Improved Computer Simulation Method for Estimating the Entropy of Macromolecules with Hard-Core Potential

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ABSTRACT: An approximate method for estimating the conformational entropy of macromolecules with computer simulation has been recently suggested. This method is further developed here for the case of polymer chains with hard-core potential and applied to relatively short ($N \leq 49$) self-avoiding walks (SAWs) on both a 3-choice square lattice and a 5-choice simple cubic lattice. The SAWs are studied on unbounded lattices and are also confined within small "boxes" which exert on the chain additional long-range interactions. Very high accuracy (0.1–1%) for the entropy is obtained with the improved method, which in most cases, is an order of magnitude better than that achieved with the first version of the method. We also discuss how to apply the method to more complex systems.

1. Introduction

An approximate method for estimating the conformational entropy of macromolecules with computer simulation has been recently suggested[1] and applied preliminarily to chains with excluded volume (EV) on square and simple cubic lattices. This method enables one to calculate the entropy from a relatively small sample of conformations obtained with *any* computer simulation technique.[2-6] In contrast to other methods for estimating the entropy,[7-11] the new method is not limited to the extreme cases of very small conformational fluctuations (e.g., harmonic fluctuations around a helical state of a polypeptide) or very large ones (at the Θ point[7,12,13]) but can be applied, in principle, to any macromolecular state. In the present work, we further develop this method for the limited case of polymer chain models with hard-core interactions and apply it preliminarily to samples of self-avoiding walks (SAWs) generated with the direct Monte Carlo (MC) procedure[2] on both a 3-choice square lattice and a 5-choice simple cubic lattice. Because of "sample attrition",[2] generation of long SAWs is significantly less efficient with the direct MC procedure than with other simulation procedures;[3-5] therefore, relatively short SAWs, of $N \leq 49$ (where N is the number of links in a walk) have been studied. However, with the direct MC technique (in contrast to other techniques[3-5]), the entropy S can also be calculated from an asymptotically exact formula,[14,15] which enables us to examine the accuracy of our results

$$S = k_B \log C_N \cong k_B[\log q + (N-1)\log(q-1) + \log(W_N/W_0)] \quad (1)$$

where k_B is the Boltzmann constant, q the lattice coordination number, C_N the total number of SAWs of N links, W_0 the total number of walks started, and W_N the number of SAWs generated. In order to test our method for conditions of stronger long-range interactions, we also confine the SAWs within a relatively small box of size $(2L+1)^d$, where d is the dimensionality. It should be pointed out that S (eq 1) consists of two parts, the entropy of an ideal chain (S_I) and the negative contribution to the entropy due to EV, which will be denoted $-S_{EV}$

$$S_I = k_B[\log q + (N-1)\log(q-1)] \quad (2)$$

$$S_{EV} = S_I - S \cong -k_B \log(W_N/W_0) \quad (3)$$

In this work we are mainly interested in S_{EV} rather than in S. Our results are also compared with estimates for the entropy obtained by series expansion.[16,17]

2. Theory

The method for estimating the entropy is based on a computer simulation procedure for generating SAWs, recently suggested,[18] which is independent of the direct MC technique employed. In what follows we first describe this procedure and then develop our method for the entropy.

2.1. Approximate Simulation Procedure for Generating SAWs. Let us describe first an exact procedure that enables one to construct SAWs with equal probability. Consider a lattice of any dimensionality with coordination number q and let us construct a SAW that starts from the origin of the coordinate system. The first bond (step) is determined in one of the q directions with equal probability $1/q$. In the next steps of the process ($k > 1$) the probability to select a direction ν ($\nu = 1,...,q$) out of $q-1$ allowed ones is not constant $1/(q-1)$, as with the direct MC technique, but becomes a function of step k in the following way: assume that we are at the kth step of the process, i.e., $k-1$ directions of the chain $\nu_1,...,\nu_{k-1}$ have already been determined, and we want to specify ν_k. The *exact* transition probability $p_k(\nu|\nu_1,...,\nu_{k-1})$ for selecting a direction ν should take into account all of the possible *partial* SAWs of $N-k+1$ bonds, which can be obtained in future steps of the process (steps $k,...,N$). Those as-yet undetermined partial SAWs should be distinguished from the $k-1$ bonds already fixed and therefore we call them the future SAWs. One can calculate $M_k{}^\nu(\nu_1,...,\nu_{k-1})$, the number of future SAWs, starting with a direction ν at step k (for a given set of $\nu_1,...,\nu_{k-1}$) and define the transition probability for ν

$$p_k(\nu|\nu_1,...,\nu_{k-1}) = M_k{}^\nu(\nu_1,...,\nu_{k-1}) / \sum_\nu M_k{}^\nu(\nu_1,...,\nu_{k-1}) \quad (4)$$

ν_k is selected by a lottery according to the p_k's and the process continues. Once a SAW i of N bonds has been constructed, one knows its construction probability, P_i, which is the product of the N sequential transition probabilities with which the directions $\nu_1,...,\nu_N$ have been chosen

$$P_i = q^{-1} \prod_{k=2}^{N} p_k(\nu_k|\nu_1,...,\nu_{k-1}) = C_N{}^{-1} \quad (5)$$

The second equality in eq 5 (which means that the SAWs are equally probable) is obtained by expressing the p_k's in terms of the $M_k{}^\nu$'s (eq 4). It should be pointed out that at each step k *all* future SAWs of length $N-k+1$ are taken into account and therefore a construction cannot fail (ν_k which might lead to a failure is associated with $M_k{}^\nu = 0$, which means zero transition probability). Obviously, this exact construction procedure is impractical for large N, and we therefore suggest approximating it by defining (in the same manner as eq 4) transition probabilities $p_k(\nu|\nu_1,...,\nu_{k-1},b)$ based on future SAWs consisting only of a small number of bonds b, rather than of $N-k+1$ (strictly speaking, the future SAW length is $b' = \text{Min}(b,N$

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$- k + 1$). In this case a probability $P_i(b)$ can also be defined

$$P_i(b) = q^{-1} \prod_{k=2}^{N} p_k(\nu_k|\nu_1,...,\nu_{k-1},b) \quad (6)$$

However, it should be pointed out that since for most steps the future SAWs are not taken into account for their entire length, not every SAW attempted with the approximate procedure can successfully be completed. Therefore, $P_i(b)$ is not normalized over the ensemble of all SAWs; i.e.

$$A = \sum_{\text{all SAWs}} P_i(b) < 1 \quad (7)$$

and a normalized probability $P_i'(b)$ is

$$P_i'(b) = P_i(b)/A \quad (8)$$

Also, in contrast to P_i (eq 5), $P_i(b)$ (and hence $P_i'(b)$) is not constant for all i but is larger for the compact SAWs than for the open ones. This can be deduced from the following argument: consider, for example, the 3-choice square lattice and $b = 1$. Obviously, for a very open SAW three future SAWs are allowed for most of the steps k, which means that the transition probability $p_k(\nu|\nu_1,...,\nu_{k-1},b) = {}^1/_3$. On the other hand, for a compact SAW, at many steps k one or two future SAWs are forbidden, i.e., the transition probability equals ${}^1/_2$ or 1, respectively, and the probability $P_i'(b)$ (eq 7 and 8) is therefore larger in this case than for an open SAW. Hence $P_i'(b)$ constitutes an increasing function of the compactness of the SAWs. In order to analyze this function in more detail, let us use r, the end-to-end distance of a SAW, as a measure of compactness. (Also, we denote by $\bar{r}$ the root-mean-square of r calculated with P_i.) The SAWs can be divided into three groups: (1) those with $r \sim \bar{r}$ (i.e., r can deviate from $\bar{r}$ by no more than one or two standard deviations, denoted ϵ), (2) the more open SAWs within $r > \bar{r} + \epsilon$, and (3) the more compact SAWs with $r < \bar{r} - \epsilon$. For large N the end-to-end distribution function based on P_i has a sharp peak close to $\bar{r}$ (see ref 19–21), which means that the majority of the SAWs (their number is denoted by n_1) belong to group, 1; i.e.

$$P_i n_1 \sim 1 \quad (9)$$

where $P_i = C_N^{-1}$. The other two groups are considerably smaller. Obviously, the normalization of $P_i'(b)$ requires that $P_i'(b) > P_i$ for the more compact SAWs of group 3 and that $P_i'(b) < P_i$ for the more open SAWs of group 2. We argue that $P_i'(b) < P_i$ also for the SAWs of group 1 and hence for the whole group 2. To show this, it should first be noticed that $\bar{r}'$, the root-mean-square end-to-end distance calculated with $P_i'(b)$, is smaller than $\bar{r}$ due to the larger probability of the compact SAWs (in fact for $b = 1$ and $N = 49$–399, $\bar{r}'$ has been found to be significantly smaller than $\bar{r}$; $\bar{r}' < \bar{r} - \epsilon$ for SAWs on both the square and the simple cubic lattices[22] (see also ref 24)). Second, it is reasonable to assume that the end-to-end distribution function, based on $P_i'(b)$, also has a sharp peak close to $\bar{r}'$, which means that

$$\sum{}' P_i'(b) \sim 1 \quad (10)$$

where $\sum'$ denotes summation over SAWs with r values close to $\bar{r}'$ (i.e., SAWs that belong to group 3). Obviously, the fact that the normalization condition for $P_i'(b)$ is approximately satisfied for the compact SAWs of group 3 (eq 10) requires that $P_i'(b) < P_i$ for the SAWs of group 1 (and hence of group 2). Otherwise, according to eq 9, the normalization of $P_i'(b)$ will be violated. This result, which has been derived on the basis of somewhat heuristic arguments, will be used in the next section to explain eq 15. It should be pointed out that $P_i'(b)$ is always approximate and therefore leads to biased statistical averages. Obviously, this bias can be decreased by improving the approximation, i.e., increasing b. Another way to remove this bias was suggested long ago by Rosenbluth and Rosenbluth[25] (for the case $b = 1$) and has also been used recently by the author.[18]

2.2. Method for Estimating the Entropy. First it should be pointed out that most simulation techniques[2-5] do not provide the *value* of the probability ($P_i = C_N^{-1}$) with which the SAWs are sampled; hence entropy (eq 1) is also unknown. In what follows we describe a method for estimating the value of P_i of SAWs generated with the direct MC procedure or with any other computer simulation technique. For that purpose let us assume that the SAWs have been *hypothetically* generated with the approximate procedure described above (section 2.1) rather than with the computer simulation method actually employed. Under this assumption one can reconstruct for each direction ν_k ($2 \le k \le N$) of SAW i the transition probability $p_k(\nu_k|\nu_1,...,\nu_{k-1},b)$ with which ν_k has been hypothetically determined, calculate $P_i(b)$ (eq 6), and thereby define three approximations for the entropy $S^A(b)$, $S'(b)$ and $S^B(b)$.

$$S^A(b) = -k_B \sum_{\text{all SAWs}} P_i \log P_i(b) = -k_B \sum P_i \log P_i'(b) - k_B \log A \quad (11)$$

$$S'(b) = -k_B \sum_{\text{all SAWs}} P_i'(b) \log P_i'(b) \quad (12)$$

$$S^B(b) = -k_B \sum_{\text{all SAWs}} P_i'(b) \log P_i(b) = S'(b) - k_B \log A \quad (13)$$

where $P_i'(b)$ and A are defined by eq 8 and $P_i = C_N^{-1}$. For $b \ll N$ the following inequalities hold:

$$S = -k_B \sum_{\text{all SAWs}} P_i \log P_i < -k_B \sum_{\text{all SAWs}} P_i \log P_i'(b) < S^A(b) \quad (14)$$

The first inequality stems from the result derived in section 2.1 that for most of the SAWs (i.e., those of groups 1 and 2), $P_i'(b)$ is smaller than P_i.[26] It should be pointed out that the contribution of the small group 3 (where $(P_i'(b) > P_i)$) to the second summation is negligible since $\log P_i'(b)$ does not vary significantly within this group, i.e., remains of order N. The second inequality results from eq 8 and 11. This means that $S^A(b)$ constitutes an upper bound for S, the correct entropy. From the principle of maximum entropy, we also obtain that $S'(b)$ (eq 12) is never larger than S

$$S'(b) \le S \quad (15)$$

Therefore, $S'(b)$ constitutes a lower bound for S. Another set of inequalities, based on eq 11 and 12–15 is the following:

$$S'(b) < S^B(b) < S^A(b) \quad (16)$$

In our previous work,[1] we suggested approximating S by $S^A(b)$. Indeed the results for $S^A(b)$ have always overestimated the true values. In the present work, we improved these estimates by calculating $S^M(b)$, the arithmetic average of $S^A(b)$ and $S^B(b)$

$$S^M(b) = [S^A(b) + S^B(b)]/2 \quad (17)$$

From inequalities 14–16 it turns out that $S^M(b)$ is always smaller than $S^A(b)$ and is bounded from below by $S'(b)$ (eq 12). $S^M(b)$ constitutes a better approximation for S than S^A, as long as $S - S^B < 2(S^A - S)$. This relation is satisfied in our calculations for the four models studied here but we are unable to prove that it is always valid. Obviously,

Table I
Entropy of Self-Avoiding Walks on a 3-Choice Square Lattice[a]

$N = 39$					$N = 49$				
L	b	S^M/Nk_B[b]	$S_{EV}{}^M/Nk_B$	$S_{EV}{}^A/Nk_B$	L	b	S^M/Nk_B	$S_{EV}{}^M/Nk_B$	$S_{EV}{}^A/Nk_B$
∞	1		0.094 (2)[e]	0.063 (1)	∞	1		0.100 (2)	0.0638 (4)
	4		0.0986 (3)	0.0959 (1)		4		0.1034 (5)	0.0994 (2)
	7	1.0068 (1)	0.0991 (1)	0.0986 (1)		7	1.0007 (3)	0.1038 (3)	0.1026 (1)
	DMC[c]	1.0066 (3)	0.0993 (3)	0.0993 (3)		DMC	1.0006 (3)	0.1038 (3)	0.1038 (3)
	series[d]	1.0068	0.0992	0.0992		series	1.0008	0.1037	0.1037
10	1		0.135 (5)	0.091 (1)	14	1		0.119 (2)	0.0797 (3)
	4		0.146 (2)	0.132 (1)		4		0.1250 (5)	0.1168 (3)
	7	0.960 (1)	0.146 (1)	0.1377 (2)		7	0.9778 (5)	0.1267 (5)	0.1212 (2)
	DMC	0.9605 (2)	0.1456 (2)	0.1456 (2)		DMC	0.9782 (3)	0.1263 (3)	0.1263 (3)

[a] N is the number of bonds in a walk, b defines our approximation, and L defines the size of the $(2L + 1) \times (2L + 1)$ box. [b] $S_{EV}{}^M$ (eq 23) and $S_{EV}{}^A$ (eq 24) denote the entropy due to excluded volume. S^M is the total entropy (eq 22). [c] DMC denotes results obtained with eq 1 and 3. [d] Series denotes the results obtained from a formula based on series expansion.[16,17] [e] The statistical error of the last digit appears in parentheses; e.g., 0.094 (2) = 0.094 ± 0.002. These errors have been calculated from two different MC runs with different random number sequences.

Table II
Entropy of Self-Avoiding Walks on a 5-Choice Simple Cubic Lattice[a]

$N = 39$					$N = 49$				
L	b	S^M/Nk_B	$S_{EV}{}^M/Nk_B$	$S_{EV}{}^A/Nk_B$	L	b	S^M/Nk_B	$S_{EV}{}^M/Nk_B$	$S_{EV}{}^A/Nk_B$
∞	1		0.051 (1)	0.0397 (2)	∞	1		0.054 (3)	0.0412 (3)
	4		0.05043 (4)	0.04991 (3)		4		0.0526 (2)	0.0519 (2)
	5	1.56371 (3)	0.05041 (3)	0.05015 (2)		5	1.5606 (1)	0.0526 (1)	0.0522 (1)
	DMC	1.5636 (4)	0.0506 (4)	0.0506 (4)		DMC	1.5603 (3)	0.0529 (3)	0.0529 (3)
	series	1.56382	0.05029	0.05029		series	1.5606	0.0525	0.0525
6	1		0.115 (5)	0.0777 (2)	7	1		0.102 (2)	0.0683 (3)
	4		0.1080 (5)	0.0974 (2)		4		0.0955 (6)	0.0857 (3)
	5	1.5067 (4)	0.1074 (4)	0.0995 (2)		5	1.5178 (5)	0.0953 (5)	0.0873 (3)
	DMC	1.5078 (3)	0.1063 (3)	0.1063		DMC	1.5181 (3)	0.0950 (3)	0.0950 (3)

[a] See explanations for Table I.

$S^M(b)$, $S^A(b)$, and $S^B(b)$ all approach S as the approximation is improved, i.e., with increasing b.

With the direct MC procedure SAWs are sampled with P_i, and therefore $S^A(b)$ can be estimated by $\bar{S}^A(b)$ from a sample of n SAWs

$$\bar{S}^A(b) = -n^{-1}k_B \sum_{t=1}^{n} \log P_{i(t)}(b) \tag{18}$$

where $i(t)$ is SAW i obtained at time t of the process. In order to estimate $S^B(b)$, one should first express it as a fraction of statistical averages with the probability P_i

$$S^B(b) = -k_B[\sum_{\text{all SAWs}} P_i P_i^{-1} P_i(b) \log P_i(b)] / \sum_{\text{all SAWs}} P_i P_i^{-1} P_i(b) \tag{19}$$

Since P_i is independent of i the factors P_i^{-1} cancel out and one obtains

$$S^B(b) = -k_B[\sum_{\text{all SAWs}} P_i P_i(b) \log P_i(b)] / \sum_{\text{all SAWs}} P_i P_i(b) \tag{20}$$

$S^B(b)$ and $S^M(b)$ can be estimated by $\bar{S}^B(b)$ and $\bar{S}^M(b)$, respectively (see derivation of eq 18)

$$\bar{S}^B(b) = -k_B[\sum_{t=1}^{n} P_{i(t)}(b) \log P_{i(t)}(b)] / \sum_{t=1}^{n} P_{i(t)}(b) \tag{21}$$

$$\bar{S}^M(b) = [\bar{S}^A(b) + \bar{S}^B(b)]/2 \tag{22}$$

It should be pointed out that the transition from eq 19 to eq 20 is incorrect for SAWs with finite attractive or repulsive interactions, where P_i is no longer constant. In that case, however, the entropy can still be estimated by $\bar{S}^A(b)$ as has been discussed in ref 1. The employment of $S^M(b)$ for estimating the entropy is therefore limited to macromolecules with hard-core potentials.

In this work we are mainly interested in $S_{EV}{}^M(b)$ and $S_{EV}{}^A(b)$, the contribution of the EV effect to the entropy (see eq 3)

$$S_{EV}{}^M(b) = S_I - S^M(b) \tag{23}$$

$$S_{EV}{}^A(b) = S_I - S^A(b) \tag{24}$$

3. Results and Discussion

The results for $S^M(b)$ (eq 22), $S_{EV}{}^M(b)$ (eq 23), and $S_{EV}{}^A(b)$ (eq 24) for SAWs on both a 3-choice square lattice and a 5-choice simple cubic lattice are summarized in Tables I and II, respectively. SAWs of length $N = 39$ and $N = 49$ have been generated with the direct MC procedure[2] and the results are averages of results obtained for two samples, each of size $W_N \sim 5000$ ($W_N = n$), constructed with different random number sequences. The chains are studied in unbounded space ($L = \infty$) and alternatively they are restricted to relatively small "boxes" of size $(2L + 1)^d$, where d is the dimensionality (i.e., the walls of the box are also excluded). The results are calculated for three values of b, which represent three approximations for the entropy. The number of walks started, W_0, ranges from 2.1×10^5 to 2.4×10^6 for the square lattice and from 3.6×10^4 to 5.4×10^5 for the simple cubic lattice. These values and the values for W_N enabled us to estimate the entropy also from the asymptotically exact expressions, eq 1 and 3; however, these results (denoted DMC in the tables) are subject to some statistical error due to the relatively small sample sizes employed. For the unbounded chains we also provide the series expansion estimates for the entropy obtained from the very accurate formula derived by Martin et al.[16] and Watts.[17]

Let us first discuss the results for the square lattice (Table I). For the unbounded chains ($L = \infty$) the results

for S_{EV}^{M} for the best approximation, $b = 7$, are equal to the series expansion results within the statistical errors 0.1% and 0.3% for $N = 39$ and $N = 49$, respectively. These results are significantly more accurate than those for S_{EV}^{A} (calculated also in ref 1), which (as expected; see section 2.2) underestimate the correct values by 0.6% and 1.1% for $N = 39$ and $N = 49$, respectively. The accuracy of the results for both S_{EV}^{M} and S_{EV}^{A} decreases with decreasing b. However, it should be pointed out that even for $b = 1$, the results for S_{EV}^{M} are still relatively accurate, deviating by ~5% from the series expansion values, as compared with the large deviation ~36% detected for the results for S_{EV}^{A}. This indicates that the present method might also be efficient for lattices with a large coordination number q, where employment of an approximation $b > 1$ is very time-consuming.

Confining the chain within the walls of a $(2L + 1) \times (2L + 1)$ box imposes additional long-range restrictions, which significantly affect the accuracy of S_{EV}^{A} but only slightly that of S_{EV}^{M}. The best results for S_{EV}^{A} underestimate the DMC values by 6% and 4%, whereas those for S_{EV}^{M} are equal to the DMC values within the statistical errors 0.7% and 0.4% for $N = 39$ and $N = 49$, respectively. In accordance with the unbounded case, for $b = 1$, the deviations of the S_{EV}^{M} values from the DMC estimates are significantly smaller than those observed for S_{EV}^{A}: 7.5% and 5.5%, as compared with 38% and 37% for $N = 39$ and $N = 49$, respectively. For the best approximation, $b = 7$, we also provide in the table the results for S^{M} (eq 22). These values are in much better agreement with the DMC values (deivations of 0.1–0.05%) than the results for S_{EV}^{M}, which follows trivially from the fact that S_{EV} constitutes only 10–12% of S_I (eq 2).

The results for the simple cubic lattice (Table II) show similar behavior to those of the square lattice; i.e., for all values of b the results for S_{EV}^{M} are significantly more accurate than the results for S_{EV}^{A}. Let us take, for example, the bounded chains for the best approximation $b = 5$. For $N = 39$, the result for S_{EV}^{M} is ~1% above the DMC value, whereas the result for S_{EV}^{A} is 6.6% below the DMC value. For $N = 49$, the DMC and the S_{EV}^{M} values are equal within the statistical error ~0.5%, whereas the result for S_{EV}^{A} deviates from the DMC value by ~8%. For the crudest approximation, $b = 1$, the difference in accuracy between the results for S_{EV}^{M} and S_{EV}^{A} is less dramatic than that detected for the square lattices, probably due to the significantly stronger EV effect in two than in three dimensions; for S_{EV}^{M}, we observe deviations of 9% and 7% from the DMC values as compared with 26% and 30% for S_{EV}^{A} for $N = 39$ and $N = 49$, respectively.

It should be pointed out that, as expected (see section 2.2), the results for S_{EV}^{A} always underestimate the correct entropy S_{EV}, in contrast to those of S_{EV}^{B} (not appearing in the tables), which in most cases overestimate S_{EV}. These two opposing effects are canceled out to a large extent in S_{EV}^{M}, which leads therefore to significantly more accurate values than both S_{EV}^{A} and S_{EV}^{B}. Better approximations for the entropy can be obtained by increasing the length b of the future SAWs. However, this will also increase the required computer time, which is mostly spent on calculating the hypothetical transition probabilities. The method can also be applied to off-lattice models. In this case, q becomes infinite, but one can approximate the continuum by a relatively small set of directions selected at random at each step.

4. Conclusions

A general method for estimating the entropy of macromolecules suggested recently has been further developed in this work for polymer chains with hard-core potential. The method has been applied to bounded and unbounded SAWs on square and simple cubic lattices, and very high accuracy (0.1–1%) for the entropy has been obtained. The results are significantly more accurate than results for the entropy obtained with the old version of the method (ref 1); in most cases the accuracy is improved by an order of magnitude. We have studied several approximations for the entropy and found that even the crudest one (with $b = 1$) has led to relatively accurate results (5–9%), which are significantly better than results obtained with the old version of the method (25–38%). This indicates that the improved method might be efficient for systems with many degrees of freedom, where employment of approximations with $b > 1$ are very time-consuming. We intend to extend the present method to more complicated systems such as branched polymers and simple continuum chain models with hard-core potential.[27,28]

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