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Monte Carlo Update for Chain Molecules: Biased Gaussian Steps in Torsional Space

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Abstract:
We develop a new elementary move for simulations of polymer chains in torsion angle space. The method is flexible and easy to implement. Tentative updates are drawn from a (conformation-dependent) Gaussian distribution that favors approximately local deformations of the chain. The degree of bias is controlled by a parameter b. The method is tested on a reduced model protein with 54 amino acids and the Ramachandran torsion angles as its only degrees of freedom, for different b. Without excessive fine tuning, we find that the effective step size can be increased by a factor of three compared to the unbiased $b = 0$ case. The method may be useful for kinetic studies, too.

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1 Introduction

Kinetic simulations of protein folding are notoriously difficult. Thermodynamic simulations may use unphysical moves and are therefore potentially easier, but existing methods need improvement. Three properties that a successful thermodynamic algorithm must possess are as follows. First and foremost, it must be able to alleviate the multiple-minima problem. Methods like the multicanonical algorithm [1, 2] and simulated tempering [3–5] try to do so by the use of generalized ensembles. Second, it must provide an efficient evolution of large-scale properties of unfolded chains. The simple pivot method [6] does remarkably well [7] in that respect. Third, it must be able to alter local properties of folded chains without causing too drastic changes in their global structure. This paper is concerned with the third problem, which is important if the backbone potentials are stiff and especially if the mobility is restricted to the biologically most relevant torsional degrees of freedom.

An update that rearranges a restricted section of the chain without affecting the remainder is local. For chains with flexible or semiflexible backbones, there exists a variety of local updates, ranging from simple single-site moves to more elaborate methods [8–12] where inner sections are removed and then regrown site by site in a configurational-bias manner [13, 14]. However, these methods break down if bond lengths and bond angles are completely rigid.

The problem of generating local deformations of chains with only torsional degrees of freedom was analyzed in a classic paper by Gō and Scheraga [15]. Based on this analysis, Dodd *et al.* [16] devised the first proper Monte Carlo algorithm of this type, the concerted-rotation method. This method works with seven adjacent torsion angles along the chain. One of these angles is turned by a random amount. Possible values of the remaining six angles are then determined by numerically solving a set of equations that guarantee that the move is local. The new conformation is finally drawn from the set of all possible solutions to this so-called rebridging problem. Variations and generalizations of this method have been discussed by several groups [17–19]. There are also methods [20–24] that combine elements of the configurational-bias and concerted-rotation approaches. One of these methods [23] uses an analytical rebridging scheme, inspired by the solution for a similar problem in robotic control [25].

The concerted-rotation approach is a powerful method that can generate large local deformations by finding the discrete solutions to the rebridging problem. However, the method is not easy to implement and large local deformations may be difficult to accomplish if, for example, the chain is folded and has bulky side groups. Hence, there are situations where this method is not the obvious choice.

In this paper, we discuss a different and less sophisticated type of Monte Carlo move in torsion angle space. This algorithm is by nature a "small-step" algorithm so large local deformations cannot take place. Drastic global changes would still occur if the steps were random. To avoid that, a biasing probability is introduced. The method becomes approximately local if the bias is made strong. Compared to a strictly local update, this method has the disadvantage that a much smaller part of the energy function is left unchanged, so the CPU time per update is larger. However, this problem is not too severe for moderate chain lengths. Moreover, both our method and strictly local ones are typically combined with some truly nonlocal update like pivot, and such an update is not faster than ours.

The algorithm proceeds as follows. We consider n torsion angles ϕ_i, where $n = 8$ in our calculations. To update these angles, we introduce a conformation-dependent $n \times n$ matrix $\mathbf{G}$ such that $\delta\bar{\phi}^T \mathbf{G} \delta\bar{\phi} \approx 0$ for changes $\delta\bar{\phi} = (\delta\phi_1, \ldots, \delta\phi_n)$ that correspond to local deformations. The steps $\delta\bar{\phi}$ are then drawn from the Gaussian distribution

$$P(\delta\bar{\phi}) \propto \exp\left[-\frac{a}{2}\delta\bar{\phi}^T(\mathbf{1} + b\mathbf{G})\delta\bar{\phi}\right] , \tag{1}$$

where $\mathbf{1}$ denotes the $n \times n$ unit matrix and a and b are tunable parameters. The parameter a controls the acceptance rate, whereas b sets the degree of bias. The new conformation is finally subject to an accept/reject step. Important to the implementation of the algorithm is that the matrix $\mathbf{G}$ is non-negative and symmetric. Hence, it is possible to take the "square root" of $\mathbf{1} + b\mathbf{G}$, which facilitates the calculations.

This method, which is quite general, is tested on a reduced model protein [26] with 54 amino acids and the Ramachandran torsion angles as its only degrees of freedom. This chain forms a three-helix bundle in its native state and exhibits an abrupt collapse transition that coincides with its folding transition. The performance of the method is studied both above and below the folding temperature, for different values of the parameters a and b. For a suitable choice of b, we find that the effective step size can be increased by a factor of three in the folded phase, compared to the unbiased $b = 0$ case. The optimal value of b corresponds to a relatively strong bias, that is an approximately local update.

2 The Model

In our calculations, we consider a reduced protein model [26] where each amino acid is represented by five or six atoms. The three backbone atoms N, C_α and C' are all

included, whereas the side chain is represented by a single atom, C_β. The C_β atom can be hydrophobic, polar or absent, which means that there are three different types of amino acids in the model. For a schematic illustration of the chain representation, see Fig. 1.

All bond lengths, bond angles and peptide torsion angles (180°) are held fixed, which leaves us with two degrees of freedom per amino acid, the Ramachandran torsion angles (see Fig. 1).

The energy function

$$E = E_{\rm loc} + E_{\rm sa} + E_{\rm hb} + E_{\rm AA} \tag{2}$$

is composed of four terms. The local potential $E_{\rm loc}$ has a standard form with threefold symmetry,

$$E_{\rm loc} = \frac{\epsilon_{\rm loc}}{2} \sum_i (1 + \cos 3\phi_i) \,. \tag{3}$$

The self-avoidance term $E_{\rm sa}$ is given by a hard-sphere potential of the form

$$E_{\rm sa} = \epsilon_{\rm sa} \sum_{i<j}{}' \left(\frac{\sigma_{ij}}{r_{ij}} \right)^{12} , \tag{4}$$

where the sum runs over all possible atom pairs except those consisting of two hydrophobic C_β. The hydrogen-bond term $E_{\rm hb}$ is given by

$$E_{\rm hb} = \epsilon_{\rm hb} \sum_{ij} u(r_{ij}) v(\alpha_{ij}, \beta_{ij}) \,, \tag{5}$$

where i and j represent H and O atoms (see Fig. 1), respectively, and

$$u(r_{ij}) = 5\left(\frac{\sigma_{\rm hb}}{r_{ij}} \right)^{12} - 6\left(\frac{\sigma_{\rm hb}}{r_{ij}} \right)^{10} \tag{6}$$

$$v(\alpha_{ij}, \beta_{ij}) = \begin{cases} \cos^2 \alpha_{ij} \cos^2 \beta_{ij} & \alpha_{ij}, \beta_{ij} > 90^\circ \\ 0 & \text{otherwise} \end{cases} \tag{7}$$

In these equations, r_{ij} denotes the HO distance, α_{ij} the NHO angle, and β_{ij} the HOC′ angle. Finally, the hydrophobicity term $E_{\rm AA}$ has the form

$$E_{\rm AA} = \epsilon_{\rm AA} \sum_{i<j} \left[\left(\frac{\sigma_{\rm AA}}{r_{ij}} \right)^{12} - 2\left(\frac{\sigma_{\rm AA}}{r_{ij}} \right)^{6} \right] , \tag{8}$$

where both i and j represent hydrophobic C_β. In the following, kT is given in dimensionless units, in which $\epsilon_{\rm hb} = 2.8$ and $\epsilon_{\rm AA} = 2.2$. Further details of the model, including numerical values of all the parameters, can be found in Ref. [26].

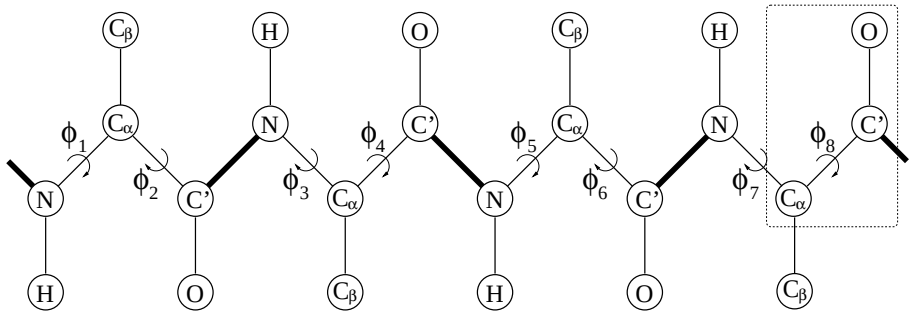

Figure 1: Update of the chain defined in Sec. 2. Eight torsion angles ϕ_i are turned. Turns such that the three atoms in the box are left unaffected are favored. Thick lines represent peptide bonds and the peptide torsion angles are fixed.

In this model, we study a designed three-helix-bundle protein with 54 amino acids. In Ref. [26], it was demonstrated that this sequence indeed forms a stable three-helix bundle, except for a twofold topological degeneracy, and that it has a first-order-like folding transition that coincides with the collapse transition. It should be noted that these properties are found without resorting to the widely used but drastic Gō approximation [27], where interactions that do not favor the desired structure are ignored.

3 The Algorithm

We now turn to the algorithm, which we describe assuming the particular chain geometry defined in Sec. 2. That this scheme can be easily generalized to other types of chains will be evident.

Consider a segment of four adjacent amino acids k, $k+1$, $k+2$ and $k+3$ along the chain, and let the corresponding eight Ramachandran angles (see Fig. 1) form a vector $\bar{\phi} = (\phi_1, \ldots, \phi_n)$, where $n = 8$. A change $\delta\bar{\phi}$ of $\bar{\phi}$ will, by construction, leave all amino acids $k' < k$, as well as the N, H and C_α atoms of amino acid k, unaffected. For all amino acids $k' > k+3$ to remain unaffected too, it is sufficient to require that the three atoms C_α, C' and O of amino acid $k+3$ (see Fig. 1) do not move. If this condition is fulfilled, the deformation of the chain is local.

Denote the position vectors of the C_α, C' and O atoms of amino acid $k+3$ by $\bar{r}_I$, $I = 1, 2, 3$. A bias toward local deformations can be obtained by favoring changes $\delta\bar{\phi}$

that correspond to small values of the quantity

$$\Delta^2 = \sum_{I=1}^{3} (\delta \bar{r}_I)^2 \,, \tag{9}$$

which for small $\delta\phi_i$ can be written as

$$\Delta^2 \approx \delta\bar{\phi}^T \mathbf{G} \delta\bar{\phi} = \sum_{i,j=1}^{n} \delta\phi_i G_{ij} \delta\phi_j \,, \tag{10}$$

where

$$G_{ij} = \sum_{I=1}^{3} \frac{\partial \bar{r}_I}{\partial \phi_i} \cdot \frac{\partial \bar{r}_I}{\partial \phi_j} \,. \tag{11}$$

Note that the three vectors $\bar{r}_I$ can be described in terms of six independent parameters, since bond lengths and angles are fixed. This implies that the $n \times n$ matrix $\mathbf{G}$, which by construction is non-negative and symmetric, has eigenvectors with eigenvalue zero for $n = 8 > 6$. A bias toward small Δ^2 means that these soft modes are favored.

We can now define the update, which consists of the following two steps.

1. Draw a tentative new $\bar{\phi}$, $\bar{\phi}'$, from the Gaussian distribution

$$W(\bar{\phi} \to \bar{\phi}') = \frac{(\det \mathbf{A})^{1/2}}{\pi^3} \exp\left[-(\bar{\phi}' - \bar{\phi})^T \mathbf{A} (\bar{\phi}' - \bar{\phi})\right] \,, \tag{12}$$

   where the matrix

$$\mathbf{A} = \frac{a}{2}(\mathbf{1} + b\mathbf{G}) \tag{13}$$

   is a linear combination of the $n \times n$ unit matrix $\mathbf{1}$ and the matrix $\mathbf{G}$ defined by Eq. 11. The shape of this distribution depends on the parameters $a > 0$ and $b \geq 0$. The parameter b sets the degree of bias toward small Δ^2. The bias is strong for large b and disappears in the limit $b \to 0$. The parameter a is a direction-independent scale factor that is needed to control the acceptance rate. Larger a means higher acceptance rate, for fixed b. If $b = 0$, then the components $\delta\phi_i$ are independent Gaussian random numbers with zero mean and variance a^{-1}. Note that $W(\bar{\phi} \to \bar{\phi}') \neq W(\bar{\phi}' \to \bar{\phi})$ since the matrix $\mathbf{G}$ is conformation dependent.

2. Accept/reject $\bar{\phi}'$ with probability

$$P_{\rm acc} = \min\left(1, \frac{W(\bar{\phi}' \to \bar{\phi})}{W(\bar{\phi} \to \bar{\phi}')} \exp[-(E' - E)/kT]\right) \tag{14}$$

for acceptance. The factor $W(\bar{\phi}' \to \bar{\phi})/W(\bar{\phi} \to \bar{\phi}')$ is needed for detailed balance to be fulfilled, since W is asymmetric.

It should be stressed that this scheme is quite flexible. For example, it can be immediately applied to chains with nonplanar peptide torsion angles. The use of the concerted-rotation method for simulations of such chains has recently been discussed [28].

A convenient and efficient implementation of the algorithm can be obtained if one takes the "square root" of the matrix $\mathbf{A}$, which can be done because $\mathbf{A}$ is symmetric and positive definite. More precisely, it is possible to find a lower triangular matrix $\mathbf{L}$ (with nonzero elements only on the diagonal and below) such that

$$\mathbf{A} = \mathbf{L}\mathbf{L}^T \,. \tag{15}$$

An efficient routine for this so-called Cholesky decomposition can be found in [29].

3.1 Implementing step 1

Given the Cholesky decomposition of the matrix $\mathbf{A}$, the first step of the algorithm can be implemented as follows.

- Draw a $\bar{\psi} = (\psi_1, \ldots, \psi_n)$ from the distribution $P(\bar{\psi}) \propto \exp(-\bar{\psi}^T\bar{\psi})$. The components ψ_i are independent Gaussian random numbers and can be generated, for example, by using the Box-Muller method

  $$\psi_i = (-\ln R_1)^{1/2} \cos 2\pi R_2 \,, \tag{16}$$

  where R_1 and R_2 are uniformly distributed random numbers between 0 and 1.

- Given $\bar{\psi}$, solve the triangular system of equations

  $$\mathbf{L}^T \delta\bar{\phi} = \bar{\psi} \tag{17}$$

  for $\delta\bar{\phi}$. It can be readily verified that the $\delta\bar{\phi} = \bar{\phi}' - \bar{\phi}$ obtained this way has the desired distribution Eq. 12.

3.2 Implementing step 2

The Cholesky decomposition is also useful when calculating the acceptance probability in the second step of the algorithm. The factor $W(\bar{\phi} \to \bar{\phi}')$ can be easily computed by using that

$$(\det \mathbf{A})^{1/2} = \prod_{i=1}^{n} L_{ii} \tag{18}$$

and that $\exp[-(\bar{\phi}'-\bar{\phi})^T \mathbf{A} (\bar{\phi}'-\bar{\phi})] = \exp(-\bar{\psi}^T \bar{\psi})$. The reverse probability $W(\bar{\phi}' \to \bar{\phi})$ depends on $\mathbf{A}(\bar{\phi}')$ and can be obtained in a similar way, if one makes a Cholesky decomposition of that matrix, too.

3.3 Pivot update

Previous simulations [26] of the model protein defined in Sec. 2 were carried out by using simulated tempering with pivot moves as the elementary conformation update. With this algorithm, the system was successfully studied down to temperatures just below the folding transition. However, the performance of the pivot update, where a single angle ϕ_i is turned, deteriorates in the folded phase. What we hope is that the exploration of this phase can be made more efficient by alternating the pivot moves with moves of the type described previously.

4 Results

The character of the proposed update depends strongly on the bias parameter b. The suggested steps have a random direction if $b = 0$. The distribution $W(\bar{\phi} \to \bar{\phi}')$ in Eq. 12 is, by contrast, highly asymmetric in the limit $b \to \infty$, with nonzero width only in directions corresponding to eigenvalue zero of the matrix $\mathbf{G}$. In particular, this implies that the reverse probability $W(\bar{\phi}' \to \bar{\phi})$ in the acceptance criterion Eq. 14 tends to be small for large b.

For the acceptance rate to be reasonable, it is necessary to use a very small step size if b is small or large. The question is whether the step size can be increased by a better choice of b. To find that out, we performed a set of simulations of the three-helix-bundle protein defined in Sec. 2 for different a and b. Two different

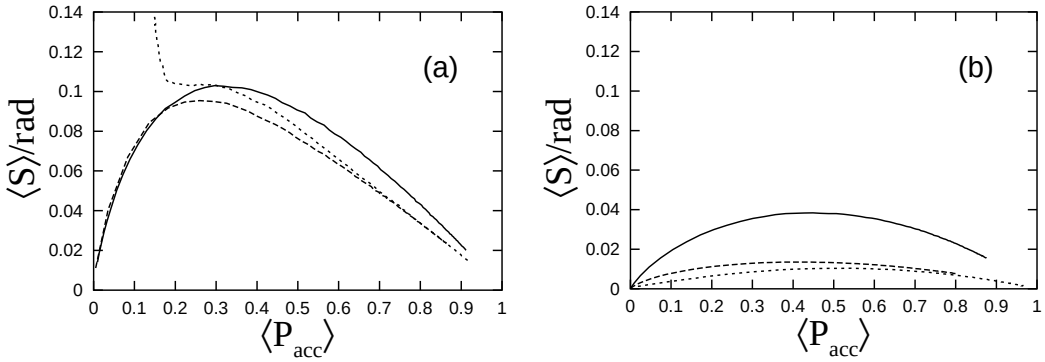

Figure 2: Average step size, $\langle S \rangle$, against average acceptance rate, $\langle P_{\rm acc} \rangle$, for different updates at (a) $kT = 0.7$ and (b) $kT = 0.6$. Shown are results for the $b = b_{\rm max}$ (full lines), $b = 0$ (dashed lines) and pivot (dotted lines) updates.

temperatures were studied, $kT = 0.6$ and 0.7, one on either side of the folding temperature $kT_f \approx 0.66$ [26].

In these runs, we monitored the step size S, where

$$S = |\delta\bar{\phi}| = \left[\sum_{i=1}^{n} (\delta\phi_i)^2\right]^{1/2} \tag{19}$$

for accepted moves and $S = 0$ for rejected ones. Measurements were taken only when the $n = 8$ angles all were in the segment that makes the middle helix of the three. We focus on this segment because it is the most demanding part to update.

The average step size, $\langle S \rangle$, depends strongly on b. A rough optimization of b was carried out by maximizing $\langle S \rangle$ as a function of a for different fixed $b = 10^k$ (k integer). The best values found were $b_{\rm max} = 10$ (rad/Å)^2 and $b_{\rm max} = 0.1$ (rad/Å)^2 at $kT = 0.6$ and $kT = 0.7$, respectively. Note that the preferred degree of bias is higher in the folded phase.

In Fig. 2, we show $\langle S \rangle$ against the average acceptance rate, $\langle P_{\rm acc} \rangle$, for $b = 0$ and $b = b_{\rm max}$ at the two temperatures; $\langle P_{\rm acc} \rangle$ is an increasing function of a for fixed b and T. Also shown are the corresponding results for the pivot update, where only one angle ϕ_i is turned ($S = |\delta\phi_i|$ if the change is accepted). At the higher temperature, we find that the $b = b_{\rm max}$ and $b = 0$ updates show similar behaviors. The pivot update is somewhat better and has its maximum $\langle S \rangle$ at low $\langle P_{\rm acc} \rangle$, where the proposed change $\delta\phi_i$ is drawn from the uniform distribution between 0 and 2π. This is consistent with the finding [7] that the pivot update is a very efficient method for self-avoiding walks, in spite of a low acceptance rate. The situation is different at the lower temperature,

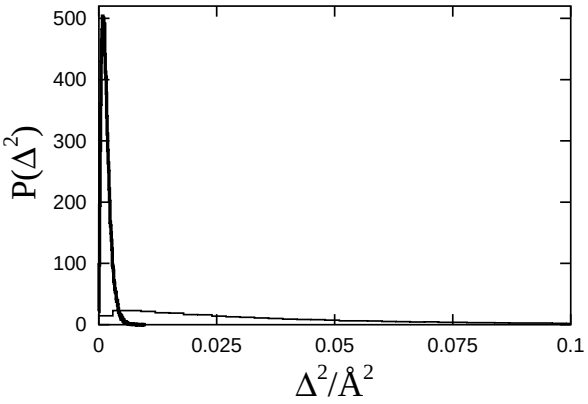

Figure 3: Distributions of Δ^2 (see Eq. 9) for the $b = b_{\max}$ (thick line) and $b = 0$ (thin line) updates at $kT = 0.6$. The values used for the parameter a correspond to maximum $\langle S \rangle$.

which is much harder to simulate. Here, the $b = b_{\max}$ update is the best. The maximum $\langle S \rangle$ is approximately three times higher for this method than for the other two. This shows that the biasing probability Eq. 12 is indeed useful in the folded phase.

The $b = 0$ update can be compared with the moves used by Shimada *et al.* [30] in a recent all-atom study of kinetics and thermodynamics for the protein crambin with 46 amino acids. These authors updated sets of two, four or six backbone torsion angles, using independent Gaussian steps with a standard deviation of 2°. Our $b = 0$ update has maximum $\langle S \rangle$ at $a \approx 6400$ (rad)$^{-2}$ for $kT = 0.6$, which corresponds to a standard deviation of 0.7°. This value is in line with that used by Shimada *et al.*, since we turn eight angles.

How local is the method for $b = b_{\max}$? To get an idea of that, we calculated the distribution of Δ^2 (see Eq. 9) for accepted moves, for $b = b_{\max}$ and $b = 0$ at $kT = 0.6$. As was previously the case, we restricted ourselves to angles in the middle helix. The two distributions are shown in Fig. 3 and we see that the one corresponding to $b = b_{\max}$ is sharply peaked near $\Delta^2 = 0$. This shows that the $b = b_{\max}$ update is much more local than the unbiased $b = 0$ update, although the average step size, $\langle S \rangle$, is considerably larger for $b = b_{\max}$.

So far, we have discussed static (one-step) properties of the updates. We also esti-

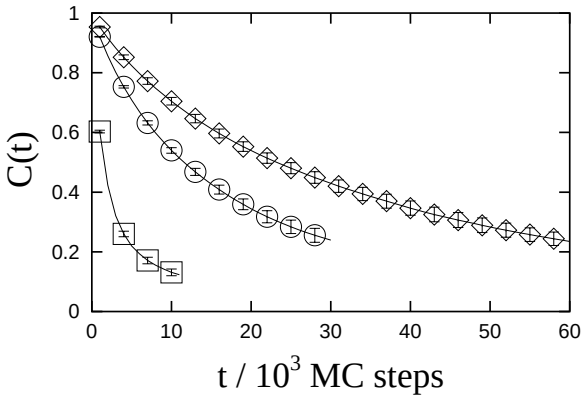

Figure 4: The autocorrelation function $C(t)$ (see the text) at $kT = 0.6$ for the $b = b_{\max}$ ($\Box$), $b = 0$ ($\circ$) and pivot ($\diamond$) updates. Step-size parameters correspond to maximum $\langle S \rangle$.

mated the dynamic autocorrelation function

$$C_i(t) = \frac{\langle \cos\phi_i(t) \cos\phi_i(0) \rangle - \langle \cos\phi_i(0) \rangle^2}{\langle \cos^2\phi_i(0) \rangle - \langle \cos\phi_i(0) \rangle^2} \tag{20}$$

for different ϕ_i. This measurement is statistically very difficult at low temperatures. However, the sixteen most central angles ϕ_i in the sequence, all belonging to the middle helix, were found to be effectively frozen at $kT = 0.6$, and the time scale for the small fluctuations of these angles about their mean values was possible to estimate. In Fig. 4, we show the average $C_i(t)$ for these sixteen angles, denoted by $C(t)$, against Monte Carlo time t, for the $b = 0$, $b = b_{\max}$ and pivot updates. One time unit corresponds to one elementary move, accepted or rejected, at a random position along the chain. We see that $C(t)$ decays most rapidly for the $b = b_{\max}$ update. So, the larger step size of this update does make the exploration of these degrees of freedom more efficient.

Let us finally comment on our choice to work with $n = 8$ angles. This number can be easily altered and some calculations were done with $n = 6$ and $n = 7$, too. For $n = 6$, the performance was worse, which is not unexpected because there are no soft modes available; there are not more variables than constraints. The results obtained for $n = 7$ were, by contrast, comparable to or slightly better than the $n = 8$ results.

5 Discussion

Straightforward Monte Carlo updates of torsional degrees of freedom tend to cause large changes in the global structure of the chains unless the step size is made very small, which is a problem in simulations of dense polymer systems. The strictly local concerted-rotation approach provides a solution to this problem but is rather complicated to implement. In this paper, we have discussed a method that may be less powerful but is much easier to implement, which suppresses rather than eliminates nonlocal deformations.

The method is flexible and not much harder to implement than simple unbiased updates. However, compared to such updates, it has two distinct advantages: the step size can be increased and the update becomes more local, as shown by our simulations of the three-helix-bundle protein in its folded phase.

Making the update more local is important in order to be able to increase the step size and thereby improve the efficiency. At the same time, it makes the dynamics more realistic; the proposed method is, in contrast to the other methods mentioned, tailored to avoid drastic deformations both locally and globally. Therefore, although this paper was focused on thermodynamic simulations, it should be noted that this method may be useful for kinetic studies, too.

Acknowledgments

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