

# Force Evaluation, Integrators, and Propagators<sup>1</sup>

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## 1 Introduction

Presented here is a guide to selected algorithms deemed to be useful for a subset of calculations needed for biomolecular simulations.

It is beneficial to make a clear distinction between *what* we want to compute (model) and *how* we compute it (method). What we compute is the more important consideration, and this is reviewed in Section 2 under the heading “Models and aims.” How we compute it is the subject of the remaining sections. The distinction is made on the following basis: (i) uncontrolled approximations such as force fields are deemed to be part of the model and (ii) controlled approximations such as numerical integrators are classified as algorithms. Ideally, only advanced users should be conscious of algorithms; general users should merely choose error tolerances and confidence levels with the algorithms automatically chosen for them by the software.

Discussed in Sections 3–5 are algorithms for the three tasks given in the title of this article. Not discussed here are force calculations based on quantum mechanics or elasticity and “protocols” that employ integrators for kinetics and propagators for sampling.

An excellent reference is the 2002 book by Schlick [20] and a good supplement is the 1987 book of Allen and Tildesley [1]. Also noteworthy is the biologically-oriented book by Leach [11] and the book by Frenkel and Smit [7]. For additional references, see [20, Appendix C].

## 2 Models and aims

Only a selected set of computational models and goals is considered here.

### 2.1 Classical atomistic model

Atomic positions  $\vec{r}_i$  obey

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

for  $i = 1, 2, \dots, N$  where the  $m_i$  are masses and the potential energy function  $U(\vec{r}_1, \vec{r}_2, \dots, \vec{r}_N)$  is a sum of  $\mathcal{O}(N)$  few-body potentials for covalent bonded forces and  $\mathcal{O}(N^2)$  2-body potentials for nonbonded forces. Let  $x$  be the collection of all positions  $\vec{r}_i$ ,  $M$  a diagonal matrix of masses (each mass replicated three times),  $v$  the collective velocity vector,  $p = Mv$  the collective momentum vector, and  $F(x) = -\nabla U(x)$  the collective force vector. Then the system (1) can be written as a Hamiltonian system of differential equations,

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

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

Periodic boundary conditions are popular—assume a periodic box of dimensions  $L \times L \times L$  replicated infinitely far in all directions. Electrostatic interactions are problematic because they cannot be cutoff with negligible error. The electrostatic energy associated with  $N$  particles is a sum over infinitely many images:

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

where the  $q_i$  are partial charges,  $\varepsilon_0$  is the dielectric constant, and the  $\vec{n}$  are lattice points obtained as integer multiples of  $L$ . The primed sum omits  $\vec{n} = \vec{0}$  for self interactions and those pairs  $(i, j)$  which are in the exclusion list. *This sum is not well defined.* A physically meaningful definition is given by De Leeuw, Perram, and Smith (1980) in which one imagines a very large number of replicas of the original box that just fill a huge sphere and that outside this sphere is a medium with dielectric coefficient  $\varepsilon_s$ . The resulting energy in the limit of an infinite sphere is

$$\begin{aligned} U^{\text{el}}(x) = & \frac{1}{2\varepsilon_0} \sum_{i,j} q_i q_j \sum'_{\vec{n}} \frac{\text{erfc}(\beta |\vec{r}_j - \vec{r}_i + \vec{n}|)}{|\vec{r}_j - \vec{r}_i + \vec{n}|} \\ & + \frac{1}{2\pi\varepsilon_0 L^3} \sum_{\vec{m} \neq \vec{0}} \frac{\exp(-\pi^2 |\vec{m}|^2 / \beta^2)}{|\vec{m}|^2} \left| \sum_j q_j \exp(2\pi i \vec{m} \cdot \vec{r}_j) \right|^2 \\ & - \frac{1}{2\varepsilon_0} \sum''_{i,j} q_i q_j \frac{\text{erf}(\beta |\vec{r}_j - \vec{r}_i|)}{|\vec{r}_j - \vec{r}_i|} + \frac{2\pi}{(\varepsilon_0 + 2\varepsilon_s)L^3} \left| \sum_i q_i \vec{r}_i \right|^2 \end{aligned} \quad (2)$$

where  $\beta$  is a cutoff parameter, the  $\vec{m}$  are wavenumbers obtained as integer multiples of  $1/L$ , and the double primed sum includes only those pairs  $(i, j)$  which are in the exclusion list. The first three terms constitute the Ewald sum published in 1921. Their combined value is unaffected by the choice of  $\beta$  (or the selection of  $\text{erfc}$  as a switching function [1, p. 159]). The fourth term is unfortunately not continuous as a function of atomic position and hence unsuitable for dynamics or minimization. Also, if water is assumed to be the surrounding medium, the coefficient  $1/(\varepsilon_0 + 2\varepsilon_s)$  is small. For these reasons it is common to neglect the surface term and use the original Ewald sum.

Realistic nonperiodic boundary conditions are also used, a recent example being [9].

## 2.2 Aims

Discussed here are the two main aims of (long-time) kinetics and thermodynamics.

The equations of motion are *chaotic* even for relatively short time scales. To make sense of trajectories, incorporate uncertainty stochastically into the model and ask only for average values. Indeed, it is usual to choose random values for the initial velocities. Sometimes random terms are added to the equations of motion to account for boundary effects. To compute expected values for some  $A(\Gamma(t))$  where  $\Gamma = [x^T, p^T]^T$ , one typically calculates an ensemble  $\{\Gamma_{(\nu)}(t)\}$  and uses

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

Typically a numerical integrator is used to compute an ensemble of 10 to 10,000 dynamical trajectories. We consider here random initial conditions only. Let  $\Gamma(0)$  be random with probability density function (p.d.f.)  $\rho_0(\Gamma)$ . Define  $\rho(\Gamma, t)$  to be the p.d.f. for  $\Gamma(t)$ . Then the desired quantity for a kinetics calculation is

$$\int A(\Gamma)\rho(\Gamma, t) d\Gamma.$$

If the Hamiltonian system has the *mixing* property, the p.d.f.  $\rho(\Gamma, t)$  converges in a weak sense to a limiting density  $\rho(\Gamma)$ , which is a function only of conserved quantities, such as  $H(\Gamma)$ .

Thermodynamics calculations (structure and energetics) can be expressed

$$\int A(\Gamma)\rho(\Gamma) d\Gamma$$

for some given p.d.f.  $\rho(\Gamma)$ . For the canonical (constant- $T$ , constant- $V$ ) ensemble it is the Boltzmann distribution

$$\rho(\Gamma) = e^{-H(\Gamma)/(k_B T)} / \int e^{-H(\Gamma)/(k_B T)} dy$$

where  $k_B$  is Boltzmann’s constant and  $T$  is temperature. Better for biomolecules is the isothermal-isobaric (constant- $T$ , constant- $P$ ) ensemble, which defines averages with

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

Phase space is sampled by a *propagator*, which might generate a Monte Carlo Markov chain or a single “dynamical” trajectory.

### 2.3 Enhanced models—polarizable forces

A consensus has emerged among researchers favoring the inclusion of electronic polarizability in simulations [8], but models and parameters are still in the development stage. Two kinds of models are induced dipoles and fluctuating point charges.

### 2.4 Reduced models

The efficiency of integrators is limited by the highest frequencies of the motion even though their amplitudes are small. These can be eliminated and efficiency increased by constraining some or all bond lengths and bond angles. We express these constraints as

$$g(x(t)) = 0 \quad \text{where} \quad g^k(x) = \|\vec{r}_{j(k)} - \vec{r}_{i(k)}\|^2 - l_k^2, \quad k = 1, 2, \dots, \mu.$$

The set of constraints is used to determine Lagrange multipliers  $\lambda(t)$  in the equations of motion:

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

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

Because typical biomolecular simulations are about 90% water, great savings in computation are attained with *an implicit solvent* [20, p. 293]. The dynamical equations are those of Langevin

dynamics:

$$\begin{aligned}\frac{d}{dt}x(t) &= v(t), \\ M\frac{d}{dt}v(t) &= -\nabla U(x(t)) - k_{\text{B}}TD(x(t))^{-1}v(t) + \sqrt{2}k_{\text{B}}TD_{1/2}(x(t))^{-\text{T}}\frac{d}{dt}W(t)\end{aligned}$$

where  $U(x)$  includes a Poisson-Boltzmann solution for electrostatics,  $D = D_{1/2}D_{1/2}^{\text{T}}$  is the diffusion tensor, and  $W(t)$  is a set of  $3N$  independent canonical Wiener processes. A canonical Wiener process  $W(t)$  is continuous and has a Gaussian distribution with mean zero and covariance  $\text{E}W_i(s)W_j(t) = \min\{s, t\}\delta_{ij}$ . The Boltzmann distribution for  $\frac{1}{2}p^{\text{T}}M^{-1}p + U(x)$  is invariant for Langevin dynamics, and it is used for thermodynamic averages. Significant deviations of implicit solvent models from explicit solvent are observed unless four or more hydration layers of explicit solvent are included [13].

The Poisson-Boltzmann solution is complicated and expensive to obtain, and this motivates the simpler and less expensive generalized Born potential [12].

The equations of Brownian dynamics, derived in [5, sec. III],

$$\frac{d}{dt}x(t) = \frac{1}{k_{\text{B}}T}D(x(t))F(x(t)) + \sqrt{2}D_{1/2}(x(t))\frac{d}{dt}W(t).$$

are a high friction limit approximation. The spatial scale of the trajectory grows as  $\sqrt{t}$  but the error from neglecting the inertial term remains bounded as  $t$  increases, so Brownian dynamics gives a reasonable approximation over long distances.

### 3 Fast force evaluation

Of actual concern here are only the nonbonded forces because their evaluation consumes almost all the CPU time.

#### 3.1 Nonperiodic nonbonded forces

The main concern here is the calculation of the electrostatic energy associated with  $N$  particles:

$$U^{\text{el}}(\vec{r}_1, \vec{r}_2, \dots, \vec{r}_N) = \frac{1}{2} \sum_{i=1}^N \sum_{j=1}^N \frac{q_i q_j}{\epsilon_0 |\vec{r}_j - \vec{r}_i|}$$

and the forces  $\vec{F}_i^{\text{el}} = -\nabla_i U^{\text{el}}(\dots)$ . Some of the techniques discussed here apply also to the longer-range  $1/r^6$  part of the Lennard-Jones potential.

The best known fast algorithms for the nonperiodic N-body calculation are multilevel methods. There are two kinds: (i) *cell methods*, such as the fast multipole method, based on an oct-tree decomposition of space, and (ii) *grid methods*, such as the Brandt-Lubrecht fast summation method, based on a hierarchy of grids. Both kinds of multilevel N-body solvers have three elements:

1. separation of length scales:

short-range + slowly varying.

The short-range interactions are calculated directly.

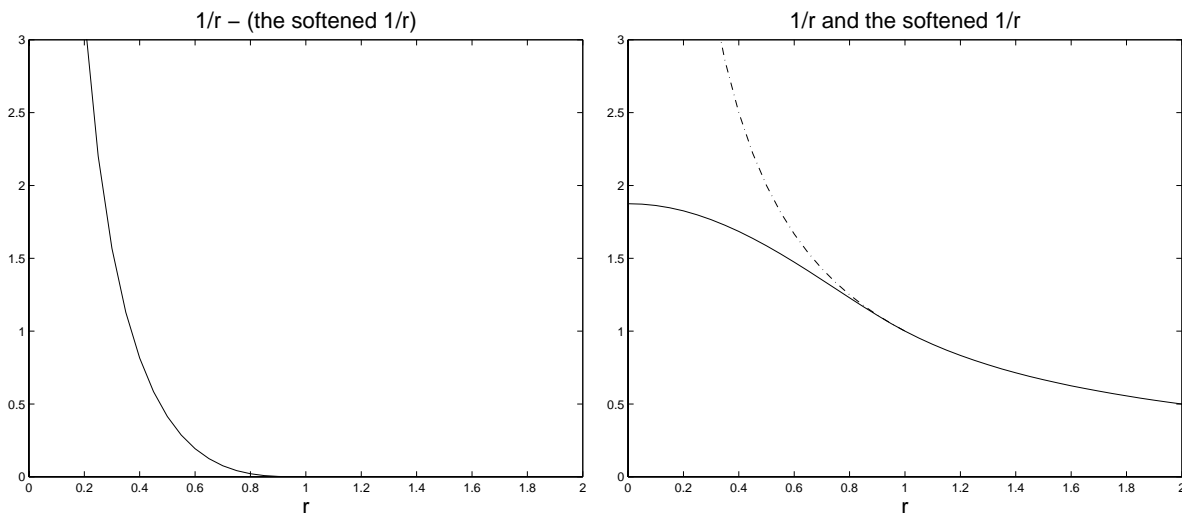
2. coarsening: *approximating* the slowly varying part with fewer values on a lattice. Barnes-Hut-type  $\mathcal{O}(N \log N)$  algorithms approximate at the source only; whereas, Greengard-Rokhlin-type  $\mathcal{O}(N)$  algorithms approximate at source and destination.
3. recursive application of 1. and 2.

The fundamental difference between cell and grid methods is the way in which they separate length scales.

For cell (or tree) method, a pairwise potential between two particles is deemed to be slowly varying if the two parent cells are “well separated.” Otherwise, the pairwise potential is short-range, and it is computed directly. Coarsening normally involves Taylor interpolation (truncated Taylor expansion). The multipole implementation exploits harmonicity of the  $1/r$  potential to permit the use of an economical basis of spherical harmonic polynomials.

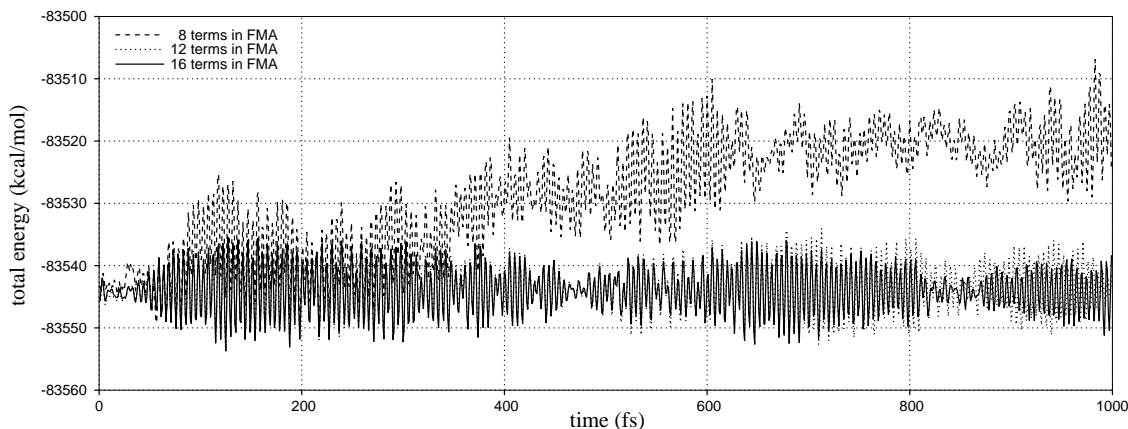
A multiple grid method achieves separation of length scales by splitting pair potentials into short-range and slowly varying parts:

$$\frac{1}{r} = \underbrace{\left(\frac{1}{r} - g_a(r)\right)}_{\text{short-ranged}} + \underbrace{g_a(r)}_{\text{slowly varying}} \quad \text{with } a = \text{cutoff.}$$



Coarsening is by interpolation (or approximation) using gridded basis functions. With this approach it is relatively easy to implement approximate forces that are continuous as a function of atomic positions [24].

In assessing the merit of an approximation  $\tilde{U}^{\text{el}}(\dots) \approx U^{\text{el}}(\dots)$ , it is not just the smallness of errors that matters. The continuity of  $\tilde{U}^{\text{el}}(\dots)$  and its derivatives also matters. For example, a continuous  $\tilde{U}^{\text{el}}(\dots)$  implies a conservative force. And empirical evidence indicates that continuous first derivatives are needed to prevent energy drift in a numerical simulation.



(Conservation of linear and angular momentum is another issue.) In one comparison [24], it is found that a multiple grid method is twice as fast as a fast multipole method for moderate accuracy appropriate for biomolecular dynamics. However, only the multiple grid method calculates continuous forces, and the multipole method is not usable unless higher accuracy is used, which increases the cost again by a factor of two.

*NAMD notes.* For van der Waals forces use `switching on` to get a continuous force (actually, continuously differentiable) and choose

```
switchdist < cutoff < pairlistdist
```

where the margin for the last value depends on `stepspercycle`  $\times$  `timestep`. If this margin is not large enough, a warning will be printed indicating a flawed force evaluation. For electrostatics use `fulldirect yes` (costly).

### 3.2 Periodic electrostatic forces

The standard way of approximating the Ewald sum is to cut off the switched potential, truncate the Fourier series, and choose the parameter  $\beta$  to give an operation count proportional to  $N^{3/2}$ .

An alternative and very fast  $\mathcal{O}(N \log N)$  algorithm is particle–mesh Ewald (PME), which is based on B-spline interpolation of complex exponentials in the Fourier series. This leads to a discrete Fourier series, which permits application of the fast Fourier Transform. The PME algorithm is related to an earlier particle–particle particle–mesh method.

*NAMD notes.* Use PME `yes` and control the error by setting `PMETolerance` to be the PME direct space tolerance (default value  $10^{-6}$ ) and choosing `PMEGridSizeX`, `PMEGridSizeY`, and `PMEGridSizeZ`.

### 3.3 Polarizable forces

Induced dipole moments are the solution of a dense system of linear equations [25]. Two ways of solving the linear system are proposed [25]. One is to solve it iteratively using a fast force method for the matrix–vector product, which is costly. Alternatively, the dipole moments can be made into additional dynamical variables in such a way that their average value approximates the solution of the linear system. However, this involves introducing several artifacts, which might be especially damaging if kinetic information is sought.

### 3.4 Implicit solvent electrostatics

The Poisson-Boltzmann equation is a nonlinear elliptic partial differential equation and is discretized using either finite volumes or finite elements. For very large spatial scales an adaptive discretization is worthwhile. Solution is by some form of a Newton iteration employing either a preconditioned conjugate gradient method or the multigrid method to solve the linear systems.

## 4 Numerical integrators for long-time kinetics

For long-time kinetics, trajectories can be accurate only statistically. Multiple trajectories of physically accurate dynamics are required with initial conditions drawn from some prescribed distribution.

### 4.1 Newtonian dynamics

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

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

can be derived from the principle of least action [16]. Clearly, the velocity definition does not affect the dynamics; e. g., Beeman's method [1] defines  $v^n = (x^{n+1} - x^{n-1})/(2\Delta t) - \Delta t M^{-1}(F(x^n) - F(x^{n-1}))/6$ .

Typical numerical integrators can be expressed in the form  $\Gamma^{n+1} = \Psi(\Gamma^n)$ . Expressing the Verlet method in such a form gives the "velocity Verlet" scheme:

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

To describe what is wanted from a numerical trajectory  $\Gamma^n \approx \Gamma(n\Delta t)$ , define the numerical density

$$\rho^n(\Gamma) = \text{p.d.f. for } \Gamma^n.$$

What we want is

$$\int A(\Gamma) \rho^n(\Gamma) d\Gamma \rightarrow \int A(\Gamma) \rho(\Gamma, n\Delta t) d\Gamma$$

for an arbitrary but well behaved  $A(\Gamma)$ .<sup>2</sup> If this is even possible for long times  $t = n\Delta t$ , what properties must the integrator possess? This is still a subject for research but current evidence indicates that  $\Gamma$  being *symplectic* is an appropriate property for statistically accurate long time integrations. An integrator  $\Gamma^{n+1} = \Psi(\Gamma^n)$  is *symplectic* if

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

Even stronger evidence suggests the importance of preserving volume in phase space, meaning that  $\det \partial_\Gamma \Psi(\Gamma) = 1$ . However, it is yet to be shown that reversibility is in general necessary. The possibility of nonsymplectic integration is discussed at the end of this subsection.

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<sup>2</sup>This is *weak* convergence of the numerical density  $\rho^n(\Gamma)$  to  $\rho(\Gamma, n\Delta t)$ .

The numerical trajectory  $\{\Gamma^n\}$  is *formally* the solution of a Hamiltonian system with Hamiltonian

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

if and only if  $\Psi$  is symplectic. A suitably truncated  $\tilde{H}(\Gamma)$  is very well conserved by the numerical solution and describes well its trajectory. However, a mere truncation of  $\tilde{H}(\Gamma)$  involves analytical derivatives of  $H$  and is expensive to compute. Defined in [22] is a family of interpolated shadow Hamiltonians

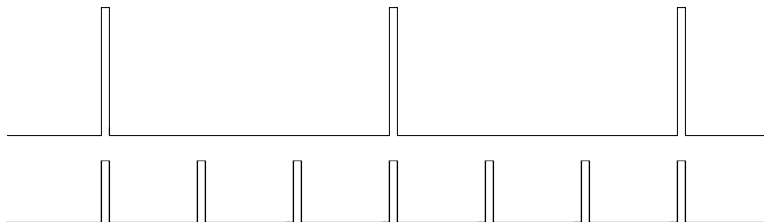
$$H_k(\Gamma) = \tilde{H}(\Gamma) + O(\Delta t^k), \quad k = 2, 4, \dots,$$

which are cheap and easy to evaluate. These are proving effective in identifying simulations of dubious accuracy.

High accuracy numerical integration is generally unwarranted due to the presence of significant statistical errors. A couple of recommended higher accuracy schemes are given in [21].

The appropriate step size varies depending on the force term being integrated, and significant savings in CPU time should be possible by using multiple time stepping—different step sizes for different interactions. A symplectic scheme for multiple time stepping (MTS) based on impulses has become popular under the name r-RESPA [26]. As an example, consider the use of two different step sizes have a 3:1 ratio. First split  $U = U^{\text{slow}} + U^{\text{fast}}$ . Define an (outer) time step of MTS to be 3 Verlet steps, each with step size  $\frac{1}{3}\Delta t$ :

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



Nonbonded interaction potentials have to be split into a short-range part and a slowly varying part as was the case for multiple grid methods for electrostatics. The most obvious split for Ewald electrostatics does not work well, however [18, 19, 27].

Unfortunately, the large step sizes expected for MTS cannot be realized in practice due to a step size barrier. Theory and experiment [14] indicate that for nondamping integrators energy growth occurs unless

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

where the period is the numerical period of the fastest normal mode. For Verlet the limit is only  $\sqrt{2}/(2\pi)$  times the period. Calculating these limits from the data in [20, Table 13.1] yields the following table of step size limits:



(outer) step size (fs)

	Verlet	MTS
no constraints	2.2	3.3
with H constraints	3.1	4.6
many constraints	9.4	13.9

*NAMD notes.* To use multiple time stepping without energy drift, set `timestep 1.041666666666667` and `fullElectFrequency 3` yielding an outer step size of 3.125 fs. (For an outer step size of 5 with imperceptible drift use `molly on`, `timestep 1.`, and `fullElectFrequency 5`.)

The step size restrictions for non-damping integrators make it attractive to seek alternatives. Damping is unacceptable unless it is balanced with random noise. For lower fidelity long time integrations, a

symplectic integrator + weak Langevin coupling

may work. Such a method is Langevin MOLLY [10], which is based on the symplectic *mollified impulse* method (MOLLY) where

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

in the impulse MTS (r-RESPA) method. Yet longer step sizes are attained with **targeted** Langevin coupling [15]. An outer step size of 16 fs can be obtained compared to only 3.2 fs using r-RESPA.

*NAMD notes.* Langevin MOLLY can obtain an outer step size of 8 fs with  $\gamma = 0.2 \text{ ps}^{-1}$ . To use it, set `langevin on`, `langevinTemp 298.`, `langevinDamping 0.2`, `molly on`, `mollyTolerance 0.00001`, `timestep 1.0`, `fullElectFrequency 4`, and `nonbondedFreq 2`. Failure to achieve tolerance results in a warning.

## 4.2 Constrained dynamics

The Verlet scheme can be extended to handle constraints using the SHAKE discretization:

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

where

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

The velocity is defined by  $v^n = (x^{n+1} - \Delta t^2 \partial_x g(x^n)^T \lambda^n - x^{n-1}) / (2\Delta t)$ . A variant of this scheme, called RATTLE, defines the velocity so that it is consistent with the constraints. SHAKE is, of course, dynamically equivalent to RATTLE, and RATTLE is symplectic.

An iteration is needed to solve the constraint equations for the Lagrange multipliers. Commonly this is done by Newton-Gauss-Seidel, although Newton-SOR is faster [2]. An accurate solution is needed to avoid energy drift.

It is common to use all-rigid models for water and special methods like SETTLE [17] have been developed.

*NAMD notes.* Rigid waters is an option in NAMD, which is implemented using SETTLE. Rigid hydrogen covalent bonds is an option in NAMD. Their implementation uses SHAKE with a default value of `1e-8` for `rigidTolerance`. Lack of convergence aborts the simulation.

### 4.3 Stochastic dynamics

The Brooks-Brünger-Karplus scheme for Langevin dynamics is

$$M \frac{1}{\Delta t^2} (x^{n+1} - 2x^n + x^{n-1}) = F(x^n) - k_B T D(x^n)^{-1} \frac{1}{2\Delta t} (x^{n+1} - x^{n-1}) + \sqrt{2k_B T D_{1/2}(x^n)^{-T}} \frac{1}{\sqrt{\Delta t}} Z^n$$

where  $Z^n$  is a collection of independent random numbers from a Gaussian distribution with mean 0 and variance 1. There are significant challenges dealing with the inversion of the diffusion tensor; see, e.g., [3].

For a diagonal diffusion tensor there are better methods. Good simple methods include a 1982 scheme of van Gunsteren and Berendsen and the Langevin impulse method [23]. The most efficient integrator is the multiple time step LN method [20, p. 438].

For Brownian dynamics the customary choice of numerical integrator is the Euler(-Maruyama) method, introduced in this context by Ermak and McCammon [5]. This method advances coordinates for a time step  $\Delta t$  by the simple recipe

$$\frac{1}{\Delta t} (x^{n+1} - x^n) = \frac{1}{k_B T} D(x^n) F(x^n) + \sqrt{2} D_{1/2}(x^n) \frac{1}{\sqrt{\Delta t}} Z^n.$$

## 5 Propagators for thermodynamics

Propagators generate points  $\Gamma^n$  in phase space having a prescribed distribution. For the canonical (or NVT) ensemble the density factors as a product  $\rho_x(x)\rho_p(p)$ , which enables the random configurations  $x^n$  to be generated independently. Similarly for the isothermal-isobaric (or NPT) ensemble.

Markov chain Monte Carlo (MC) methods are rigorous sampling techniques. Modifications to the equations of motion for MD can produce correct phase space averages from a single trajectory if the system is ergodic. In the case of deterministic differential equations, ergodicity is probably present only in the thermodynamic limit  $N \rightarrow \infty$ . In any case, the numerical implementation of MD introduces a bias due to finite  $\Delta t$ .

### 5.1 Markov chain Monte Carlo methods

Averages over configuration space are computed using a discrete (stochastic) Markov process. A suitable Markov chain can be constructed by applying the Metropolis acceptance criterion to an *ergodic* random move generator.

Monte Carlo methods are not so often used for macromolecules because of the difficulty of specifying good moves and the high incremental costs of computing long-range forces. See [20, p. 380] for further discussion.

Hybrid Monte Carlo uses molecular dynamics to generate possible moves. It is sufficient that the integrator be reversible and preserve phase-space volume. Unfortunately, rejection rate increases with the system size  $N$  due to integrator-produced fluctuations in the energy. Higher order integrators is one solution,

## 5.2 NVT dynamics

NVT sampling is possible using a Nosé thermostat, which results from integrating the Hamiltonian system for

$$H(x, s, \bar{p}, p_s) = \frac{1}{2}s^{-2}\bar{p}^T M^{-1}\bar{p} + U(x) + \frac{1}{2Q}p_s^2 + N_d k_B T \ln s$$

where  $Q$  is a thermal inertia parameter and  $N_d$  is the number of degrees of freedom ( $3N - 3$  if the total momentum is fixed). Initialize  $\bar{p}(0) = s(0)p(0)$  and use

$$\frac{\int_0^t A(x(\tau), s(\tau)^{-1}\bar{p}(\tau))s(\tau)^{-1} d\tau}{\int_0^t s(\tau)^{-1} d\tau}$$

to approximate an NVT average for  $A(x, p)$ . There is a slightly more convenient non-Hamiltonian version of this called Nosé-Hoover dynamics, but the article [4] gives evidence of excessive drift in the extended energy and instead propose a Nosé-Poincaré thermostat.

Langevin dynamics produces an NVT ensemble.

*NAMD notes.* Langevin dynamics with a diagonal tensor is available in NAMD.

## 5.3 NPT dynamics

The Langevin piston method [6] for NPT sampling involves integrating

$$\begin{aligned} \frac{d}{dt}x(t) &= M^{-1}p(t) + \frac{1}{3QV(t)}p_V(t)x(t), & \frac{d}{dt}p(t) &= F(x(t)) - \frac{1}{3QV(t)}p_V(t)p(t), \\ \frac{d}{dt}V(t) &= \frac{1}{Q}p_V(t), & \frac{d}{dt}p_V(t) &= P(t) - P_{\text{ext}} - \gamma p_V(t) + \sqrt{2\gamma k_B T Q} \frac{d}{dt}W(t) \end{aligned}$$

where

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

*NAMD notes.* NAMD implements the Langevin piston method.

## 5.4 Time correlation functions

Correlation functions should be computed from accurate Newtonian dynamics trajectories using initial conditions drawn from the desired ensemble, and, in particular, the equations of motion should be bereft of artificial temperature and pressure controls [1, p. 59]. In practice, this dictum is often ignored, e. g., the Langevin piston method is designed with kinetics in mind.

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