

Method for accelerating chain folding and mixing

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An algorithm based on allowing the form of the intermolecular potential to fluctuate is introduced into molecular dynamics and Monte Carlo simulations. It is shown that this method accelerates the approach to equilibrium in frustrated systems. It provides a very useful method for determining all of the local minima in complex systems. Examples are mixing in dense binary liquids and folding of long polymer chains. When this method is combined with umbrella sampling techniques it accelerates the simulations of a wide class of chemically important systems.

I. INTRODUCTION

Consider the case of a dense binary liquid. If the initial state of the system is such that one component occupies the top half and the other the bottom half of the container it takes a very long time for the system to mix. In order to mix particles must find channels for bypassing each other and if the repulsive forces are strong enough there will be very large energy barriers that must be crossed. Very long Monte Carlo or Molecular dynamics simulations would be required to equilibrate such a system.

Consider the case of a long n -alkane chain. In order to fold, such a chain must execute a walk in which the methylene groups separated by four or more C-C bonds must avoid each other because of their strong steric repulsions. In the folding process it is easy for a very long chain to fold into a frustrated configuration, one from which it is difficult for the system to fold further. The chain may then appear to be "glassy." In such cases the folding process can be very slow. Moreover, it is difficult to enumerate all of the local energy minima for a very long chain.

These two systems are paradigms for many important problems in computational chemistry. It is important to design algorithms that can accelerate the mixing and folding processes. In this note we investigate two novel methods for accelerating these processes. We call one of these methods the fluctuating sigma method. The basic gist of the method is to allow the Lennard-Jones diameters of the nonbonded interaction to fluctuate. We introduce a cost function for these fluctuations into the potential and we show how to use molecular dynamics or Monte Carlo methods to generate the configurations of this system. In molecular dynamics we introduce a fictitious kinetic energy for the sigma fluctuations and we use extended Lagrangian methods to generate the motion in which the atomic centers move and the diameters fluctuate. In Monte Carlo we sample both new positions and new diameters and accept or reject the moves using the usual Metropolis method (a more sophisticated version like variable step size Monte Carlo can also be used). The other method we call the fluctuating potential method. The basic gist of this method is to allow the torsion angle potentials in chain molecules to fluctuate between two or more functional forms. In its simplest incarnation only two forms are used;

one being the correct potential and the other being a form with the same relative minima but with greatly reduced barriers between *gauche* (G) and *trans* (T) conformations. These methods lead to a rapid exploration of configuration space. Local energy minima, not accessible by the traditional methods, are readily visited. In addition, by using umbrella sampling techniques, we can also generate averages over the Boltzmann probabilities for the exact system.

The methods are applied to paradigmatic problems in mixing and chain folding. It is demonstrated that the fluctuating potential method offers a very powerful alternative to standard methods. The methods outlined here are easily generalized and we expect that these ideas will lead to many new methods.

II. THE POTENTIAL FLUCTUATION METHOD

A. The sigma fluctuation method

First we consider a fictitious dense liquid of N identical spheres interacting according to a Lennard-Jones (6-12) potential,

$$V(\{r_{ij}\}, \{\sigma_{ij} = (\sigma_i + \sigma_j)/2\}) = \sum_{i>j}^N 4\epsilon \left[\left(\frac{\sigma_i + \sigma_j}{2r_{ij}} \right)^{12} - \left(\frac{\sigma_i + \sigma_j}{2r_{ij}} \right)^6 \right], \quad (2.1)$$

where the individual atomic diameters, (σ_i) are allowed to fluctuate between $\lambda\sigma_i^0$ and σ_i^0 and where λ is a positive constant smaller than unity, and σ_i^0 is the usual Lennard-Jones (LJ) diameter of atom i . Here both the positions and diameters can vary and the instantaneous configurational state of the fluid is defined by the instantaneous positions and diameters (r_i, σ_i) . Sometimes it will prove useful to introduce an energy cost function for the diameters, $F[(\sigma_i)]$, into Eq. (2.1). An example might be $F[(\sigma_i)] = \sum_{i=1}^N C(\sigma_i - \sigma_i^0)^n$ but many other choices are possible and in point of fact one can sometimes take $F=0$.

If molecular dynamics is to be used to simulate this fictitious fluid we define a Hamiltonian,

$$H_\sigma = \sum_{i=1}^N \frac{p_i^2}{2m} + \sum_{i=1}^N \frac{m'_i \sigma_i^2}{2} + V[(r_i), (\sigma_i)] + F[(\sigma_i)], \quad (2.2)$$

where m'_i is a fictitious mass associated with the fictitious sigma velocity $\dot{\sigma}_i$. One can use either constant energy or constant temperature molecular dynamics. In the latter case Nosé thermostats can be used. It might then be of advantage to thermostat the σ 's at low temperature and the normal positions at the ambient temperature of interest.

In Monte Carlo simulations reported here, a σ move is made for every ν moves in the atomic coordinates and these moves are separately accepted using the Metropolis criterion.

These procedures generate a very efficient walk in the enlarged configuration space (r_i, σ_i) . Umbrella sampling techniques can then be used to evaluate averages in the ensemble of fixed σ 's. It is easy to show that

$$\langle A \rangle_{\sigma^0} = \frac{\langle A e^{-\beta[V[(r_i), (\sigma_i^0)] - V[(r_i), (\sigma_i)]]} \rangle_{\sigma}}{\langle e^{-\beta[V[(r_i), (\sigma_i^0)] - V[(r_i), (\sigma_i)]]} \rangle_{\sigma}}, \quad (2.3)$$

where the subscript σ^0 indicates an average in the fixed σ ensemble, whereas the subscript σ indicates an average in the fluctuating sigma ensemble.

The above model allows the σ 's to vary continuously between $\lambda\sigma_i^0$ and σ_i^0 . A better approach is to have the σ 's take on a set of distinct values and in the simplest case only two values with the largest value being the σ_i^0 value. This avoids many of the pitfalls of the continuous approach.

Let w be a random number, $0 \leq w \leq 1$, and let $s(w)$ be a sigmoidal switching function that goes from 0 to 1 as w increases and is 0.5 at w_0 . Defining σ_i

$$\sigma_i(w_i) = [1 - s(w_i)]\sigma_i^0 + s(w_i)\lambda_i\sigma_i^0 \quad (2.4)$$

which now varies between the correct σ_i^0 and a smaller $\sigma_i^{\min} = \lambda_i\sigma_i^0$. The potential function is then

$$V\{(r_i), [\sigma_i(w_i)]\} = \sum_{i>j}^N 4\epsilon \left\{ \left[\frac{[\sigma_i(w_i) + \sigma_j(w_j)]}{2r_{ij}} \right]^{12} - \left[\frac{[\sigma_i(w_i) + \sigma_j(w_j)]}{2r_{ij}} \right]^6 \right\} + \sum_{i=1}^N F_i(w_i), \quad (2.5)$$

where $F(w_i)$ is a cost function for the random number. This can also be expressed as

$$V(r_{ij}, w_{ij}) = [1 - s(w_{ij})]V(r_{ij}, \sigma_{ij}^0) + s(w_{ij})V(r_{ij}, \sigma_{ij}) + F(w_{ij}), \quad (2.6)$$

where the first V on the right-hand side is the correct LJ potential and the second V is the LJ potential with a smaller σ_{ij} , and where the F is a cost function for the random variable.

In molecular dynamics one would now define an effective Hamiltonian,

$$H_w = \sum_{i=1}^N \frac{p_i^2}{2m} + \sum_{i=1}^N \frac{m'_i w_i^2}{2} + V\{(r_i), [\sigma_i(w_i)]\}. \quad (2.7)$$

This Hamiltonian will generate dynamics in which the positions and w_i 's fluctuate, but now the σ 's will never get smaller than the defined minimum values and never larger than the maximum values. This gives more control.

It is a simple matter to apply Monte Carlo or molecular dynamics to this model. In Monte Carlo one can remove the cost function because the random variable can only vary between 0 and 1. One can make ν particle moves followed by a resampling of w_{ij} . In the case of molecular dynamics the (w_{ij}) are not restricted by anything but the cost function which confines them to be roughly in the range $0 \leq w_{ij} \leq 1$.

B. The torsion angle potential fluctuation method

The above models can also be used for chain folding. The usual potential models for chain molecules are composed of dihedral angle terms and nonbonded interaction terms. We simply apply the fluctuating sigma model to the nonbonded potential terms.

In the chain folding problem, the dihedral angle potential plays an important role since the high potential energy barrier separating the *trans* and *gauche* conformations restricts the rate of barrier crossing at room temperature and prevents the polymer chain from visiting many of the local potential minima efficiently during the simulation. A method which lets the dihedral angle potential fluctuate between the actual torsion angle potential and a potential with the same relative energy minima but with reduced energy barriers can be used. Let us consider the Ryckaert and Belleman dihedral angle potential,¹

$$V_0(\phi) = \sum_{i=1}^6 a_i \cos^{i-1}(\phi), \quad (2.8)$$

where ϕ is the dihedral angle which changes from -180° to $+180^\circ$, and there are three potential minima at $\phi = 0^\circ$, 120° , and -120° . These three potential minima correspond to the *trans* (T), *gauche*⁺ (G^+), and *gauche*⁻ (G^-) conformers and are separated by the *trans-gauche* and *gauche-cis* potential barriers. The dihedral angle potential can be made to fluctuate in such a way as to increase the barrier crossing rate but not change the energy minima corresponding to those conformations by taking,

$$V(\phi, w) = [1 - s(w)]V_0(\phi) + s(w)V_m(\phi), \quad (2.9)$$

where $s(w)$ is the sigmoidal switching function as defined for the sigma fluctuations and the function $V_m(\phi)$ has lower potential barriers than $V_0(\phi)$,

$$V_m(\phi) = \left[A_m \cos^2\left(\frac{3}{2}\phi\right) + (1 - A_m) \right] V_0(\phi), \quad (2.10)$$

where $0 \leq A_m \leq 1$, is the parameter which determines how much the potential barrier is reduced. Plots of these two potential functions, $V_0(\phi)$ and $V_m(\phi)$ with $A_m = 0.5$, are shown in Fig. 1. This continuous potential form will be easier to implement in the molecular dynamics method

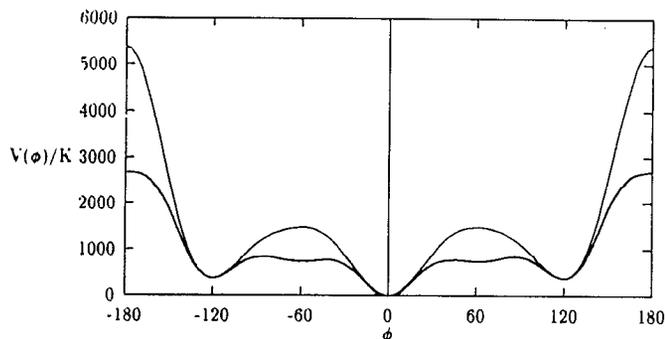


FIG. 1. Ryckaert and Belleman's dihedral angle potential in Eq. (2.8) (thin line) and the lower limit of our fluctuating dihedral angle potential as in Eq. (2.10) with $A_{\min}=0.5$ (thick line).

where the potential derivatives is used. In Monte Carlo methods, more simplified potential forms can be used.

III. THE MIXING OF FLUIDS

Consider a dense LJ liquid in a periodic box of edge L with cubic symmetry. Let us arbitrarily define a variable ξ_i that we associate with each particle i which is defined such that $\xi_i = +1$ if the z coordinate of particle i is in the upper half of the box $0 < z_i < L/2$ and $\xi_i = -1$ if i is in the lower half of the box $-L/2 < z_i < 0$. If we define an order parameter such that

$$\xi(t) = \frac{2}{N} \sum_{i=1}^{N/2} \xi_i(t), \quad (3.1)$$

where the sum only goes over the $N/2$ atoms originally above the dividing plane. Initially $\xi(0) = 1$ but as atoms mix it will decay. At equilibrium ξ will fluctuate around 0. This order parameter gives us a good measure of the time it takes for the system to mix.

Two Monte Carlo (MC) simulations are done at $\rho^* = 0.9$ and $T^* = 1.0$ with 216 particles initially on a fcc lattice. A rectangular periodic box was used in which the box length along the z direction is twice as large as along the x and y directions. Because of the periodic boundary condition in the z direction, there are two interfaces separating the $\xi_i = +1$ and -1 particles. Particles moving through both interfaces contribute to the mixing. In the first simulation, the σ 's are constant and in the second, all the σ 's fluctuate together according to Eq. (2.4). The $s(w)$ was chosen as a step function at w_0 , so that σ fluctuates between only two values σ_0 and σ_{\min} . No cost function, $F[(\sigma_i)]$, is used in this Monte Carlo simulation and the probability of σ_{\min} is determined only by w_0 . The MC step-size for (r_i) when $\sigma = \sigma_{\min}$ is chosen larger than the step-size when $\sigma = \sigma_0$ because both are chosen to give an acceptance rate of 0.5. The time dependence of the order parameter $\xi(t)$ is computed with $\sigma_{\min} = 0.80\sigma_0$, $w_0 = 0.95$, and $\nu = 100$. The results are shown in Fig. 2. The fluctuating sigma method mixes the fluids almost three times as fast as the simulation with fixed σ .

In Fig. 3 the energy record of the total LJ potential energy with fixed σ_0 for the two simulations are presented.

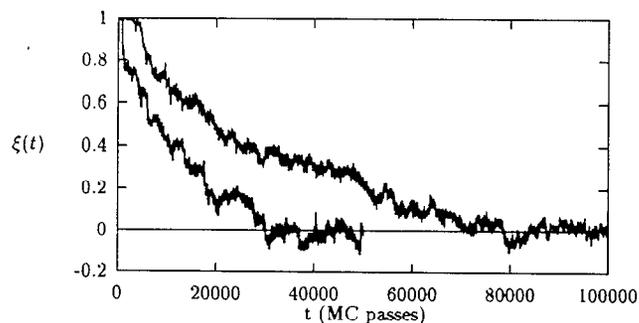


FIG. 2. Instantaneous order parameter as a function of the number of MC passes. The upper curve is the result for a rigid sigma simulation. The lower curve is the result for the fluctuating sigma simulation at the same temperature and density for which $\sigma_{\min} = 0.8\sigma_0$, $w_0 = 0.95$, and $\nu = 100$.

It should be noted that even in the fluctuating sigma method, we are plotting the potential energy corresponding to the rigid σ_0 value $V[(r_i), (\sigma_i^0)]$. Thus where $\sigma = \sigma_{\min}$ in these runs, configurations will be generated in which there will be some overlaps of spheres of diameter σ_0 and for these configurations there will be a concomitantly large values of the potential energy based on σ_0 . Thus the energy in the fluctuating sigma method varies between a high energy band corresponding to the σ_{\min} configurations and a low energy band corresponding to the σ_0 configurations. The high energy configurations will only have very small weighting in the umbrella sampling and will thus make an insignificant contribution to averages. Both methods are started at the same initial configuration on a fcc lattice. The potential energy records in these two methods show that the fluctuating sigma method generates much faster melting than the rigid sigma method. As a further test the $g(r)$ from both runs is presented in Fig. 4. The $g(r)$ computed from the fluctuating sigma method using umbrella sampling given by Eq. (2.3) agrees so well with the $g(r)$ computed using constant sigma Monte Carlo that no difference can be observed in this figure. The fluctuating sigma method is thus capable of determining the correct pair correlation function.

There are three parameters in the fluctuating sigma method as implemented above; namely, σ_{\min} which determines the minimum value in the sigma fluctuation, the constant w_0 which determines the probability of sampling σ_{\min} in the simulation, and ν , the number of samplings of particle coordinates between resamplings of σ . With smaller σ_{\min} and w_0 , the system has smaller repulsive potential radius and becomes dilute more frequently, thus allowing a faster mixing. But if σ_{\min} is too small, the system will need a certain number of passes to relax back to equilibrium structure after the σ changes back to σ_0 . If there are too few relaxation passes, ν , the system will be in a nonsteady state and the umbrella sampling will give incorrect results. Figure 5 shows the speed of mixing and $g(r)$ for $\sigma_{\min} = 0.75\sigma_0$ and $\nu = 1$. The system mixes more than four times faster than the rigid sigma method, but the $g(r)$ determined from umbrella sampling is now not correct. Some of the configurations with high potential energy still

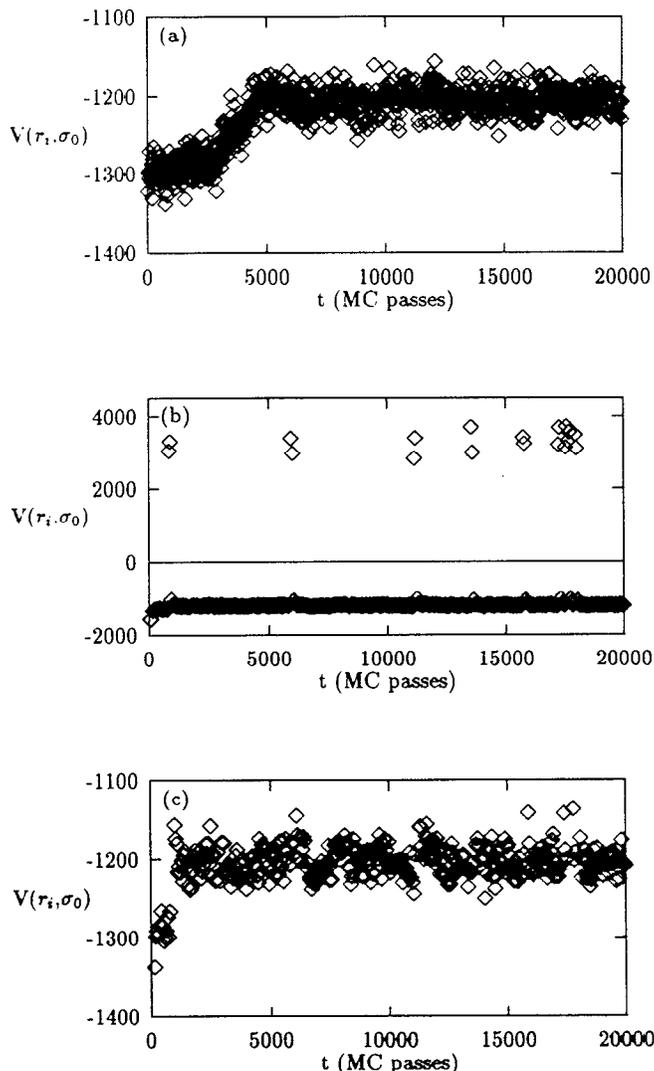


FIG. 3. The total potential energy, $V[(r_i), (\sigma_i^0)]$, as a function of the number of MC passes. (a) The rigid sigma simulation potential energy (the system begins to melt at about 4000 passes); (b) the fluctuating sigma simulation in which the potential energy exhibits fluctuations between two energy bands corresponding to overlapping and nonoverlapping configurations; (c) the low energy band in the fluctuating sigma simulation, the system melts almost instantly.

contribute to $g(r)$ because the system did not have time to relax to equilibrium after changing from σ_{\min} to σ_0 . An energy filter could be applied to the umbrella sampling to filter out those nonequilibrium configurations which have a higher energy. For this purpose a threshold energy is defined and only those configurations which have energies below the threshold contribute to the averages. A proper choice of the threshold energy in this filter method requires previous knowledge of the total potential energy variation. This filter method should be useful in situations where a rapid method of locating potential minima is needed but the exact equilibrium properties are not required. Figure 6 shows the dependence of $g(r)$ on ν . With a larger ν , correct properties can always be accurately determined with the umbrella sampling method because now the system will

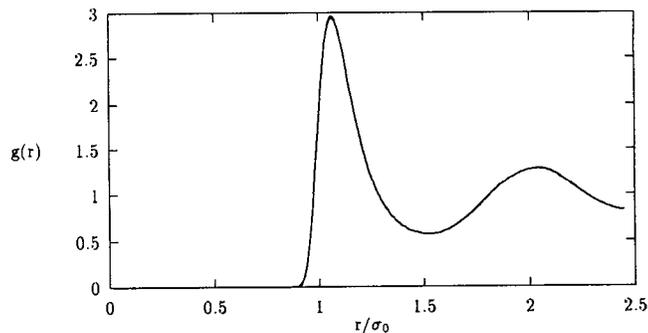


FIG. 4. The radial distribution function $g(r)$ for the rigid sigma simulation (solid line) and the fluctuation sigma simulation with umbrella sampling (dashed line).

have enough time to relax back to equilibrium.

In the preceding all of the σ 's fluctuate at once. It is of interest to compare this scheme to one in which the σ 's individually fluctuate between σ_{\min} and σ_0 . We find that the fluid mixes as fast as when all of the σ 's breathe together. However now the weighting function in the umbrella sampling is found to be very small for almost every configuration generated when the individual σ_i 's are allowed to fluctuate, because there are always LJ σ_0 overlaps at $\sigma = \sigma_{\min}$. These overlaps introduce large variations in

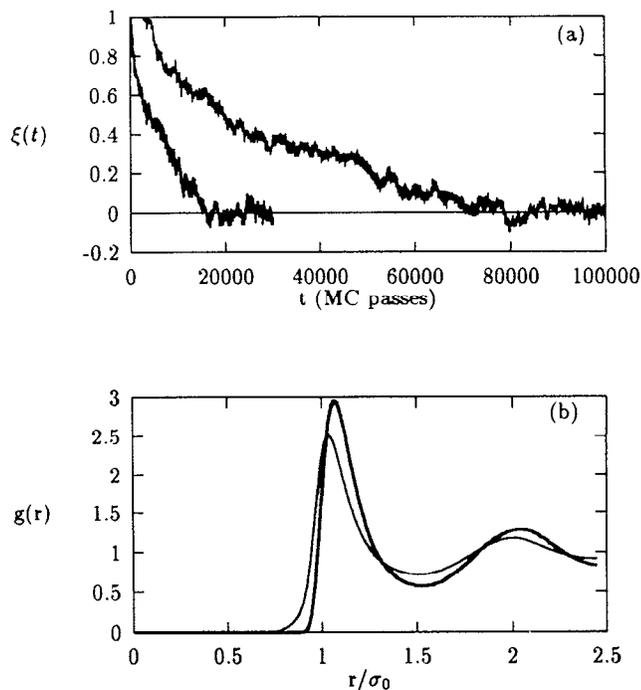


FIG. 5. With $\sigma_{\min} = 0.75\sigma_0$, $w_0 = 0.95$, and $\nu = 1$. (a) The instantaneous order parameter as a function of the number of MC passes. The upper curve is for the rigid sigma simulation and the lower curve is for the fluctuating sigma simulation. (b) The radial distribution function, $g(r)$, for the rigid sigma simulation (thick line) and for the fluctuating sigma simulation with umbrella sampling (thin line). The $g(r)$ determined with an energy filter (dashed line) coincides with the rigid sigma thick line.

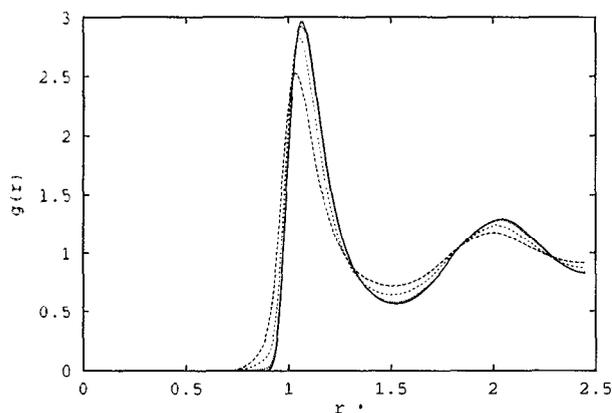


FIG. 6. The radial distribution function, $g(r)$, as a function of ν with $\sigma_{\text{min}}=0.75\sigma_0$ and $\omega_0=0.95$, for the rigid sigma method (solid line), with $\nu=1$ (long dash line), $\nu=10$ (shorter dash line), and $\nu=100$ (point line).

the radial distribution function because the denominator in Eq. (2.3) exhibits very large relative fluctuations. Thus if one wants to determine structural averages directly from the sigma fluctuation method it is better to let all of the σ 's breathe together. This strategy has the advantage of giving higher accuracy and is easier to implement for dense fluids.

IV. CHAIN FOLDING

The system studied here is a flexible n -alkane molecule C_nH_{2n+2} . Each methylene group is treated as a LJ center. Aside from the Cartesian coordinates we also treat the $n-3$ dihedral angles (ϕ_k). Each successive dihedral angle is assumed to move in the Ryckaert-Bellmans dihedral angle potential, $V_0(\phi)$. This potential is asymmetric with the *trans* conformer being more stable than the two *gauche* conformers (labeled G^+ and G^-) with a very high barrier for the *cis* conformer (see Fig. 1). In addition each methylene sphere interacts with all methylene spheres separated from it by four or more C-C bonds. The C-C bond stretching potential is taken to be harmonic with equilibrium bond length of 1.53 Å, while the bond angle bending potential is harmonic in terms of the cosine of the angle with equilibrium bond angle of 109.47°. The harmonic force constant for the bond stretching and bond angle bending are taken to be 2490 kJ/(mol Å²) and 520 kJ/mol, respectively. We treat two different systems, n -pentane and $C_{50}H_{102}$.

A constant sigma n -pentane chain is simulated at $T=500$ K with the sigma fluctuation method. It is found that the nonbonded repulsions preclude the system from visiting certain of the nine conformational states. For example in a very long run one simply does not observe the two G^+G^- conformers. The fluctuating sigma method as defined in Eq. (2.6) does allow the system to visit such conformers and is therefore very useful for enumerating these states. It thus permits the cataloging of all locally stable conformational states. Moreover it allows the system to fold rapidly. The fixed and fluctuating sigma methods are run for the same number of passes. Ramachandran

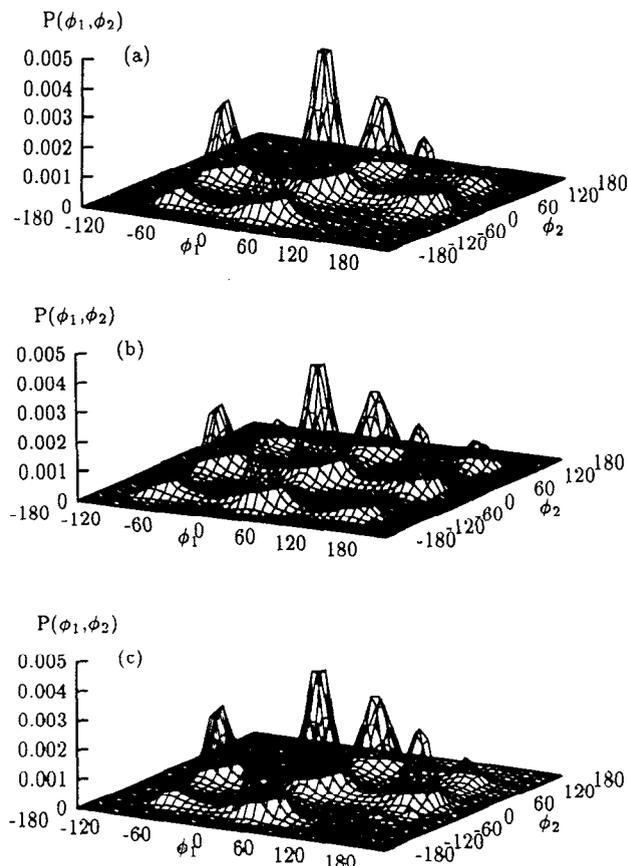


FIG. 7. The Ramachandran plot for n -pentane for both the rigid and fluctuating sigma simulations. (a) The rigid sigma simulation; (b) the fluctuating sigma simulation without the weighting function; and (c) the fluctuating sigma simulation with the weighting function.

plots are shown in Fig. 7. Plate (a) corresponds to the fixed sigma simulation. Plate (b) corresponds to the fluctuating sigma method without using Eq. (2.3) to correct the sampling. Plate (c) corresponds to the fluctuating sigma method corrected using Eq. (2.3). It should be noted that the (a) and (c) plates agree; that is, the fixed and fluctuating sigma methods give the same averages. It should also be noted from the (b) plate that the unweighted fluctuating sigma method allows the states G^+G^- to be visited whereas these states are not visited by the fixed sigma method. Figure 8 shows the record of end-to-end distances for the fixed and fluctuating sigma methods. Clearly the fluctuating sigma method visits two additional folded states than does the fixed sigma method.

For longer chains with n carbons, a number of quantities were used to characterize the properties of the chain. The instantaneous end-to-end distance \mathcal{D} and the radius of gyration,

$$\mathcal{R} = \sqrt{\frac{1}{n^2} \sum_{i=1}^n \sum_{j=1}^n r_{ij}^2}$$

are monitored and give an indication of the speed of folding or unfolding of the chain. After the chain reached equilibrium, the distribution functions of the end-to-end dis-

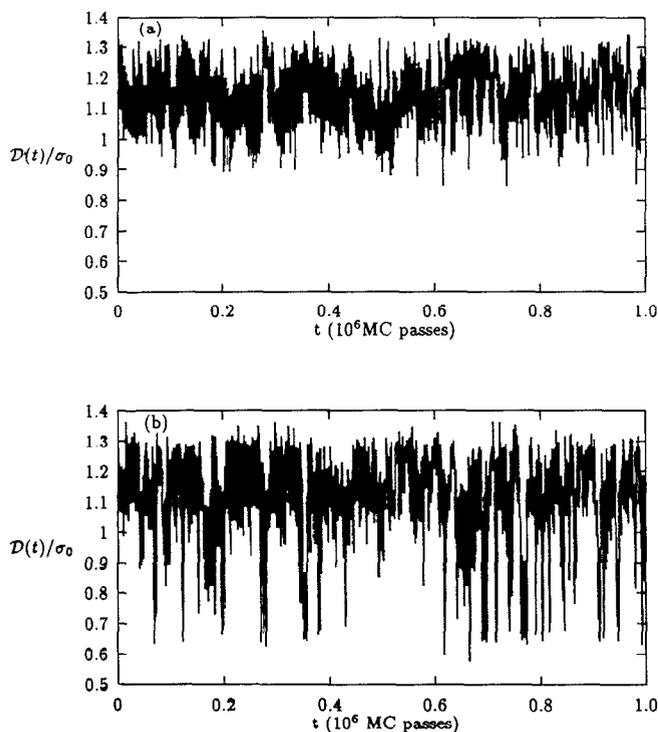


FIG. 8. The running record of the end-to-end distance \mathcal{D} in n -pentane for both the rigid and the fluctuating sigma simulations. (a) The rigid sigma simulation; (b) the fluctuating sigma simulation.

tance and the radius of gyration are calculated. Another quantity monitored is the number, \mathcal{N}_c , of distinct conformations the chain passed through during the simulation. Each dihedral angle has three stable conformational states labeled by the integer 1, 2, and 3 corresponding to the G^- , T , and G^+ states. Thus the conformation of a chain is completely specified by a string of $n-3$ integers. For example, the nine states of n -pentane are specified by 11, 12, 13, 21, 22, 23, 31, 32, and 33. If a long chain starts in an all trans conformation, as the simulation progresses, the sequence changes and one can count the number of distinct sequences, \mathcal{N}_c , where a "distinct" sequence is a sequence that has not occurred before. So \mathcal{N}_c is an indication of how efficiently the simulation explores the conformational space.

The molecule n - $C_{50}H_{102}$ is started in the all-*trans* conformation at temperature of $T=300$ K. We expect that the fluctuating potential method will explore the state space more efficiently than the rigid potential method because barrier crossing will be much slower in the later case. The end-to-end distance and radius of gyration are monitored. Figure 9 gives the record of these two quantities for the fixed and fluctuating potential methods (with $w_0=0.7$, $A_m=0.5$, $\sigma_m=0.7\sigma_0$, and $\nu=100$) for the same number of passes. From this it can be seen that (a) the fluctuating potential method relaxes much faster than the rigid potential method for the folding. (b) At about one million passes, in the rigid potential simulation, the chain was caught in a frustrated configuration. In the fluctuating potential method, the absence of large energy barriers in one

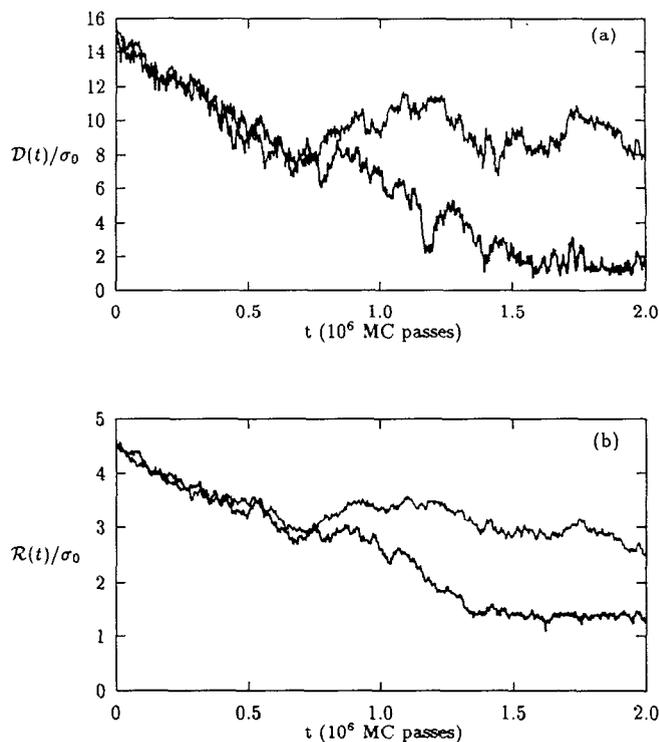


FIG. 9. The $C_{50}H_{102}$ chain folding at $T=300$ K for two simulations started from the same all *trans* conformation. The instantaneous end-to-end distance (\mathcal{D}) and the radius of gyration (\mathcal{R}) are plotted in (a) and (b), respectively. The upper curve is the simulation result for the rigid potential and the lower curve in the plot is the simulation result for the fluctuating potential using $\sigma_{\min}=0.7\sigma_0$, $A_{\min}=0.5$, $w_0=0.7$, and $\nu=100$.

form of the potential makes it much easier for the chain to continuously fold without being trapped in the local minimum.

In the course of the folding we count the number of distinct conformations through which the system passes. These are shown in the Fig. 10 as a function of the number of MC passes. The fluctuating potential method generates a much larger number of distinct conformers than the fixed potential method. This indicates that our fluctuating potential method enables the chain to explore the conformational space more efficiently.

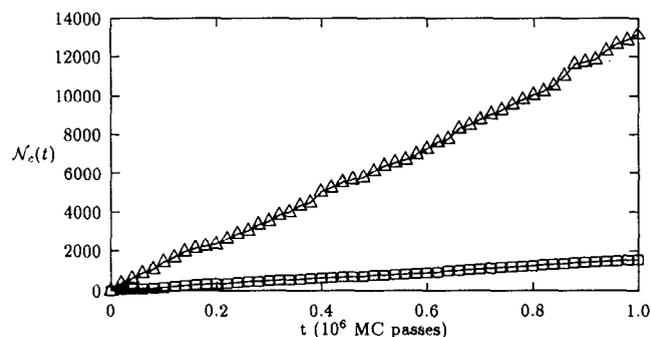


FIG. 10. The number of distinct conformations, $\mathcal{N}_c(t)$, visited in time by $C_{50}H_{102}$ at $T=300$ K for the rigid potential simulation (square) and for the fluctuating potential simulation (triangle).

In chain molecules there are two kinds of frustration, frustration due to the geometrical and topological constraints and frustration due to the roughness of the energy landscape which in turn is due to the strong repulsive non-bonded interactions. In this section we have shown that the fluctuating potential method helps to rapidly relax the topological frustration. The sigma fluctuation method discussed in connection with fluid mixing in the previous section can be used to relax the frustration due to the roughness of the energy landscape. This will be important when a long chain folds into a globular structure or when long chains are in a polymer melt or in membranes.

V. DISCUSSION

In this paper we propose several methods for accelerating simulation. The sigma fluctuation method is found to be particularly effective in accelerating mixing and melting in dense systems. The fluctuating potential method is shown to be capable of accelerating the rate of equilibration and the determination of accurate equilibrium averages in chain molecules with torsion angle barriers. These initial tests and preliminary applications of the method show that there is much to be gained in applying these methods to more complicated problems.

Our method is similar to the tandem J -walk method (J -walkers at different temperatures are run in tandem) invented by Frantz *et al.*² and is likewise able to reduce

quasi-ergodicity in Monte Carlo simulations. The MC procedures introduced here differ from the tandem J -walker since we used umbrella sampling. In our methods one has more freedom in choosing the tandem potential. For example in the torsion angle potential fluctuation method we distort the potential to eliminate crucial barriers but we do not change the energy differences between the stable states. This has the distinct advantage of sampling the correct distribution of conformers while at the same time accelerating the barrier crossing events. The sigma fluctuation method for binary fluid mixing corresponds to very high temperatures in the J -walk method. In addition, by introducing the cost functions in the potential, it is possible to incorporate the fluctuating sigma method and the fluctuating potential method into molecular dynamics.

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