RUGGED METROPOLIS SAMPLING WITH SIMULTANEOUS UPDATING OF TWO DYNAMICAL VARIABLES

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The Rugged Metropolis (RM) algorithm is a biased updating scheme, which aims at directly hitting the most likely configurations in a rugged free energy landscape. Details of the one-variable (RM\textsubscript{1}) implementation of this algorithm are presented. This is followed by an extension to simultaneous updating of two dynamical variables (RM\textsubscript{2}). In a test with Met-Enkephalin in vacuum RM\textsubscript{2} improves conventional Metropolis simulations by a factor of about four. Correlations between three or more dihedral angles appear to prevent larger improvements at low temperatures. We also investigate a multi-hit Metropolis scheme, which spends more CPU time on variables with large autocorrelation times.

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I. INTRODUCTION

Simulations of biomolecules are one of the major challenges in computational science. Rugged free energy landscapes are typical for such systems. In this context a Rugged Metropolis (RM) algorithm was introduced in Ref. [1]. The motivation of RM was an elaboration of the funnel picture of protein folding, which was originally formulated by Bryngelson and Wolynes [2]. RM uses a biased Metropolis algorithm, with the bias of the updating proposal obtained using data from previous simulations at higher temperatures. Although the possibility of constructing biased Metropolis algorithms has been known for many years [3], and these have occasionally been used in the statistical physics [4,5] and bio-chemical [6–8] literature, it seems that a systematic understanding of the possibilities of biased Metropolis procedures is still in its infancy. For instance, it was only recently noted [9] that biased one-variable updates allow one to imitate the heat bath (Gibbs sampler) updates and can still be efficient when the conventional calculation of heat bath probabilities becomes prohibitively slow.

The RM approach is distinct from generalized ensemble simulations. Generalized ensembles (for reviews and recent work see [10]) also use information from higher temperatures, but in an entirely different way. In a sense generalized ensembles build bridges in a rugged free energy landscape, while the RM scheme aims to enhance the likelihood for a direct hit of the needle in the haystack. In fact RM updates can be implemented within any generalized ensemble. In a test case of RM updates within a replica exchange simulation, the improvement was multiplicative [1].

The main technical challenge within the RM scheme is to obtain, from available time series data, estimates of the multi-variable probability densities (pds) in a form that allows for their fast numerical evaluation. So far this was only achieved for one-variable pds, resulting in the RM\textsubscript{1} update scheme. However, it is well-known that many degrees of freedom in a protein molecule are coupled. In addition, one needs multi-variable moves to avoid steric clashes [11] (cf. [8] and references therein for more recent literature). As a next approximation to the desired RM probabilities, in this paper we deal with pds of two variables to develop and test the corresponding RM\textsubscript{2} update scheme.

In the present paper all our Monte Carlo (MC) simulations are done in the canonical ensemble for the brain peptide Met-Enkephalin in vacuum, which has been a frequently used test case since its initial numerical investigation in Ref. [12]. For this (artificial) system the coil-globule transition temperature is at \(T_\theta \approx 295\) K and the folding temperature is at \(T_f \approx 230\) K according to Ref. [13]. Long living traps are found at the glass transition temperature, which is for Met-Enkephalin below the folding temperature at \(T_g \approx 180\) K [14]. In our simulations we cover a range from 400 K down to 220 K and measure integrated autocorrelation times (see, e.g., Ref. [15] for the definition) to determine the performance of our algorithms.

In section II we review the RM scheme and its RM\textsubscript{1} approximation, filling in many details which inevitably had to be omitted in the letter format of Ref. [1]. On the fly we also investigate a multi-hit updating procedure, which spends more computer time on variables with large integrated autocorrelation times. In section III we introduce and test a RM\textsubscript{2} scheme. Summary and conclusions follow in section IV.

II. RM AND THE RM\textsubscript{1} APPROXIMATION

We consider biomolecule models for which the energy \(E\) is a function of a number of dynamical variables \(v_i, i = 1, \ldots, n\). The fluctuations in the Gibbs canonical ensemble are described by a probability den-
They are accurate to about ±1 in the last digit.

| var | angle | residues | 400 K | 300 K | 300 K |
|-----|-------|----------|-------|-------|-------|
| v1  | \( \chi^1 \) | Tyr-1 | 0.107 | 0.070 | 0.272 |
| v2  | \( \chi^2 \) | Tyr-1 | 0.182 | 0.128 | 0.345 |
| v3  | \( \chi^\nu \) | Tyr-1 | 0.497 | 0.377 | 0.680 |
| v4  | \( \phi \) | Tyr-1 | 0.392 | 0.340 | 0.547 |
| v5  | \( \psi \) | Gly-2 | 0.096 | 0.044 | 0.139 |
| v6  | \( \omega \) | Gly-2 | 0.049 | 0.034 | 0.046 |
| v7  | \( \phi \) | Gly-3 | 0.112 | 0.045 | 0.076 |
| v8  | \( \psi \) | Gly-3 | 0.106 | 0.038 | 0.064 |
| v9  | \( \omega \) | Gly-3 | 0.041 | 0.025 | 0.031 |
| v10 | \( \phi \) | Gly-3 | 0.088 | 0.035 | 0.076 |
| v11 | \( \psi \) | Phe-4 | 0.115 | 0.040 | 0.077 |
| v12 | \( \omega \) | Phe-4 | 0.047 | 0.030 | 0.368 |
| v13 | \( \chi^1 \) | Phe-4 | 0.109 | 0.086 | 0.277 |
| v14 | \( \chi^2 \) | Phe-4 | 0.192 | 0.166 | 0.403 |
| v15 | \( \phi \) | Met-5 | 0.082 | 0.042 | 0.139 |
| v16 | \( \psi \) | Met-5 | 0.122 | 0.063 | 0.156 |
| v17 | \( \omega \) | Met-5 | 0.062 | 0.047 | 0.073 |
| v18 | \( \chi^1 \) | Met-5 | 0.117 | 0.092 | 0.362 |
| v19 | \( \chi^2 \) | Met-5 | 0.159 | 0.121 | 0.585 |
| v20 | \( \chi^\nu \) | Met-5 | 0.269 | 0.211 | 0.709 |
| v21 | \( \chi^\nu \) | Met-5 | 0.455 | 0.385 | 0.835 |
| v22 | \( \phi \) | Met-5 | 0.129 | 0.086 | 0.258 |
| v23 | \( \psi \) | Met-5 | 0.378 | 0.267 | 0.469 |
| v24 | \( \omega \) | Met-5 | 0.114 | 0.096 | 0.873 |
| E   |       |         | 0.168 | 0.119 | 0.375 |

The Metropolis importance sampling would be perfect, if we could propose new configurations \{v'\_i\} with their canonical pd. This is not possible as no Metropolis simulation would be necessary if the canonical pd were known. But conventional Metropolis simulations work well at sufficiently high temperatures \( T' \) and can thus provide an estimate \( \overline{\rho}(v_1, \ldots, v_n; T') \) of the pd \( \rho(v_1, \ldots, v_n; T') \). Due to the funnel picture, we expect that such an estimate can be used to feed useful information into the simulation at a sufficiently close-by lower temperature \( T < T' \) \[1\]. The idea of the RM scheme is to propose a transition from a configuration \{v\_i\} to a new configuration \{v'\_i\} with the pd \( \overline{\rho}(v_1, \ldots, v'_n; T) \) and to accept it with the probability

\[
P_a = \min \left[ 1, \frac{\exp(-\beta E')}{\exp(-\beta E)} \overline{\rho}(v_1, \ldots, v'_n; T') \right]
\]

where \( \beta = 1/(kT) \). This equation biases the a-priori probability of each dihedral angle with an estimate of its pd from a higher temperature. Arbitrary generalized ensembles can be treated similarly by replacing \( \exp(-\beta E') \) and \( \exp(-\beta E) \) in Eq. (1) by the appropriate probabilities \( P_g(E') \) and \( P_g(E) \) of the generalized ensemble.

For a range of temperatures

\[
T_1 > T_2 > \ldots > T_r > \ldots > T_{f-1} > T_f
\]

the simulation at the highest temperature, \( T_1 \), is performed with the usual Metropolis algorithm and the results are used as input for the simulation at \( T_2 \). The estimated pd \( \overline{\rho}(v_1, \ldots, v_n; T_{r-1}) \) is expected to be a useful approximation of \( \rho(v_1, \ldots, v_n; T_r) \), therefore allowing the scheme to zoom in on the native structure that is dominant at the physically relevant final temperature \( T_f \).

To get things started, we need to construct an estimator \( \overline{\rho}(v_1, \ldots, v_n; T_r) \) from the numerical data of the RM simulation at temperature \( T_r \). Although this is neither simple nor straightforward, a variety of approaches offer themselves to define and refine the desired estimators.

In Ref. [1] the approximation

\[
\overline{\rho}(v_1, \ldots, v_n; T_r) = \prod_{i=1}^{\text{n}} \overline{\rho}_i(v_i; T_r)
\]

was investigated, where \( \overline{\rho}_i(v_i; T_r) \) are estimators of reduced one-variable pdfs defined by

\[
\rho_i(v_i; T) = \int_{-\pi}^{\pi} dv_j \rho(v_1, \ldots, v_n; T).
\]

The resulting algorithm, called RM\(_1\), constitutes the simplest RM scheme possible.

Let us fill in the details of the RM\(_1\) implementation [1]. To update with the RM\(_1\) weights it is convenient to rely on the cumulative distribution functions defined by

\[
F_i(v) = \int_{-\pi}^{v} dv' \rho_i(v').
\]

The estimate of \( F_{10} \), the cumulative distribution function for the dihedral angle Gly-3 \( \phi \) (\( \rho_{10} \)), from the vacuum simulations at our highest temperature, \( T_1 = 400 \text{K} \), is shown in Fig. 1 (this is the same angle for which histograms at 400 K and 300 K are shown in Ref. [1]). For our plots in the present paper we use degrees, while we use radiant in our theoretical discussions and in the computer programs. Fig. 1 is obtained by sorting all \( n_{\text{dat}} \)
values of $v_{10}$ in our time series in ascending order and increasing the values of $F_{10}$ by $1/n_{\text{dat}}$ whenever a measured value of $v_{10}$ is encountered. Using a heapsort approach, the sorting is done in $n_{\text{dat}} \log_2(n_{\text{dat}})$ steps (see, e.g., Ref. [15]).

Next we divide the ordinate between 0 and 1 into $n_{\text{tab}}$ equal segments. The value of $n_{\text{tab}}$ has to be small enough that a table of size $n \times n_{\text{tab}}$ fits conveniently into the computer RAM. For each integer $j = 1, \ldots, n_{\text{tab}}$ the value $F_{i,j} = j/n_{\text{tab}}$ defines a unique value $v_{i,j}$ through $F_{i,j} = F_i(v_{i,j})$ as is indicated in the figure (for which $i = 10$). Furthermore, for each choice of a dihedral angle (i.e., a particular value of $i$) we define the differences

$$\Delta v_{i,j} = v_{i,j} - v_{i,j-1} \quad \text{with} \quad v_{i,0} = -\pi . \quad (6)$$

The grid in Fig. 1 shows the discretization for the variable $v_{10}$ and the choice $n_{\text{tab}} = 16$. While the discretization for $F_{10}$ on the ordinate is uniformly spaced, widely varying intervals are obtained for $v_{10}$ on the abscissa. The Metropolis procedure for one update of a dihedral angle $v_i$ is now specified as follows:

1. Place the present angle $v_i$ on the discretization grid, i.e., find the integer $j$ through the relation $v_{i,j-1} \leq v_i < v_{i,j}$. For one-variable updates $j$ is available in the computer memory if it is stored at the previous update. Otherwise, $j$ can be re-calculated in $n_2$ steps for the choice $n_{\text{tab}} = 2^{n_2}$ [9].

2. Pick an integer $j'$ uniformly distributed in the range 1 to $n_{\text{tab}}$.

3. Propose $v_i' = v_{i,j'} + x^\tau \Delta v_{i,j'}$, where $0 \leq x^\tau < 1$ is a uniformly distributed random number.

4. Accept $v_i'$ with the probability

$$p_a = \min \left[ 1, \frac{\exp(-\beta E') \Delta v_{i,j'}}{\exp(-\beta E) \Delta v_{i,j}} \right] . \quad (7)$$

It is through the widely varying ratios $\Delta v_{i,j'}/\Delta v_{i,j}$ that importance sampling for the rugged variables becomes improved. Back to our illustration in Fig. 1: The short and the long interval on the abscissa are proposed with equal probabilities, i.e., the a-priori probability density for our angle is high in short intervals and low in long intervals. The CPU time consumption of the RM$_1$ scheme is practically identical with that of the conventional Metropolis algorithms, because the bulk of the CPU time is spend on the calculation of the new energy $E'$.

### A. Numerical results

The performance of the RM$_1$ algorithm is tested at 300 K using input from a simulation at 400 K. The temperature of 400 K is high enough so that the conventional Metropolis algorithm is efficient, while it is low enough to provide useful input for the simulation at 300 K, a temperature at which one experiences a considerable slowing down in a conventional Metropolis simulation of Met-Enkephalin.

Our Metropolis simulations are performed with a variant of SMMP (Simple Molecular Mechanics for Proteins) [17]. For each simulation a time series of $2^{17} = 131,072$ configurations is kept, sampling every 32 sweeps. A sweep is defined by updating each dihedral angle once, which we do in the sequential order of the angles listed in table I. Usually sequential updating is more efficient than random updating [15]. Before starting with the measurements, $2^{18} = 262,144$ sweeps are performed for reaching equilibrium. Thus, the entire simulation at one temperature uses $2^{18} + 32 \cdot 2^{17} = 4,456,448$ sweeps. On a 19 GHz Athlon PC this takes under 12 hours. For each dihedral angle the acceptance rate of the Metropolis algorithm was monitored at run time and, following the recipes of [15], the integrated autocorrelation time $\tau_{\text{int}}$ is calculated from the recorded time series.

Acceptance rates for dihedral angle movements are compiled in table I. For the energy entry it is the ratio of all accepted over all proposed moves. Results are given for simulations with the conventional Metropolis algorithm at 400 K and 300 K, and for the RM$_1$ simulations at 300 K. The RM$_1$ updating uses a discretization with $n_{\text{tab}} = 2^7 = 128$ from the 400 K Metropolis data. Acceptance rates greater than 0.3 are desirable [15]. From the table we notice that the acceptance rates vary greatly from angle to angle. For the Metropolis simulation the values are in the interval [0.041, 0.497] at 400 K and in [0.025, 0.387] at 300 K. For both temperatures $v_9$ corresponds to the lowest value, while $v_3$ and $v_{21}$ correspond to the highest values.
Our RM$_1$ updating at 300 K increases the acceptance rate for each angle, often even beyond the Metropolis acceptance rate at 400 K, as is obvious from the average value listed for the energy. A second look reveals that the increase in the acceptance rate varies greatly from angle to angle. While for some angles the problem of low acceptance rates is entirely solved, for others the improvement remains modest. For instance for all $\omega$ angles the increase is dramatic, e.g., from 0.034 to 0.416 for $v_6$. Angles with little improvements are $v_7$ (0.045 to 0.076), $v_8$ (0.038 to 0.064), $v_{10}$ (0.035 to 0.070), and $v_{11}$ (0.040 to 0.077). Better, but still not particularly impressive, is the increase in the acceptance rates of $v_5$, $v_{15}$ and $v_{16}$. All these are $\phi$, $\psi$ angles around $C_o$ atoms. For all other angles RM$_1$ updating has moved the acceptance rate above or at least close to 0.3.

The improvement for $\omega$ angles is most easily understood. Figure 2 shows the cumulative distribution function for $v_9$ (Gly-2 $\omega$) at 400 K, which is the angle of lowest acceptance rate in the conventional Metropolis updating. This distribution function corresponds to a histogram narrowly peaked around $\pm \pi$, which is explained by the specific electronic hybridization of the CO-N peptide bond. From the grid shown in Fig. 2 it is seen that the RM$_1$ updating concentrates the proposal for this angle in the range slightly above $-\pi$ and slightly below $+\pi$. Thus the procedure has a similar effect as the often used restriction to the range $[\pi-\pi/9, \pi+\pi/9]$, which is also the default implementation in SMMP (the range $[\pi, \pi+\pi/9]$ is, of course, $[-\pi, -\pi+\pi/9]$ in our plots).

Although acceptance rates give some insights, the decisive quantity for the performance of an algorithm is the more difficult to calculate integrated autocorrelation time $\tau_{\text{int}}$. To achieve a pre-defined accuracy, the computer time needed is directly proportional to $\tau_{\text{int}}$.

In Table II the integrated autocorrelation times are compiled for all angles and for the energy. The values are statistically consistent with those of Ref. [1]. Deviations are due to re-runs and using different procedures for estimating integrated autocorrelation times. In all tables they are given in units of 32 sweeps, as this is the step-size of our MC time series. Error bars are shown in parenthesis. For these calculations we use the routines of Ref. [15] together with a jackknife error analysis as explained there. The angles $v_7$, $v_8$, $v_{10}$, $v_{11}$, $v_{15}$ and $v_{16}$ exhibit autocorrelation times $> 100$ in the conventional Metropolis simulation at 300 K. Note that four of these are those with the worst improvement of acceptance rates when moving to the RM$_1$ updating, while the remaining two belong to the subsequent group with still rather poor improvement.

The increase in magnitude in the autocorrelation times for these six angles is remarkable when the temperature of the conventional Metropolis simulation is lowered from 400 K to 300 K. This shows that the standard Metropolis algorithm is efficient at 400 K but not so at 300 K. On the other hand, the distribution of the variables is not dramatically changed, at least to the extent that this can be judged from one-variable histograms, as is illustrated in Ref. [1] for $v_{10}$. This is the reason why the 400 K simulation provides useful input for the RM$_1$ simulation at 300 K.

### Table II. Integrated autocorrelation times for dihedral angle movements in units of 32 sweeps.

| var | 400 K | 300 K | 300 K | 300 K |
|-----|-------|-------|-------|-------|
|     | Metro | Metro | RM$_1$ | RM$_2$ |
| $v_1$ | 2.11 (06) | 15.2 (1.5) | 9.07 (58) | 6.03 (47) |
| $v_2$ | 1.18 (02) | 2.70 (16) | 1.63 (09) | 1.70 (12) |
| $v_3$ | 1.03 (01) | 2.18 (14) | 1.26 (04) | 1.24 (04) |
| $v_4$ | 1.44 (03) | 4.44 (23) | 3.28 (21) | 2.82 (14) |
| $v_5$ | 5.44 (20) | 54.5 (5.4) | 26.3 (1.5) | 20.0 (1.3) |
| $v_6$ | 2.95 (07) | 23.3 (2.7) | 8.65 (58) | 6.00 (34) |
| $v_7$ | 5.83 (20) | 103 (14) | 52.9 (4.3) | 24.3 (1.3) |
| $v_8$ | 7.36 (22) | 125 (12) | 74.2 (6.9) | 35.0 (2.7) |
| $v_9$ | 4.39 (13) | 32.0 (2.2) | 14.2 (1.0) | 8.84 (48) |
| $v_{10}$ | 9.08 (88) | 124 (12) | 80.6 (6.9) | 34.3 (2.8) |
| $v_{11}$ | 5.39 (45) | 105 (08) | 72.4 (5.5) | 31.3 (1.9) |
| $v_{12}$ | 3.37 (08) | 15.6 (1.5) | 5.68 (39) | 3.92 (17) |
| $v_{13}$ | 1.81 (05) | 8.79 (46) | 5.69 (54) | 3.59 (22) |
| $v_{14}$ | 1.15 (02) | 1.65 (10) | 1.40 (07) | 1.26 (06) |
| $v_{15}$ | 6.72 (28) | 105 (12) | 45.6 (2.7) | 27.5 (4.5) |
| $v_{16}$ | 9.28 (28) | 133 (09) | 75.2 (5.2) | 33.9 (2.1) |
| $v_{17}$ | 1.90 (04) | 9.69 (79) | 3.89 (36) | 2.29 (08) |
| $v_{18}$ | 1.66 (05) | 12.0 (1.6) | 6.48 (78) | 5.11 (28) |
| $v_{19}$ | 1.17 (02) | 1.65 (08) | 1.16 (03) | 1.17 (03) |
| $v_{20}$ | 1.02 (01) | 1.08 (02) | 1.03 (02) | 1.02 (02) |
| $v_{21}$ | 1.00 (01) | 1.00 (01) | 1.00 (01) | 1.02 (01) |
| $v_{22}$ | 3.20 (12) | 35.9 (4.0) | 18.2 (1.2) | 12.0 (0.8) |
| $v_{23}$ | 1.50 (04) | 20.3 (1.8) | 11.0 (0.6) | 5.96 (35) |
| $v_{24}$ | 1.07 (02) | 1.22 (05) | 1.00 (01) | 1.00 (01) |
| $E$ | 4.89 (21) | 50.7 (5.0) | 26.0 (1.4) | 14.2 (0.7) |
The RM_1 updating reduces the integrated autocorrelation times at 300 K by factors of about two, for instance for \( \tau_7 \) from 103 to 53. The \( \tau_{int} \) values vary greatly from angle to angle. While some angles show no autocorrelations after 32 sweeps (\( \tau_{int} = 1 \) or close to it), the largest value on record for RM_1 updating at 300 K is \( \tau_{int} = 80 \pm 7 \) for \( \nu_{10} \) (down from 124 for Metropolis updating at 300 K). That the RM_1 updating does not reduce the large autocorrelation times more efficiently has obviously to do with correlations between different angles. Notably even moves of some of the \( \omega \) angles, like \( \nu_3 \) with \( \tau_{int} = 14.2 \pm 1.0 \), appear considerably correlated with the rest of the molecule. RM variants which move several dynamical variables collectively are required and our RM_2 implementation for simultaneous updates of two dihedral angles is discussed in section III. First let us address a multi-hit Metropolis procedure.

### B. Multi-hit updating

Our sequential updating hits each angle once. The greatly varying integrated autocorrelation times of table II suggest that the computer time may be more efficiently used by performing several Metropolis hits for variables with large integrated autocorrelation times, to be called “bad” variables in the following.

To find an optimal choice for the number of hits per variable requires some thought. At 300 K the integrated autocorrelation times of the dihedral angles vary between \( \tau_{int} = 1 \) and \( \tau_{int} \approx 133 \) for the conventional Metropolis updating and still between \( \tau_{int} = 1 \) and \( \tau_{int} \approx 80 \) for the RM_1 algorithm. It is certainly not a good idea to choose the number of hits per variable in proportion to \( \tau_{int} \), because we expect correlations between angles to be the main obstacle for reducing large integrated autocorrelation times. A scheme with a large number of hits mimics the heat-bath algorithm (e.g., Ref. [15]), which sets the upper bound to the gain in performance, but does not resolve the problem of correlations between angles. So a modest increase in the number of hits per bad variable may increase the performance of the updating, while a further increase will result in the contrary.

A guideline for choosing the number of hits is obtained from the observation that the previously obtained acceptance rates per update attempt do not change when performing multiple hits. It appears reasonable to increase the hits of bad variables while bounding the number of hits times the acceptance rate by 0.3 from above. As the acceptance rates change considerably when switching from regular Metropolis to RM_1 updating, we employ different schemes for the two cases. Results for the two different multi-hit schemes are collected in table III.

The numbers in the first “hits” column are used for the regular Metropolis updating. They are arranged to add up to 48, i.e., twice the total number of variables. The additional computer time needed is balanced by reducing the number of sweeps between measurements from 32 to 16 (a sweep is now defined by applying the new updating procedure in sequential order once to each angle). By comparing tables II and III we see that the multi-hit updating improves the Metropolis algorithm at 300 K considerably: the integrated autocorrelation time for the energy is down by about 40%.

The numbers in the second “hits” column are used for RM_1 and RM_2 updating. As RM_1 updating increases acceptance rates already significantly, there is little opportunity for additional improvements due to multiple hits. By that reason the numbers of the column add only up to 39 hits per sweep. This is balanced by reducing the number of sweeps between measurements from 32 to 20 (the integer nearest to 32 \times 24/39). There are still significant decreases in autocorrelations times for the bad variables, but the indicator for overall performance, the integrated autocorrelation time of the energy, shows only a modest 5% decrease when comparing to RM_1 without multiple hits and practically no change for RM_2 updating, introduced next. The apparent reason is that these updating schemes are already much closer to a heat-bath scenario, so that the improvement due to multiple hits becomes offset by the additional computer time needed.

| var | 48 | 400 K | 300 K | 39 | 300 K | 300 K |
|-----|----|-------|-------|----|-------|-------|
| hits | Metro | Metro | hits | RM_1 | RM_2 |
| v_1 | 2 | 2.05 (07) | 14.2 (1.1) | 1 | 7.29 (52) | 5.66 (42) |
| v_2 | 1 | 1.37 (03) | 3.29 (23) | 1 | 1.56 (04) | 1.91 (05) |
| v_3 | 1 | 1.04 (04) | 2.15 (10) | 1 | 1.39 (04) | 1.51 (06) |
| v_4 | 1 | 1.47 (03) | 5.49 (57) | 1 | 2.74 (12) | 3.09 (16) |
| v_5 | 3 | 3.73 (08) | 48.1 (5.7) | 2 | 21.8 (1.7) | 20.3 (1.0) |
| v_6 | 1 | 4.19 (09) | 19.3 (1.2) | 1 | 7.12 (35) | 5.11 (22) |
| v_7 | 4 | 3.96 (21) | 61.7 (3.5) | 4 | 42.3 (29) | 20.7 (1.2) |
| v_8 | 4 | 5.06 (19) | 81.8 (5.2) | 4 | 50.5 (4.1) | 24.1 (1.2) |
| v_9 | 2 | 4.21 (13) | 25.0 (1.6) | 1 | 12.7 (1.0) | 8.14 (47) |
| v_{10} | 4 | 5.28 (20) | 86.1 (6.4) | 4 | 48.0 (4.4) | 24.7 (1.6) |
| v_{11} | 4 | 3.72 (14) | 81.1 (7.2) | 4 | 53.7 (4.8) | 25.5 (1.4) |
| v_{12} | 2 | 3.04 (13) | 11.3 (0.6) | 1 | 4.82 (42) | 4.01 (26) |
| v_{13} | 1 | 2.39 (05) | 9.36 (96) | 1 | 4.36 (29) | 3.45 (26) |
| v_{14} | 1 | 1.34 (03) | 2.03 (15) | 1 | 1.23 (03) | 1.28 (03) |
| v_{15} | 4 | 4.65 (16) | 61.1 (4.4) | 2 | 35.5 (3.2) | 20.3 (1.0) |
| v_{16} | 4 | 6.29 (20) | 86.7 (8.5) | 2 | 61.5 (5.0) | 29.5 (1.9) |
| v_{17} | 1 | 2.86 (06) | 7.48 (42) | 1 | 3.16 (30) | 2.18 (07) |
| v_{18} | 1 | 2.03 (05) | 11.7 (1.1) | 1 | 7.79 (91) | 6.48 (51) |
| v_{19} | 1 | 1.64 (04) | 2.57 (15) | 1 | 1.16 (02) | 1.32 (03) |
| v_{20} | 1 | 1.09 (01) | 1.21 (02) | 1 | 1.01 (01) | 1.02 (01) |
| v_{21} | 1 | 1.00 (01) | 1.02 (02) | 1 | 1.00 (01) | 1.00 (01) |
| v_{22} | 2 | 2.98 (08) | 26.2 (1.8) | 1 | 19.2 (1.6) | 13.9 (0.9) |
| v_{23} | 1 | 1.51 (05) | 13.3 (1.1) | 1 | 11.4 (1.0) | 5.60 (31) |
| v_{24} | 1 | 1.44 (03) | 1.63 (04) | 1 | 1.02 (01) | 1.03 (02) |
| E | 4.25 (17) | 32.9 (1.4) | 24.9 (2.2) | 14.7 (1.3) |
III. THE RM$_2$ APPROXIMATION

We now generalize the RM$_1$ scheme of Eq. (7) to the simultaneous updating of two dihedral angles. For $i_1 \neq i_2$ the reduced two-variable pdfs are defined by

$$
\rho_{i_1,i_2}^2(v_{i_1}, v_{i_2}; T) = \int_{-\pi}^{+\pi} \prod_{j \neq i_1,i_2} dv_j \, \rho(v_j, \ldots, v_n; T) . \tag{8}
$$

The one-variable cumulative distribution functions $F_{i}$, and the discretization $v_{i,j}$, $j = 0, \ldots, n_{\text{tab}}$ are already given by Eqs. (5) and (6). We define conditional cumulative distribution functions by

$$
F_{i_1,i_2,j}(v) = \int_{-\pi}^{\pi} dv_{i_2} \int_{v_{i_1,j-1}}^{v_{i_1,j}} dv_{i_1} \, \rho_{i_1,i_2}^2(v_{i_1}, v_{i_2}) \tag{9}
$$

for which the normalization $F_{i_1,i_2,j}(\pi) = 1/n_{\text{tab}}$ holds. To extend the RM$_1$ updating to two variables we define for each integer $k = 1, \ldots, n_{\text{tab}}$ the value $F_{i_1,i_2,j;k} = k/(n_{\text{tab}})^2$. Next we define $v_{i_1,i_2,j,k}$ through $F_{i_1,i_2,j;k} = F_{i_1,i_2,j}(v_{i_1,i_2,j,k})$ and also the differences

$$
\Delta v_{i_1,i_2,j;k} = v_{i_1,i_2,j;k} - v_{i_1,i_2,j;k-1} \quad \text{with} \quad v_{i_1,i_2,j;0} = -\pi . \tag{10}
$$

The RM$_2$ Metropolis procedure for the simultaneous update of $(v_{i_1}, v_{i_2})$ is then specified as follows:

1. Find the grid index $j$ for the present angle $v_{i_1}$ through $v_{i_1,j-1} \leq v_{i_1} \leq v_{i_1,j}$, just like for RM$_1$ updating.

2. Find the grid index $k$ for the present angle $v_{i_2}$ through $v_{i_1,i_2,j,k-1} \leq v_{i_2} \leq v_{i_1,i_2,j,k}$.

3. Pick two integers $j'$ and $k'$, each uniformly distributed in the range 1 to $n_{\text{tab}}$. (This could be extended to cover asymmetric ranges $n_{\text{tab}}^1 \times n_{\text{tab}}^2$.)

4. Propose $v_{i_1}' = v_{i_1,j-1} + x_1^2 \Delta v_{i_1,j'}$, where $0 \leq x_1^2 < 1$ is a uniformly distributed random number.

5. Propose $v_{i_2}' = v_{i_1,i_2,j',k'-1} + x_2^2 \Delta v_{i_1,i_2,j',k'}$, where $0 \leq x_2^2 < 1$ is a second uniformly distributed random number.

6. Accept $(v_{i_1}', v_{i_2}')$ with the probability

$$
p_a^2 = \min \left[ 1, \frac{\exp(-\beta E')}{{\exp(-\beta E) + 1}} \frac{\Delta v_{i_1,j'} \Delta v_{i_1,i_2,j',k'}}{\Delta v_{i_1,j} \Delta v_{i_1,i_2,j,k}} \right] . \tag{11}
$$

As before, estimates of the conditional cumulative distribution functions and the intervals $\Delta v_{i_1,i_2,j;k}$ are obtained from the conventional Metropolis simulation at 400 K. In the following we focus on the pairs $(v_7, v_8)$, $(v_{10}, v_{11})$ and $(v_{15}, v_{16})$. These angles correspond to the largest integrated autocorrelation times of the RM$_1$ procedure and are expected to be strongly correlated with one another because they are pairs of dihedral angles around a $C_\alpha$ atom.

The bias of the acceptance probability given in Eq. (11) is governed by the areas

$$
\Delta A_{i_1,i_2,j;k} = \Delta v_{i_1,j} \Delta v_{i_1,i_2,j,k} .
$$

For $i_1 = 6$ and $i_2 = 7$ our 400 K estimates of these areas are depicted in Fig. 3. For the RM$_2$ procedure these areas take the role which the intervals on the abscissa of Fig. 1 play for RM$_1$ updating. The small and the large areas are proposed with equal probabilities, so the a-priori probability for our two angles is high in a small area and low in a large area. In Fig. 3 the largest area is 503.4 times the smallest area. Areas of high probability correspond to allowed regions in the Ramachandran map of a Gly residue [18].
Note that the order of the angles matters. The difference between Fig. 3 and Fig. 4 is that we plot in Fig. 3 the areas $A_{7,8,j,k}$ and in Fig. 4 the areas $A_{8,7,j,k}$ while the labeling of the axes is identical. This means that for Fig. 3 sorting is first done on the angle $v_7$ (regardless of the value of $v_8$) and then done on $v_8$ for which the corresponding value of $v_7$ is within a particular bin $\Delta v_7$, but for Fig. 4 it is first done on $v_8$ and then on $v_7$. In Fig. 4 the largest area is 396.4 times the smallest area.

Fig. 5 and Fig. 6 give plots for the $(v_{10}, v_{11})$ and $(v_{15}, v_{16})$ pairs in which the angle with the smaller subscript is sorted first. The ratio of the largest area over the smallest area is 650.9 for $(v_{10}, v_{11})$ and 2565.8 for $(v_{15}, v_{16})$. The large number in the latter case is related to the fact that $(v_{15}, v_{16})$ is the pair of $\phi$, $\psi$ angles around the $C_\alpha$ atom of Phe-4, for which positive $\phi$ values are disallowed [18].

The RM$_2$ scheme which we have tested adds updates for the three pairs $(v_7, v_8)$, $(v_{10}, v_{11})$ and $(v_{15}, v_{16})$ after one-angle updates for all the 24 angles with the RM$_1$ scheme. For each pair both orders of sorting are used, so that we add altogether six new updates. The bookkeeping for this process is a bit tricky, because an accepted update changes not only $(j, k) \rightarrow (j', k')$, but also the the $j$ from the RM$_1$ updating of the angles. The latter corresponds to a different table and needs to be re-calculated from the new value of the angle. As already mentioned, this can be done in $\log_2(n_{\text{tab}})$ steps [9]. Similarly, accepted RM$_1$ updates can change the initial RM$_2$ $(j, k)$ values, so that they may have to be re-calculated. The six RM$_2$ update tables, each of size $16 \times 16$, are built from the 400 K Metropolis simulation, and the areas of four of them are precisely those shown in Figs. 3 to 6.

### A. Numerical Results

We have checked the correctness of our updating procedure by comparing high precision energy averages and other observables with results from previous calculations. The acceptance rates of the one-variable updates remain the same as they were for RM$_1$ procedure. For the acceptance rate of a pair we average over the two cases. Table IV compares the two-angle RM$_2$ acceptance rates at 300 K to those obtained by proposing the same two-angle updates with the standard Metropolis procedure. At 300 K an increase by factors in the range from three to nearly ten is found. However, the values remain surprisingly low, presumably due to substantial correlations with additional angles.

| variable pair     | 400 K | 300 K | 300 K | 300 K |
|-------------------|-------|-------|-------|-------|
|                   | Metro | Metro | RM$_2$| RM$_2$|
| $(v_7, v_8)$      | 0.044 | 0.0060| 0.019 | 0.020 |
| $(v_{10}, v_{11})$| 0.041 | 0.0051| 0.021 | 0.022 |
| $(v_{15}, v_{16})$| 0.018 | 0.0051| 0.048 | 0.050 |

Integrated autocorrelation times are calculated to evaluate the improvement of the overall performance. For this purpose the number of sweeps between measurements is reduced from 32 to 26 to account for the additional CPU time needed for the two-angle moves. The results are presented in Table II. Despite the small acceptance rates for the two-angle moves, the integrated autocorrelation times for the targeted angles are substantially reduced. For all the six angles they are smaller by factors larger than two when compared with the RM$_1$ results. Interestingly this speed-up propagates through the entire system and the integrated autocorrelation time for the energy is found to be about a factor of two smaller than for the RM$_1$ algorithm.
Multi-hit updates allow us to focus even more on the angles with large autocorrelation times. For the one-angle updates we use the same numbers of hits as for RM$_1$ updating (see table III). In addition we use four hits for the pairs $(v_2,v_3)$ and $(v_{10},v_{11})$ and two hits for the $(v_{15},v_{16})$ pair. For each pair both orders of the updating are used. Altogether we perform 39 one-angle and 20 two-angle hits per sweep, which is balanced by reducing the number of sweeps between measurements to 13 (the integer nearest to $32 	imes 24/59$). The results for integrated autocorrelation times are a mixed bag (compare the last columns of tables II and III). While the values for the targetted angles indeed go down, in particular for $v_8$, the improvement does not propagate to the energy.

TABLE V. Multi-hit Metropolis at low temperatures.

| var | 48     | 280 K | 260 K | 240 K | 220 K |
|-----|--------|-------|-------|-------|-------|
|     |        | hits  |       |       |       |
| $v_1$ | 2     | 24.5 (1.7) | 59.8 (4.8) | 246 (18) | 658 (60) |
| $v_2$ | 3     | 70.7 (5.0) | 236 (27) | 531 (47) | 1672 (148) |
| $v_3$ | 1     | 34.8 (2.4) | 65.0 (4.8) | 185 (10) | 453 (28) |
| $v_4$ | 4     | 156 (16) | 526 (88) | 1425 (118) | 4434 (405) |
| $v_5$ | 4     | 191 (17) | 627 (78) | 1591 (135) | 4965 (485) |
| $v_6$ | 2     | 60.2 (5.0) | 114 (96) | 467 (33) | 1809 (219) |
| $v_7$ | 4     | 189 (15) | 613 (69) | 1530 (131) | 5236 (443) |
| $v_8$ | 4     | 214 (18) | 625 (82) | 1901 (148) | 5781 (437) |
| $v_9$ | 2     | 20.1 (1.1) | 44.3 (3.2) | 158 (98) | 557 (44) |
| $v_{10}$ | 1    | 15.7 (0.9) | 36.8 (2.9) | 119 (97) | 279 (17) |
| $v_{11}$ | 4   | 239 (90) | 308 (31) | 999 (78) | 2283 (170) |
| $v_{12}$ | 4   | 204 (12) | 449 (34) | 1600 (129) | 4537 (344) |
| $v_{13}$ | 1   | 11.9 (0.7) | 22.8 (1.2) | 78.8 (2.7) | 278 (15) |
| $v_{14}$ | 1   | 24.1 (2.6) | 55.5 (3.6) | 208 (11) | 755 (46) |
| $v_{15}$ | 2   | 64.5 (4.7) | 136 (10) | 343 (16) | 898 (54) |
| $v_{16}$ | 1   | 37.2 (1.8) | 84.4 (5.1) | 360 (26) | 830 (63) |
| $E$     | 7.16 (4.0) | 148 (08) | 484 (29) | 1536 (121) |

In tables V and VI we present results down to 220 K for the multi-hit improved Metropolis and RM$_2$ algorithms, where the distribution of hits is the same as listed in table III. We always construct the RM$_2$ table from the previous RM$_2$ runs at the next higher temperature. We also generate RM$_2$ data without using the multi-hit scheme, with the resulting autocorrelation times consistently higher than those reported in table VI. We have not listed the angles $v_2$, $v_3$, $v_4$, $v_{14}$, $v_{19}$, $v_{20}$, $v_{21}$ and $v_{24}$ in tables V and VI, because they are not significantly correlated with the rest of the molecule.

When lowering the temperature towards 220 K, the autocorrelation times increase rapidly. To control $\tau_{\text{int}}$ we double the number of sweeps between measurements each time, when decreasing the temperature. So it is 64 at 280 K, 128 at 260 K, 256 at 240 K and 512 at 220 K. For the multi-hit Metropolis simulations this was still not sufficient and we performed two additional runs, with $4 \times 256$ sweeps at 240 K and with $4 \times 512$ sweeps at 220 K. This explains the relatively small error bars in the last two columns of table V. In the tables we continue to report $\tau_{\text{int}}$ in units of 32 sweeps, multiplying the measured $\tau_{\text{int}}/32$ value with the number of sweeps between measurements. It is seen that even for the RM$_2$ simulation the $\tau_{\text{int}}$ increases are not compensated by the increase of computer time. In contrast to that, the decrease in acceptance rates is rather moderate, less than a factor of two when the temperature is lowered from 300 K to 220 K.

The results of tables V and VI show that our RM$_2$ sampling accelerates the conventional Metropolis simulations by a rather temperature independent factor. As we can assume that the multi-hit Metropolis simulations already improve conventional Metropolis simulations by about 40%, the RM$_2$ acceleration is by a factor between four and five with respect to a conventional Metropolis simulation. For large scale simulations factors larger than two are clearly of importance, but it remains a bit puzzling why the improvement does not increase upon lowering the temperature, as it is found when using generalized ensembles. Apparently coordinated moves of three and more angles are needed.

### IV. SUMMARY AND CONCLUSIONS

We have reviewed the one-variable approximation RM$_1$ of the rugged Metropolis (RM) scheme of Ref. [1] and worked out a two-variable approximation RM$_2$ for simultaneous moves of two dihedral angles. As before the test system has been Met-Enkephalin. A gain of a factor of four over conventional Metropolis simulations has been demonstrated at 300 K.
Although the elaboration of the RM scheme seems to be on track, much work is left to be done. Even for a system as simple as Met-Enkephalin it remains unclear which kinds of correlations are responsible for the still low acceptance rates of the two-angles moves. On the other hand it is encouraging to see that the autocorrelations times of these angles are nevertheless substantially reduced and that this effect propagates through the entire system. Other test cases need to be investigated to get a broader understanding of the observed features. In particular one would like to know how the performance gain depends on the system size.

Somewhat puzzling is the lack of enhanced improvements at lower temperatures. The real future of biased updating procedures may lie in their implementation for generalized ensembles.

Presently the leading method for simulations of biomolecules is molecular dynamics (see [19] for a textbook). This is to some extent surprising, because Markov Chain Monte Carlo (MC) simulations allow for large changes of conformations in a single move, so thermodynamically relevant equilibrium configurations can, in principle, be reached quickly. However, in simulations of biomolecules with an explicit inclusion of solvent interactions, large MC moves face the problem that there will not be a suitable cavity in the solvent to accommodate a large distortion of the molecule shape. While the RM method discussed in this paper decreases the likelihood of steric clashes in a vacuum simulation, it has no immediate translation into the situation of explicit solvent models.

The way out may be the use of implicit solvent models, for which the change in the molecule-solvent and solvent-solvent interaction energies can be calculated instantaneously, like in a vacuum simulation. Indeed RM$_1$ simulations for implicit solvent models, based on the solvent-accessible area method implemented in [17], have already been performed [20]. The algorithmic improvements were similar as found for the vacuum situation. However there is evidence [20,21] that the class of solvent models used does not parametrize the solvent interactions properly. It appears that quite generally the reliability of implicit solvent models has not yet been well established.

Finally we like to mention that MC moves may be fine-tuned on a local level as done in the approach of Ref. [22]. This is also possible for models which include solvents explicitly. So MC may still be a viable alternative to molecular dynamics for explicit solvent models.

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[1] B.A. Berg, Phys. Rev. Lett. 90, 180601 (2003).
[2] D. Bryngelson and P.G. Wolynes, Proc. Nat. Acad. Sci. USA 84, 7524 (1987).
[3] W.K. Hastings, Biometrika 57, 97 (1970).
[4] A.D. Bruce, J. Phys. A 18, L873 (1985).
[5] A. Milchev, D.W. Heermann, and K. Binder, J. Stat. Phys. 44, 749 (1986).
[6] M.W. Deem and J.S. Bader, Mol. Phys. 87, 1245 (1996).
[7] G. Favrin, A. Irbäck, and F. Sjunnesson, J. Chem. Phys. 114, 8154 (2001).
[8] J.P. Ulmschneider and W.L. Jorgensen, J. Chem. Phys. 118, 4261 (2003).
[9] A. Bazavov and B.A. Berg, hep-lat/0503006.
[10] G. La Penna, S. Morante, A. Perico, and G.C. Rossi, J. Chem. Phys. 121, 10725 (2004); B. Berg, H. Noguchi, and Y. Okamoto, Phys. Rev. E 68, 036126 (2003); U.H.E. Hansmann, Physica A 321, 152 (2003); A. Mitsutake, Y. Sugita and Y. Okamoto, Biopolymers (Peptide Science) 60, 96 (2001).
[11] N. Go and H.A. Scheraga, Macromolecules 3, 178 (1970).
[12] Z. Li and H.A. Scheraga, Proc. Nat. Acad. Sci. USA, 85, 6611 (1987).
[13] U.H. Hansmann, M. Masuya, and Y. Okamoto, Proc. Natl. Acad. Sci. USA 94, 10652 (1997).
[14] N.A. Alves and U.H. Hansmann, Int. J. Mod. Phys. C 11, 301 (2000).
[15] B.A. Berg, Markov Chain Monte Carlo Simulations and Their Statistical Analysis, World Scientific, 2004.
[16] M.J. Sippl, G. Nemethy, and H.A. Scheraga, J. Phys. Chem. 88, 6231 (1984) and references given therein.
[17] F. Eisenmenger, U.H. Hansmann, S. Hayryan, and C.-K. Hu, Comp. Phys. Commun. 138, 192 (2001).
[18] G.E. Schultz and R.H. Schirmer, Principle of Protein Structure, Springer, New York, 1979.
[19] D. Frenkel and B. Smit, Understanding Molecular Simulation, Academic Press, San Diego, 1996.
[20] B.A. Berg and H.-P. Hsu, Phys. Rev. E 69, 026703 (2004).
[21] Y. Peng, U.H. Hansmann, and N.A. Alves, J. Chem. Phys. 118, 2374 (2003); Y. Peng and U.H. Hansmann, Biophys. J. 82, 3269 (2003).
[22] D. Bouzida, S. Kumar, and R. Swendsen, Phys. Rev. A 45, 8894 (1992).