Journal of Mathematical Chemistry 18 (1995) 25–35

Theory and algorithms for mixed Monte Carlo–stochastic dynamics simulations

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Received 3 May 1995

The recently introduced mixed MC–SD method is a fundamentally new procedure which essentially eliminates the distinction between Monte Carlo and dynamics. Unlike other methods which utilize forces, Brownian motion or dynamical steps to generate new trial configurations in a Monte Carlo search, mixed MC–SD does stochastic dynamics on the cartesian space of a molecule and Monte Carlo on the torsion space of the molecule simultaneously. After each dynamical step, a random deformation of a rotatable torsion is performed and accepted or rejected according to the Metropolis criteria. The next dynamical step is performed from the most recent configuration and the velocities from the previous dynamical step. The smooth merging of Monte Carlo and dynamics requires the use of the stochastic velocity Verlet integration scheme. Here, the velocity Verlet stochastic dynamics method is derived, and the reasons why it can be joined with Metropolis Monte Carlo in a continuous fashion are explored.

1. Introduction

Early simulations were used to study equilibrium and transport properties of structureless systems governed by simple potentials [1]. Today, simulations are used to study complex systems such as protein structure [2] and to compute free energies [3]. Since it is extremely useful to compare simulation results with experiment, there is a great desire and need for algorithms which efficiently sample all thermally accessible regions of configuration space, and generate a canonical ensemble [4]. This ensemble may be generated in a variety of ways by using the standard Metropolis algorithm [5], Langevin dynamics [6], isokinetic Gaussian thermostats [7], or Nose dynamics [8]. Limitations of the Monte Carlo method have led to many attempts at generating a better random walk [9]. The recognition that the dynamics of Nose require an ergodic Hamiltonian [10] has led to varying attempts to extend the method [11]. It is clear that a great deal of effort has been and will continue to be expended in the attempt to more efficiently sample configuration space, and to generate a canonical ensemble.

When simulations are used to study flexible organic molecules, the problems of sampling the space and generating a canonical ensemble are magnified because

motion in these systems takes place on multiple time scales [12]. Bond lengths and bond angles move on a femtosecond to picosecond time scale, while many torsional changes occur on a nanosecond time scale. Truly quantitative molecular design applications involving flexible molecules requires algorithms capable of sampling local wells and capable of crossing the large energy barriers separating these wells while yielding the correct population distributions. These considerations led to the development of the mixed MC–SD method. In the mixed MC–SD method, stochastic dynamics in Cartesian space and Metropolis Monte Carlo in torsion space are performed in alternating steps. After every dynamical step a random trial torsional deformation is performed and accepted or rejected according to the Metropolis criteria. Regardless of the outcome of the Metropolis test, the next dynamical step is done from the current configuration using the velocities from the previous dynamical step. This is radically different from many of the schemes [9] which utilize dynamical operations to generate a new trial configuration for a Monte Carlo random walk. The mixed MC–SD method actually merges dynamics and Monte Carlo into a single unified algorithm which eliminates the distinction between the deterministic and the stochastic.

Several examples of the speed and accuracy of the mixed MC–SD method have been recently published [13,14]. In the first case [13], several small systems such as anharmonic two well potentials and n-pentane were shown to give identical results with Metropolis Monte Carlo, stochastic dynamics, and the mixed MC–SD method even up to the fourth moment of the energy for n-pentane. Additionally, it was demonstrated that the mixed MC–SD method converged 3 orders of magnitude faster than stochastic dynamics in conformational free energy calculations of n-pentane. In the second case, it was demonstrated that the mixed MC–SD method is essential for computing binding free energies of small host-guest complexes containing rotatable torsional angles [14]. In this example it was demonstrated that stochastic dynamics alone was incapable of reproducing quantitative experimental binding free energies, and that the mixed MC–SD scheme was capable of reproducing quantitative binding free energies. In fact, the mixed MC–SD algorithm was used to quantitatively design a new synthetic molecular peptide host [14].

The need to use velocity Verlet stochastic dynamics in the mixed MC–SD method was alluded to in the original paper [13]. The reasons why this integration scheme is needed will be demonstrated, and the velocity Verlet stochastic dynamics algorithm is derived. It should be noted that only a simple, classical Metropolis Monte Carlo scheme has been used in the mixed MC–SD method. The mixed MC–SD algorithm should be totally compatible with any of the more sophisticated Monte Carlo schemes cited in ref. [9].

2. The velocity Verlet stochastic dynamics algorithm

The stochastic equation of motion is

$$m\,dv/dt = f[x(t)] + R(t) - m\gamma v\,. \tag{1}$$

The mass is m, v is the velocity, x is the position, f is the deterministic force, γ is the friction coefficient, and R is the random force. From the fluctuation–dissipation theorem with δ-function memory, the time correlation of the random variables is

$$\langle R(t)R(t')\rangle = 2m\gamma kT\delta(t-t')\,. \tag{2}$$

The time is t, k is Boltzmann's constant, T is the temperature, and the pointed brackets indicate equilibrium ensemble averaging.

The first step in solving the stochastic equation of motion is to divide eq. (1) by m, add γv to both sides, and multiply by the integrating factor $\exp(\gamma t)$. This gives

$$d/dt\,[\exp(\gamma t)v(t)] = \exp(\gamma t)\{f[x(t)] + R(t)\}/m\,. \tag{3}$$

Integrating from t_0 to $t(\Delta t = t - t_0)$, adding $v(t_0)\exp(\gamma t_0)$ to both sides of the equation, and multiplying both sides of the equation by $\exp(-\gamma t)$ gives

$$\begin{aligned} v(t) = {} & v(t_0)\ \exp(-\gamma\Delta t) + \exp(-\gamma t)/m \int_{t_0}^{t} dt'\ f[x(t')]\exp(\gamma t') \\ & + \exp(-\gamma t)/m \int_{t_0}^{t} dt'\ R(t')\ \exp(\gamma t')\,. \end{aligned} \tag{4}$$

Partial integration of the first integral in eq. (4) neglecting higher order terms gives

$$\exp(-\gamma t)/m \int_{t_0}^{t} dt'\, f[x(t')]\ \exp(\gamma t') = f[x(t)][1 - \exp(-\gamma\Delta t)]/(m\gamma)\,.$$

Making this substitution, eq. (4) becomes

$$\begin{aligned} v(t) = {} & v(t_0)\ \exp(-\gamma\Delta t) + f[x(t_0)][1 - \exp(-\gamma\Delta t)]/(m\gamma) \\ & + \exp(-\gamma t)/m \int_{t_0}^{t} dt'\ R(t')\ \exp(\gamma t')\,. \end{aligned} \tag{5}$$

Given that $v = dx/dt$, integrating eq. (5) from t_0 to t yields the position equation

$$\begin{aligned} x(t) = {} & x(t_0) + v(t_0)[1 - \exp(-\gamma\Delta t)]/\gamma + f[x(t_0)]\{\gamma\Delta t - [1 - \exp(-\gamma\Delta t)]\}/ \\ & (m\gamma^2) + 1/(m\gamma) \int_{t_0}^{t} dt'\ R(t')\{1 - \exp[-\gamma(t' - t)]\}\,. \end{aligned} \tag{6}$$

The first three terms on the right hand side of eq. (6) are obtained from the elementary integration of the corresponding terms in eq. (5). The stochastic integral in eq. (6) is obtained from partial integration (neglecting higher order terms) of the double integral that arises from integrating eq. (5):

$$\int_{t_0}^{t} \exp(-\gamma t')/m \int_{t_0}^{t'} dt'' \; R(t'') \; \exp(\gamma t'') \, .$$

Recalling that $t = t_0 + \Delta t$, and defining $R1(t, t_0 + \Delta t)$ as

$$1/(m\gamma) \int_{t_0}^{t_0+\Delta t} dt' \; R(t')\{1 - \exp[-\gamma(t' - t)]\} \, ,$$

eq. (6) (omitting the subscript on t_0) may be rewritten as

$$\begin{aligned} x(t + \Delta t) = x(t) + v(t)[1 - \exp(-\gamma \Delta t)]/\gamma \\ + f[x(t)]\{\gamma \Delta t - [1 - \exp(-\gamma \Delta t)]\}/(m\gamma^2) + R1(t, t + \Delta t) \, . \end{aligned} \tag{7}$$

It should be noted that the integrals of the random force $R(t)$ are stationary, Markovian, Gaussian stochastic processes because the random forces themselves are stationary, Markovian, Gaussian stochastic processes [15]. Integrating this position equation backward in time gives

$$\begin{aligned} x(t - \Delta t) = x(t) + v(t)[1 - \exp(\gamma \Delta t)]/\gamma \\ + f[x(t)]\{-\gamma \Delta t - [1 - \exp(\gamma \Delta t)]\}/(m\gamma^2) + R1(t, t - \Delta t) \, . \end{aligned} \tag{8}$$

Solving eqs. (7) and (8) simultaneously to eliminate $v(t)$ gives

$$\begin{aligned} x(t + \Delta t) = x(t)[1 + \exp(-\gamma \Delta t)] - x(t - \Delta t) \; \exp(-\gamma \Delta t) \\ + f[x(t)] \Delta t [1 - \exp(-\gamma \Delta t)]/(m\gamma) + R1(t, t + \Delta t) \\ + R1(t, t - \Delta t) \; \exp(-\gamma \Delta t) \, . \end{aligned} \tag{9}$$

Integrating eq. (9) another timestep to $t + 2\Delta t$ gives

$$\begin{aligned} x(t + 2\Delta t) = x(t + \Delta t)[1 + \exp(-\gamma \Delta t)] - x(t) \; \exp(-\gamma \Delta t) \\ + f[x(t + \Delta t)] \Delta t [1 - \exp(-\gamma \Delta t)]/(m\gamma) + R1(t, t + 2\Delta t) \\ + R1(t + \Delta t, t) \; \exp(-\gamma \Delta t) \, . \end{aligned} \tag{10}$$

Since velocity in the velocity Verlet is $v(t) = [x(t + \Delta t) - x(t - \Delta t)]/2\Delta t$, adding eq. (9) and eq. (10) and doing a little rearranging gives

$$v(t+\Delta t) = v(t)\ \exp(\gamma\Delta t) + \{f[x(t)] + f[x(t+\Delta t)]\}[1-\exp(-\gamma\Delta t)]/(2m\gamma) + [R1(t, t+\Delta t) + R1(t+\Delta t, t+2\Delta t)]/(2\Delta t) + \exp(-\gamma\Delta t)[R1(t, t-\Delta t) + R1(t+\Delta t, t)]/(2\Delta t)\,. \tag{11}$$

The final step in obtaining the velocity Verlet stochastic dynamics equations is the treatment of the stochastic forces. Recalling the definition of $R1(t, t+\Delta t)$:

$$1/(m\gamma)\int_t^{t+\Delta t} dt'\ R(t')\{1-\exp[-\gamma(t'-t)]\}\,,$$

the stochastic integral obtained from integrating backward in time, $R1(t+\Delta t, t)$:

$$1/(m\gamma)\int_{t+\Delta t}^{t} dt'\ R(t')\{1-\exp[-\gamma(t'-t)]\}\,,$$

may be redefined as $R2(t, t+\Delta t)$:

$$1/(m\gamma)\int_t^{t+\Delta t} dt'\ R(t')\{\exp[-\gamma(t'-t)]-1\}\,.$$

This allows the velocity integration given in eq. (11) to be written so that every quantity is moving forward in time:

$$v(t+\Delta t) = v(t)\ \exp(\gamma\Delta t) + \{f[x(t)] + f[x(t+\Delta t)]\}[1-\exp(-\gamma\Delta t)]/(2m\gamma) + [R1(t, t+\Delta t) + R1(t+\Delta t, t+2\Delta t)]/(2\Delta t) + \exp(-\gamma\Delta t)[R2(t-\Delta t, t) + R2(t, t+\Delta t)]/(2\Delta t)\,. \tag{12}$$

Equation (7) is the position integration and eq. (12) is the velocity integration. It should be noted that this integration scheme is accurate to third order in Δt. Since $R1(t, t+\Delta t)$ and $R2(t, t+\Delta t)$ are two different integrals over the same time step, they are correlated and obey a bivariate Gaussian distribution

$$G(R1, R2) = [4\pi\partial_1{}^2\partial_2{}^2(1-\partial_{12}{}^2)]^{-1/2}\ \exp\{-[\partial_1{}^2 R1 + \partial_2{}^2 R2 - 2\partial_1\partial_2\partial_{12} R1 R2]/[2\partial_1{}^2\partial_2{}^2(1-\partial_{12}{}^2)]\}\,.$$

The parameters $\partial_1, \partial_2, \partial_{12}$ may be determined from the following relations:

$$\partial_1{}^2 = \langle R1R1\rangle;\quad \partial_2{}^2 = \langle R2R2\rangle;\quad \partial_1\partial_2\partial_{12} = \langle R1R2\rangle\,,$$

and eq. (2):

$$\langle R(t)R(t')\rangle = 2m\gamma kT\delta(t-t')\,.$$

For example,

$$
\begin{aligned}
\partial_1{}^2 &= \langle R1R1\rangle \\
&= (m\gamma)^{-2}\int_t^{t+\Delta t} dt'\,\{1-\exp[-\gamma(t'-t)]\}\{1-\exp[-\gamma(t''-t)]\} \\
&\quad\times\int_t^{t+\Delta t} dt''\,\langle R(t')R(t'')\rangle \\
&= (m\gamma)^{-2}\int_t^{t+\Delta t} dt'\,\{1-\exp[-\gamma(t'-t)]\}\{1-\exp[-\gamma(t''-t)]\} \\
&\quad\times\int_t^{t+\Delta t} dt''\,2m\gamma kT\delta(t-t') \\
&= 2kT/(m\gamma)\int_t^{t+\Delta t} dt'\,\{1-\exp[-\gamma(t'-t)]\}^2 \\
&= kT/(m\gamma^2)[2\gamma\Delta t-3+4\,\exp(-\gamma\Delta t)-\exp(-2\gamma\Delta t)]\,.
\end{aligned}
$$

Solving in a similar manner,

$$\partial_2{}^2 = \langle R2R2\rangle = kT/(m\gamma^2)[-2\gamma\Delta t+3-4\,\exp(\gamma\Delta t)+\exp(2\gamma\Delta t)]\,,$$

$$\partial_1\partial_2\partial_{12} = \langle R1R2\rangle = kT/(m\gamma^2)[\exp(\gamma\Delta t)-2\gamma\Delta t+\exp(-\gamma\Delta t)]\,.$$

3. The mixed MC–SD method

The first attempts [13] at mixing MC with SD utilized the leap frog SD algorithm [16]. This worked for one particle in various simple potentials. When an atomic system was tested, the simulation immediately overheated with the extent of the overheating directly related to the MC acceptance rate. The cause was immediately traced to the discontinuities of the intramolecular derivatives. Of course this was not too surprising since the mixed MC–SD procedure can be viewed as a dynamical algorithm with repeated and violent random changes inflicted upon the configuration. Since dynamics is a procedure which smoothly and gradually changes the configuration in an essentially continuous fashion, the question is: does there exist a dynamical integration scheme which will not blow up when the configuration is randomly and frequently violently distorted, and will this united product result in a method which actually generates a canonical ensemble? It has not only been demonstrated that the answer to both of these questions is yes, but that this new method is very powerful when applied to molecular systems containing rotatable torsional degrees of freedom [13,14].

Naturally, a dynamics that produces a canonical ensemble was chosen for the mixed MC–SD method. The random and friction forces are, however, irrelevant in

illustrating why the velocity Verlet can be successfully mixed with Monte Carlo, while the Verlet, Beeman, and leap frog cannot. Figure 1 shows the equations for how MC can be mixed with Verlet MD, and velocity Verlet MD.

The integration loop in the mixed MC Verlet MD scheme is: compute forces, integrate positions, integrate velocities, attempt and MC step. If the MC step fails, continue the dynamics. If the MC step passes, load the new positions into $x(t)$ and continue on to the next dynamical step. This is schematically illustrated in fig. 2.

Fig. 2(A) shows that the position integration to $x(t + \Delta t)$ requires knowledge of the position at $x(t)$ and at $x(t - \Delta t)$. Admixing MC into this integration scheme by loading an accepted MC step into $x(t)$ is illustrated in fig. 2(B). Clearly, $x(t)$ and $x(t - \Delta t)$ in this case are not really separated by Δt. The resulting discontinuity leads to overheating. The ordering of the integration loop, as illustrated in fig. (1B), is slightly different in the mixed MC velocity Verlet scheme: integrate positions, compute forces, integrate velocities, attempt an MC step. Figure 3(A) shows that the position integration to $x(t + \Delta t)$ only requires knowledge of the position at $x(t)$.

The velocity integration requires knowledge of forces at t and $t + \Delta t$, not at $t - \Delta t$. This is the critical point. As illustrated in fig. 3(B), admixing MC into this integration scheme by loading an accepted MC step into $x(t)$ will cause no disconti-

(A) Verlet MD with MC

Compute f = f[x(t)]

$x(t+\Delta t) = 2x(t) - x(t-\Delta t) + m^{-1}f(t)\Delta t^2$

$v(t) = [x(t+\Delta t) - x(t-\Delta t)] / 2\Delta t$

Do MC; If Accept -----> load new position into x(t)

(B) Velocity Verlet MD with MC

$x(t+\Delta t) = x(t) + v(t)\Delta t + m^{-1}f(t)\Delta t^2$

Compute f = f[x(t)]

$v(t+\Delta t) = v(t) + m^{-1}[f(t+\Delta t) + f(t)]\Delta t / 2$

Do MC; If Accept -----> load new position into x(t)

Fig. 1. Part A shows how Monte Carlo may be mixed with Verlet molecular dynamics. Part B shows how Monte Carlo may be mixed with velocity Verlet molecular dynamics. Note the discontinuity that is introduced into the Verlet integration by admixing Monte Carlo into the dynamics, and the smooth way that Monte Carlo may be introduced into the velocity Verlet integration.

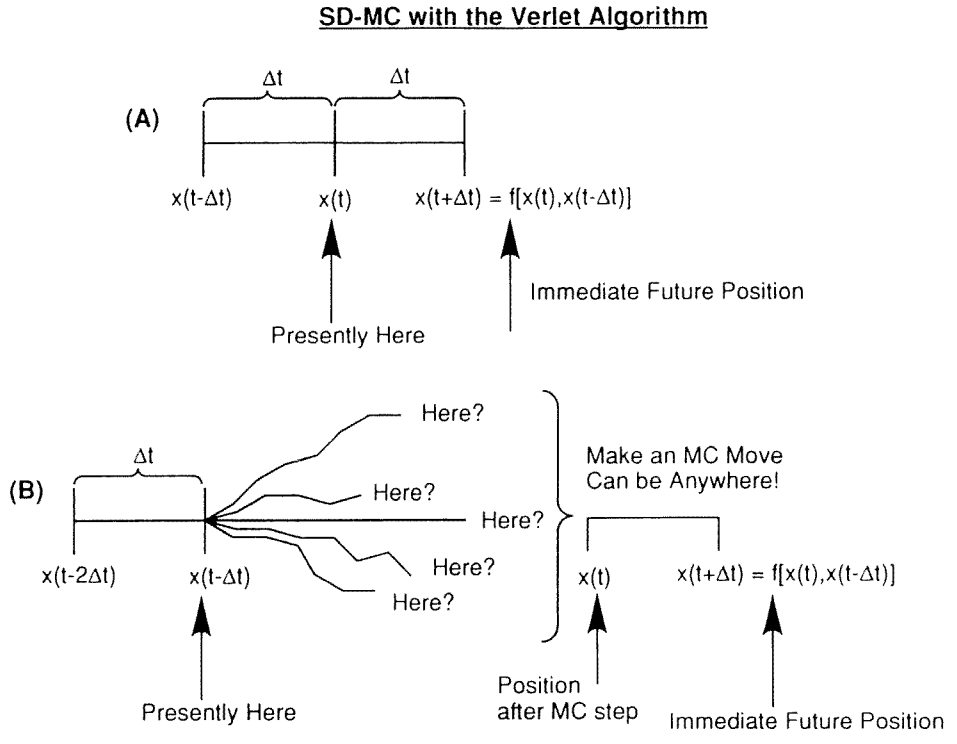

Fig. 2. Part A shows the functional dependence of the position integration in Verlet molecular dynamics. Note that the new position is a function of the present position and the previous position. Part B shows that the admixing of a Monte Carlo step into this scheme will cause discontinuities because the present position will no longer really be separated by a differential distance from the prior position.

nuity in the equations because there is no memory of what happened at $x(t - \Delta t)$. It should be noted that the velocities are unaffected by the results of the Metropolis test.

4. Implementing the mixed MC–SD algorithm

The implementation of the method is straightforward, just as is illustrated in fig. (2B). The only real complexity is in keeping track of the correlations among the random variables. To get started,

I. assign initial coordinates and velocities,

II. compute initial forces,

III. assign forces to $R1(t - \Delta t, t)$; $R1(t, t + \Delta t)$; $R1(t + \Delta t, t + 2\Delta t)$ by sampling three times from a Gaussian of zero mean and width ∂_1 setting $R1(t - \Delta t, t)$ = sample 1; $R1(t, t + \Delta t)$ = sample 2; $R1(t + \Delta t, t + 2\Delta t)$ = sample 3,

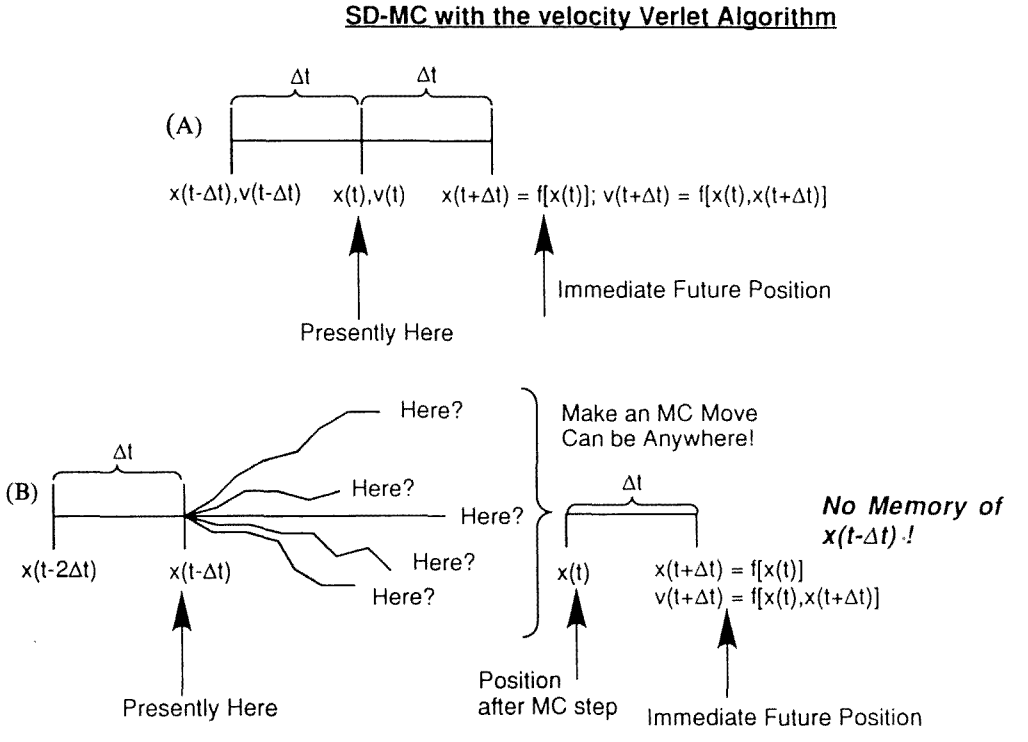

Fig. 3. Part A shows the functional dependence of the position and velocity integration in velocity Verlet molecular dynamics. Note that the new position is only a function of the present position. The new velocity is a function of the present position and the new position. Hence, the forces used to update the velocities are always separated by Δt whether or not a Monte Carlo step is accepted and loaded into $x(t)$. Part B shows that the admixing of a Monte Carlo step into this scheme will cause no discontinuities because there is no memory the past events.

IV. assign forces to $R2(t-\Delta t,\ t)$; $R2(t,\ t+\Delta t)$ by sampling twice from a Gaussian of zero mean and width $[\partial_2{}^2(1-\partial_{12}{}^2)]^{1/2}$ setting $R2(t-\Delta t,\ t) = \text{sample } 1+R1(t-\Delta t,\ t)A/B$; $R2(t,\ t+\Delta t) = \text{sample } 2+R1(t,\ t+\Delta t)A/B$, where

$$A = \exp(\gamma\Delta t) - 2\gamma\Delta t + \exp(-\gamma\Delta t)\,,$$

$$B = 2\gamma\Delta t - 3 + 4\ \exp(-\gamma\Delta t) - \exp(-2\gamma\Delta t)\,.$$

The production phase may now be started as follows:

I. compute the new positions according to eq. (7),

II. compute the new forces,

III. compute the new velocities according to eq. (12),

IV. load $R1(t, t+\Delta t)$ into $R1(t-\Delta t, t)$; load $R1(t+\Delta t, t+2\Delta t)$ into $R1(t, t+\Delta t)$,

V. obtain the new $R1(t+\Delta t, t+2\Delta t)$ as described in getting started part III,

VI. obtain the new $R2(t-\Delta t, t)$, $R2(t, t+\Delta t)$ as described in getting started part IV,

VII. attempt an MC step, if successful load into $x(t)$ as the new coordinates,

VIII. go back to I.

5. Conclusion

It should be clearly stated that the validity of the mixed MC–SD procedure has not been formally demonstrated. What has been previously shown is that the mixed MC–SD technique produces the same distributions as canonical dynamics and Monte Carlo in a variety of test systems, and that the convergence of the mixed MC–SD technique was superior in all cases tested [13,14]. The method has been probed in more detail to investigate stability. In a variety of simulations the temperature always converged to within 2 degrees of the target temperature regardless of the MC acceptance rate (up to 50%), and gave the same potential distributions as MC and SD alone. These results are only obtained when MC is mixed with the velocity Verlet stochastic dynamics method. Mixing other integration schemes with MC resulted in immediate overheating which increased as the MC acceptance rate increased. The smooth, seamless merging of MC and SD that occurs when the velocity Verlet integration scheme is used, results in a very powerful algorithm for generating a canonical ensemble in flexible molecular systems. Alternatively, this method may have important theoretical implications because it eliminates all distinction between the stochastic and the dynamic.

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