

$$\rho(\Gamma) \propto \mathrm{e}^{-H(\Gamma)/(k_\mathrm{B}T)}.$$

Better for biomolecules is constant-T, constant-P, for which

$$\rho(x,p,V) \propto \mathrm{e}^{-(H(x,p)+PV)/(k_\mathrm{B}T)}, \quad 0 < V < +\infty,$$
$$\vec{r}_i \in \text{ box scaled to have volume } V.$$

Phase space is sampled by a *propagator*.

Constraints

High frequencies limit integrator efficiency.
Constraining bond lengths and angles removes them.
Write these constraints as

$$g(x(t)) = 0$$

where $g^k(x) = \|\vec{r}_{j(k)} - \vec{r}_{i(k)}\|^2 - l_k^2$, $k = 1, 2, \ldots, \mu$.
Constraints determine Lagrange multipliers $\lambda(t)$
in the equations of motion

$$\frac{\mathrm{d}}{\mathrm{d}t}x(t) = M^{-1}p(t), \quad \frac{\mathrm{d}}{\mathrm{d}t}p(t) = F(x(t)) + \partial_x g(x(t))^{\mathsf{T}}\lambda(t)$$

where $\partial_x g$ is the Jacobian matrix for g.

Implicit solvent

Dynamical equations are those of Langevin dynamics:

$$\frac{\mathrm{d}}{\mathrm{d}t}x(t) = v(t), \qquad M\frac{\mathrm{d}}{\mathrm{d}t}v(t) = -\nabla U(x(t))$$
$$- k_{\mathrm{B}}TD(x(t))^{-1}v(t) + \sqrt{2}k_{\mathrm{B}}TD_{1/2}(x(t))^{-\mathsf{T}}\frac{\mathrm{d}}{\mathrm{d}t}W(t)$$

where $U(x)$ includes a Poisson-Boltzmann solution,
$D = D_{1/2}D_{1/2}^{\mathsf{T}}$ is a diffusion tensor, and
$\frac{\mathrm{d}}{\mathrm{d}t}W(t)$ is standard white noise, i. e., $W(t)$ is Gaussian
with $\mathsf{E}W(t) = 0$ and $\mathsf{E}W_i(s)W_j(t) = \min\{s,t\}\delta_{ij}$.
Implicit solvent deviates from explicit solvent
unless four layers of explicit solvent are included.

Cheaper and less accurate is a generalized Born potential.

Outline

I. Models and aims

II. Fast force evaluation
   - nonperiodic bonded forces
   - periodic electrostatic forces
   - polarizable forces
   - implicit solvent electrostatics

III. Numerical integrators for long-time kinetics

IV. Propagators for thermodynamics

Multilevel methods for electrostatics

- *cell methods*, such as the fast multipole method, based on an oct-tree decomposition of space, and
- *grid methods*, such as the Brandt-Lubrecht fast summation method, based on a hierarchy of grids.

Both have three elements:

1. separation of length scales:

$$\text{short-range} \; + \; \text{slowly varying}.$$

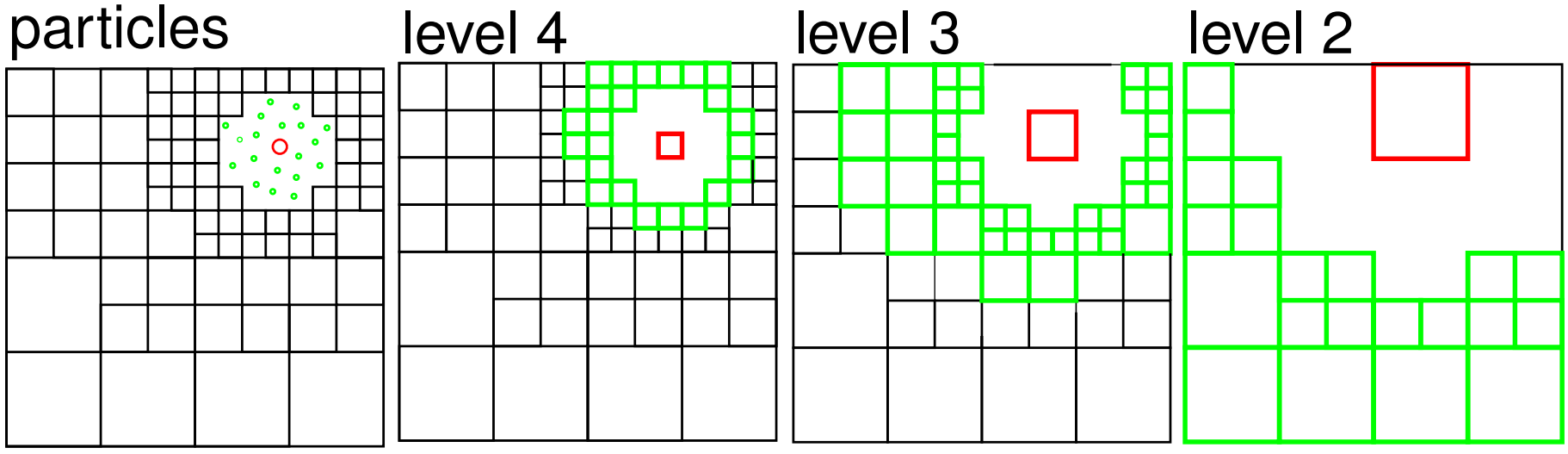
   with short-range interactions calculated directly.
2. coarsening: *approximating* the slowly varying part with fewer values on a lattice.
3. recursive application of 1. and 2.

Cell methods

The effect of a charged particle is

- represented directly at a short length scale,
- is pooled with other charges and represented by a Taylor expansion at longer length scales.

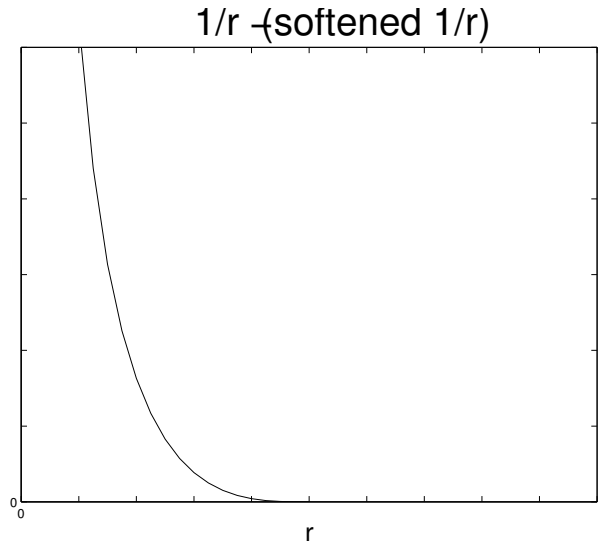
(Use of harmonic polynomials reduces number of terms.)



Grid methods

A multiple grid method separates length scales by splitting pair potentials into short-range and slowly varying parts:

$$\frac{1}{r} =$$



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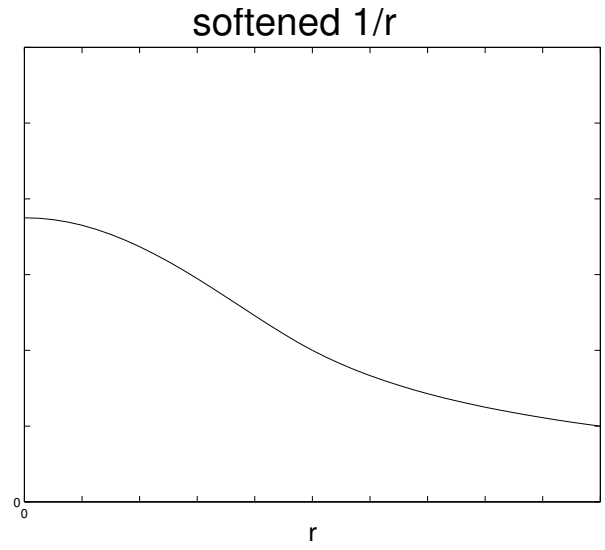
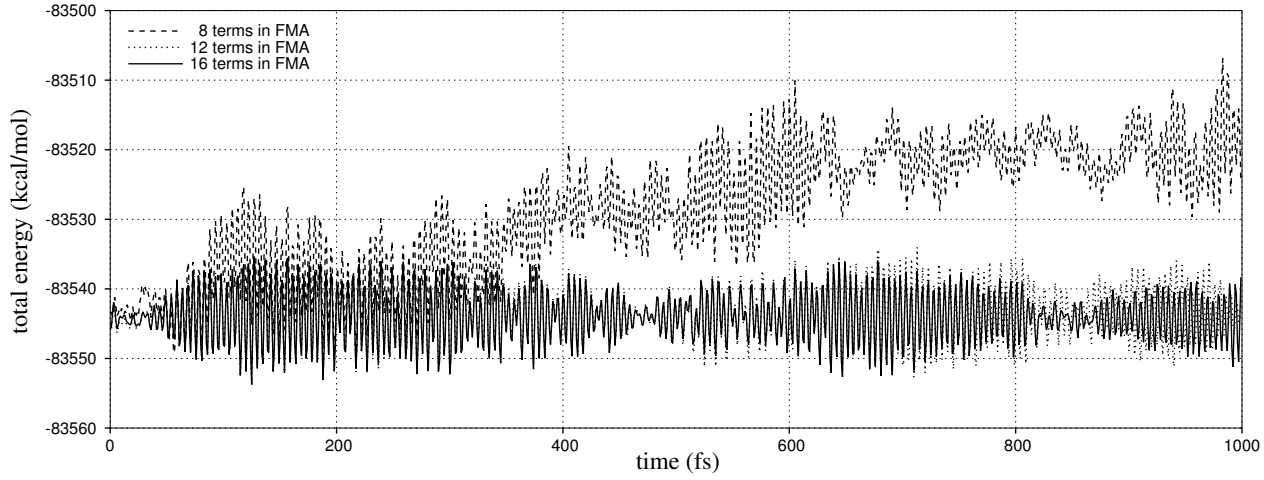


Coarsening is by interpolation from a grid.

Continuous forces are easily obtained.

Comparison

The multipole method is not usable unless high accuracy is requested due to discontinuous forces.



In one comparison, the multiple grid method is 4 times as fast as the fast multipole method for MD.

Continuous forces

Exercise 4

NAMD note. For van der Waals forces use switching on to get a C^1 force and choose

$$\text{switchdist} < \text{cutoff} < \text{pairlistdist}.$$

If the margin pairlistdist $-$ cutoff is not large enough, a warning is printed (indicating a flawed force evaluation).

Ewald algorithms

- standard Ewald cuts off the short-range potential and truncates the Fourier series.
  Optimal β gives an $\mathcal{O}(N^{3/2})$ operation count.
- particle–mesh Ewald (PME) interpolates the Fourier basis functions from a mesh resulting in a discrete Fourier series.
  Use of an FFT gives an $\mathcal{O}(N \log N)$ algorithm.

NAMD note. Use PME yes and control the error by setting PMETolerance (default value 10^{-6}) and choosing PMEGridSizeX, PMEGridSizeY, and PMEGridSizeZ.

Outline

I. Models and aims

II. Fast force evaluation

III. Numerical integrators for long-time kinetics
   - Newtonian dynamics
   - constrained dynamics
   - stochastic dynamics

IV. Propagators for thermodynamics

Verlet integrator

Numerical integrators generate $\Gamma^n \approx \Gamma(n\Delta t)$. The Verlet method is

$$M\frac{1}{\Delta t^2}\left(x^{n+1} - 2x^n + x^{n-1}\right) = F(x^n).$$

Exercise 6 (order of accuracy)
Velocity definition,

$$v^n = \frac{1}{2\Delta t}\left(x^{n+1} - x^{n-1}\right),$$

does not affect dynamics.

Velocity Verlet integrator

Typical integrators can be expressed as $\Gamma^{n+1} = \Psi(\Gamma^n)$.
An example is the "velocity Verlet" scheme:

$$\begin{aligned} x^{n+1} &= x^n + \Delta t v^n + \frac{1}{2}\Delta t^2 M^{-1} F(x^n), \\ Mv^{n+1} &= Mv^n + \frac{1}{2}\Delta t F(x^n) + \frac{1}{2}\Delta t F(x^{n+1}). \end{aligned}$$

Symplectic integrators

Evidence indicates that Ψ being *symplectic* is appropriate for statistically accurate long time integrations. Exercise 3
An integrator $\Gamma^{n+1} = \Psi(\Gamma^n)$ is *symplectic* if

$$\partial_\Gamma \Psi(\Gamma)^{\mathrm{T}} \begin{bmatrix} 0 & I \\ -I & 0 \end{bmatrix} \partial_\Gamma \Psi(\Gamma) = \begin{bmatrix} 0 & I \\ -I & 0 \end{bmatrix}.$$

The evidence is even more compelling for Ψ being *volume preserving*,

$$\det \partial_\Gamma \Psi(\Gamma) = 1.$$

Energy fluctuations

Energy $H(\Gamma^n)$ fluctuates for a symplectic integrator.

Exercise 5 step size resonance

Shadow Hamiltonian

However, there is *formally* a shadow Hamiltonian

$$\tilde{H}(\Gamma) = H(\Gamma) + \sum_{j=q}^{\infty} \Delta t^j \eta_j(\Gamma)$$

which is exactly conserved.
And there are interpolated shadow Hamiltonians

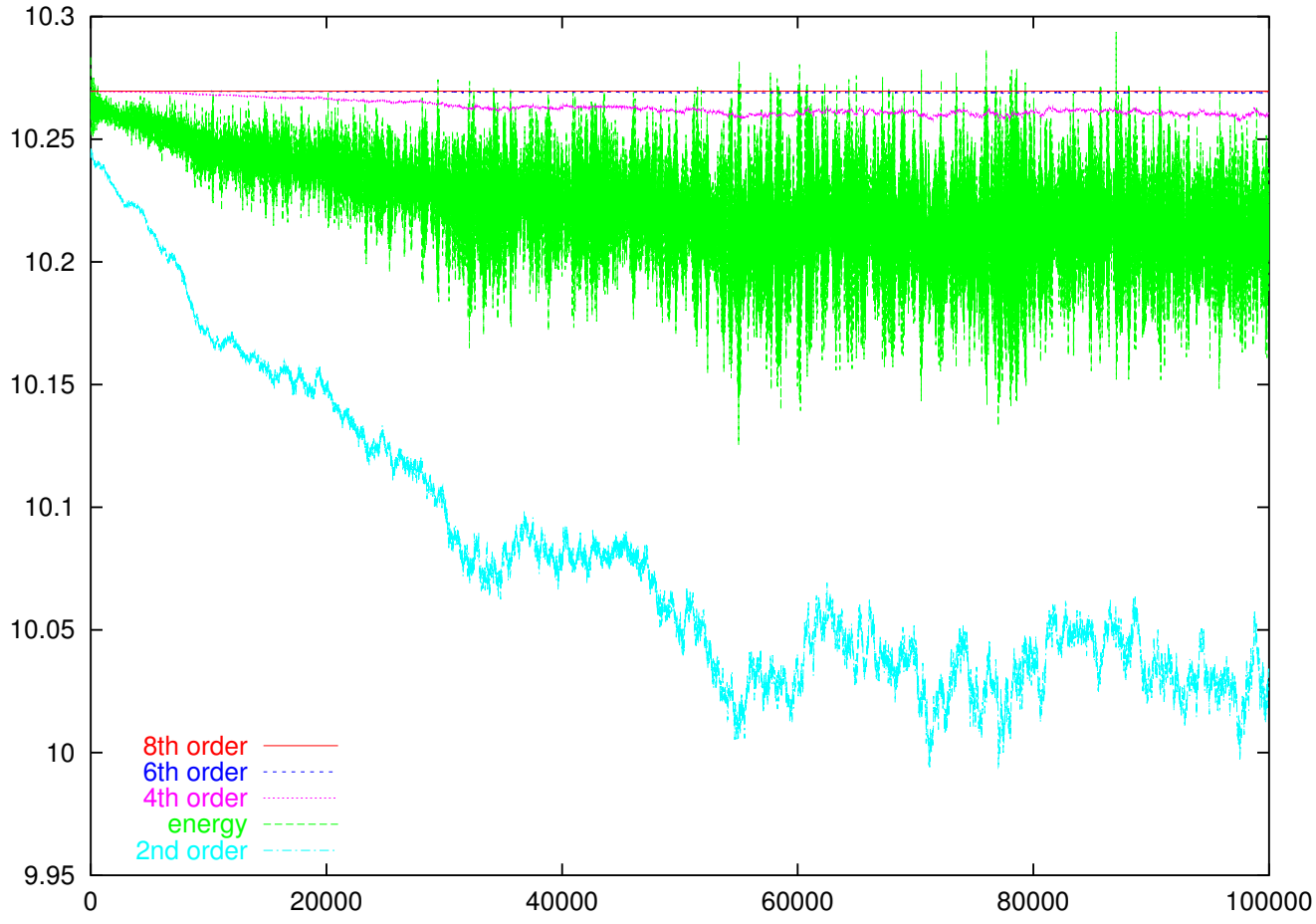
$$H_k(\Gamma) = \tilde{H}(\Gamma) + O(\Delta t^k), \quad k = 2, 4, \ldots,$$

which are very inexpensive to evaluate. Exercise 7

They help to identify deficiencies in a simulation.

Conservation of shadow Hamiltonian

energies vs. time for decalanine for 100 ps

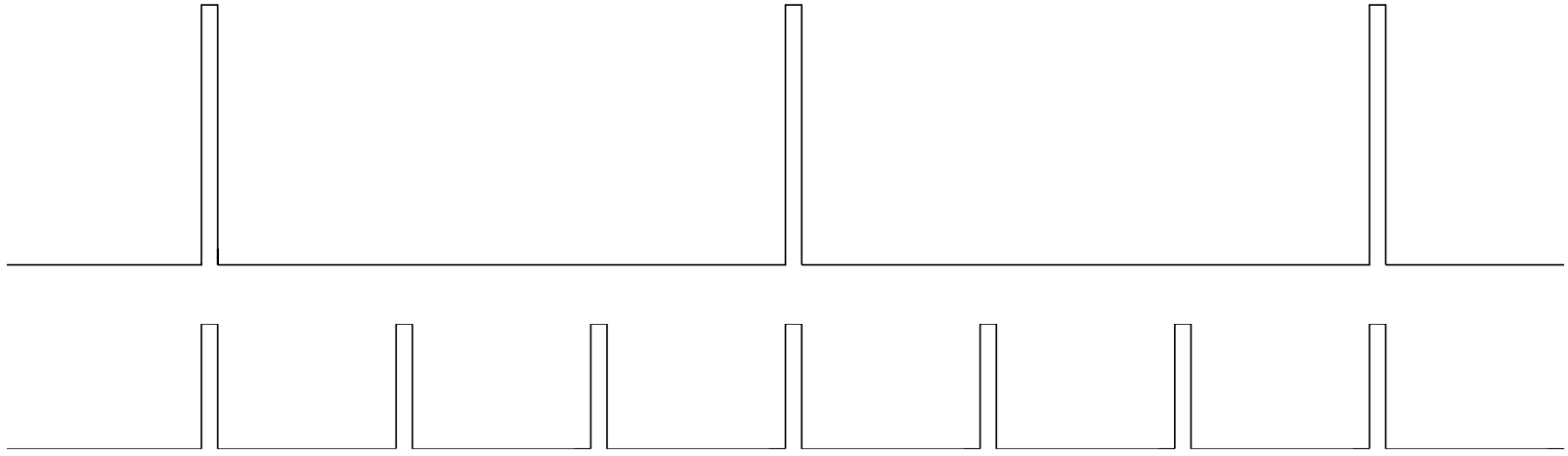


Multiple time stepping

MTS based on impulses (r-RESPA) is symplectic.

Example. Split $U = U^{\text{slow}} + U^{\text{fast}}$. Define an (outer) time step of MTS to be 3 Verlet steps, each of size $\frac{1}{3}\Delta t$:

1. at steps $n = 0, 1, 2, \ldots$, use $U^{\text{slow}} + \frac{1}{3}U^{\text{fast}}$, and
2. at steps $n = \frac{1}{3}, \frac{2}{3}, \frac{4}{3}, \frac{5}{3}, \frac{7}{3}, \frac{8}{3}, \ldots$, use $\frac{1}{3}U^{\text{fast}}$.



Each $U_{ij}^{\text{nonbonded}}$ is split into a slow $+$ a short-range part.

Step size barriers

Energy growth occurs for nondamping integrators unless

$$\text{(outer) } \Delta t < \tfrac{1}{3} \text{ period}$$

where "period" = numerical period of fastest normal mode.
Limit on (outer) step size:

	Verlet	MTS
no constraints	2.2 fs	3.3 fs
with H constraints	3.1 fs	4.6 fs

Accuracy further limits the Verlet Δt.

NAMD note. To use multiple time stepping without energy drift, set

timestep 1.041666666666667 and fullElectFrequency 3.

Nonsymplectic integrators

Damping may be acceptable if balanced with random noise:

symplectic integrator + weak Langevin coupling

Such a method is *Langevin MOLLY* where

$U_{\mathrm{slow}}(x)$ is replaced by $U_{\mathrm{slow}}(\text{vibration-averaged}(x))$

in the impulse MTS method.

By *targeting* the coupling, one can use an outer $\Delta t = 16$ fs compared to only 3.2 fs with impulse MTS.

NAMD note. One can use an outer $\Delta t = 8$ fs by setting langevin on, langevinTemp 298., langevinDamping 0.2, molly on, timestep 1.0, fullElectFrequency 4, and nonbondedFreq 2.

Constrained dynamics algorithms

SHAKE is the discretization:

$$M\frac{1}{\Delta t^2}\left(x^{n+1}-2x^n+x^{n-1}\right)=F(x^n)+\partial_x g(x^n)^{\mathsf{T}}\lambda^n$$

where

$$\lambda^n \text{ satisfies } g(x^{n+1})=0.$$

A variant, called RATTLE, defines better velocities.
An iteration is needed to solve the constraint equations.
An accurate solution is needed to avoid energy drift.

NAMD note.

Rigid waters is an option, implemented using SETTLE.

Rigid H covalent bonds is an option, implemented using SHAKE.

Stochastic dynamics algorithms

Brooks-Brünger-Karplus scheme is

$$M\frac{1}{\Delta t^2}(x^{n+1}-2x^n+x^{n-1})=F(x^n)$$

$$-k_{\mathrm{B}}TD(x^n)^{-1}\frac{1}{2\Delta t}(x^{n+1}-x^{n-1})+\sqrt{2}k_{\mathrm{B}}TD_{1/2}(x^n)^{-\mathrm{T}}\frac{1}{\sqrt{\Delta t}}Z^n$$

where Z^n are standard Gaussians, i. e.,

$$\mathsf{E}Z_i^n=0 \text{ and } \mathsf{E}Z_i^mZ_j^n=\delta_{mn}\delta_{ij}.$$

For a diagonal diffusion tensor there are better methods:

- Most efficient is the LN (MTS) method.
- Simplest is the 1982 scheme of van Gunsteren and Berendsen and the Langevin impulse method.

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- Markov chain Monte Carlo methods
- NVT dynamics
- NPT dynamics
- time correlation functions

Markov chain Monte Carlo methods

Example.
Hybrid Monte Carlo uses MD to generate possible moves.
It is enough that the integrator
be reversible and volume-preserving.
Unfortunately, rejection rate increases with system size N
due to integrator-produced fluctuations in the energy.

Higher order integrators is one solution.

NVT dynamics

- Nosé dynamics is defined by the extended Hamiltonian

$$H(x, s, \bar{p}, p_{\mathrm{s}}) = \frac{1}{2} s^{-2} \bar{p}^{\mathsf{T}} M^{-1} \bar{p} + U(x) + \frac{1}{2Q} p_{\mathrm{s}}^2 + N_{\mathrm{d}} k_{\mathrm{B}} T \ln s$$

  where $Q =$ thermal inertia and $N_{\mathrm{d}} =$ number of DOFs.

$$\langle A \rangle_{\mathsf{NVT}} \approx \frac{\int_0^t A(x(\tau), s(\tau)^{-1} \bar{p}(\tau)) s(\tau)^{-1} \, \mathrm{d}\tau}{\int_0^t s(\tau)^{-1} \, \mathrm{d}\tau}$$

- Nosé-Hoover dynamics is not Hamiltonian and gives drift in the extended energy.
- Langevin dynamics

NAMD note. Langevin dynamics with a diagonal tensor.

NPT dynamics

The Langevin piston method for NPT sampling involves integrating

$$\frac{\mathrm{d}}{\mathrm{d}t}x(t) = M^{-1}p(t) + \frac{p_{\mathrm{V}}(t)}{3QV(t)}x(t), \quad \frac{\mathrm{d}}{\mathrm{d}t}p(t) = F(x(t)) - \frac{p_{\mathrm{V}}(t)}{3QV(t)}p(t),$$

$$\frac{\mathrm{d}}{\mathrm{d}t}V(t) = \frac{p_{\mathrm{V}}(t)}{Q}, \quad \frac{\mathrm{d}}{\mathrm{d}t}p_{\mathrm{V}}(t) = P(t) - P - \gamma p_{\mathrm{V}}(t) + \sqrt{2\gamma k_{\mathrm{B}}TQ}\frac{\mathrm{d}}{\mathrm{d}t}W(t)$$

where

$$P(t) = \frac{1}{3QV(t)}\left(p(t)^{\mathsf{T}}M^{-1}p(t) + x(t)^{\mathsf{T}}F(x(t))\right).$$

NAMD note. Langevin piston method.

Time correlation functions

Correlation functions should be computed from accurate Newtonian dynamics trajectories using initial conditions drawn from the desired ensemble (Allen and Tildesley, 1987).

In practice, this dictum is often ignored, e. g., the Langevin piston method is designed with kinetics in mind.