Reconstruction of a first-order phase transition from computer simulations of individual phases and subphases

Martin Ebeling and Walter Nadler

Institut für Theoretische Chemie, Universität Tübingen, Auf der Morgenstelle 8, D-72076 Tübingen, Germany

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We present a method for investigating first-order phase transitions using Monte Carlo simulations. It relies on the multiple-histogram method and uses solely histograms of individual phases. In addition, we extend the method to include histograms of subphases. The free energy difference between phases, which is necessary for attributing the correct statistical weights to the histograms, is determined by a detour in control parameter space via auxiliary systems with short relaxation times. We apply this method to a recently introduced model for structure formation in polypeptides for which other methods fail.

At first-order phase transitions, Monte Carlo (MC) simulations encounter a particular problem of critical slowing down: since transitions between the coexisting phases are very rare, the relaxation time is extremely long and usually increases exponentially with system size. To obtain equilibrated data via MC simulations for a system of appreciable size near the transition, prohibitively long simulations would have to be performed.

A convenient way to visualize the problem, as well as to analyze simulation results, is to employ histograms. Since the Hamiltonian and most observables of interest are functions of one or a few order parameters, such as magnetization or internal energy, a histogram of the frequency of their occurrence, recorded during the simulation, is sufficient to generate all information of interest. Using the single- and the multiple-histogram method (SHM/MHM) [1], one or several histograms determined for a system at specific sets of control parameters can be used efficiently to predict the system behavior over a wide range of control parameter values. In such histograms the coexistence of phases corresponds to the coexistence of several peaks; see, e.g., Fig. 1. The infrequent switching between individual phases makes it difficult to generate a single equilibrated histogram covering all phases, i.e., showing all peaks correctly.

Most approaches to this problem introduce suitable changes to the system Hamiltonian so that transition states, which are encountered only rarely in the original system, will be sampled much more frequently in a simulation, thereby leading also to a higher frequency of switching between phases [2–5]. Common to all these methods is the idea that in a *single* simulation a histogram can be determined that covers all interesting regions of state space. A drawback is that possibly a plethora of parameters, which render the necessary changes in the system Hamiltonian, have to be optimized.

In this paper we want to present another approach to the problem. It is based on the realization that an equilibrated histogram of a system confined to an individual phase, i.e., an individual peak in the full histogram, can be generated much more easily. Under those conditions the relaxation times are usually small, at least much

smaller than the switching times between phases in the critical regime. For a first-order phase transition, these single-phase histograms already cover all relevant system states because, even at the critical point, transition states between the phases are encountered only very infrequently, and hence their contribution to the partition function is negligible. Several single-phase histograms can then be combined by the MHM to reconstruct the complete histograms at or near the first-order transition.

However, there is a technical problem involved: the relative contributions of various histograms, in effect the free energy differences between them, have to be determined. This is a notoriously difficult task. A prerequisite for their correct determination, e.g., by the acceptance ratio method (ARM) developed by Bennett in his definitive treatment of the subject [6], is that the histograms in question overlap at least partially. This is usually not the case, particularly not for systems with strong first-order transitions. To overcome this difficulty, we use a detour in control parameter space via auxiliary systems with much shorter relaxation times, which resemble the actual system to an extent sufficient to guarantee
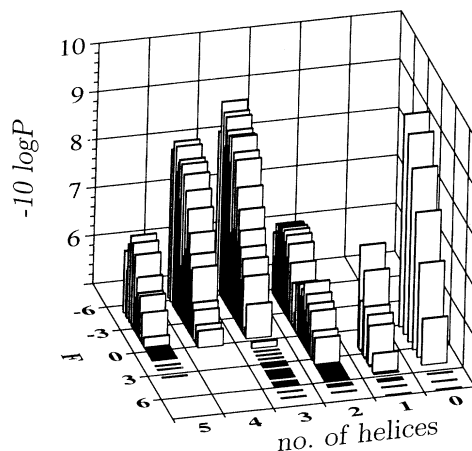

FIG. 1. Reconstructed histogram for $L=40$, $\beta|E_{HB}|=3.4$ (transition region), projected onto the (F, N_{hel}) plane.

significant overlaps between actual and auxiliary histograms [7]. We will apply this scheme to the temperature-driven first-order phase transition in a recently introduced simple model of secondary and tertiary structure formation in polypeptides [8], where the methods of Refs. [2–5] fail.

The conformation of a polypeptide of length L is represented by a string of local conformations $\sigma_i = h, c^+$, or c^0, $i = 1, \ldots, L$. The local conformation h corresponds to residues with dihedral angles characteristic of α helices. Any three successive monomers in helical conformation are spanned by a hydrogen bond (HB) with energy $E_{HB} < 0$. A string of l consecutive h residues $(l \geq 3)$ forms a helix of length l. The c^0 and c^+ residues denote random coil conformations. Two helices separated solely by c^0 residues are taken to interact with each other, whereas helices with at least one residue with conformation other than c^0 between them are not. The number of contacts between two interacting helices, which determines the interaction energy, is taken to be equal to the length of the shorter helix. We set the interaction energy parameter to $k = 0.6 \, E_{HB}$. Since the conformation space volume $\Omega(h)$ accessible to h residues is smaller than that for non-h residues, the conversion $c^+ \leftrightarrow h$, for example, is accompanied by a change in conformational entropy. We define $\Delta S(\sigma_i) = k_B \ln[\Omega(\sigma_i)/\Omega(c^+)]$ and assume equal statistical weights for the two random coil conformations, i.e., $\Delta S(c^0) = \Delta S(c^+) = 0$. The helix-coil transition in experimentally studied homo(poly)amino acids is adequately described by a value of $\Delta S(h)/k_B = -4.26 + \ln(2) \approx -3.57$, derived from experimental data first discussed by Zimm and Bragg [9].

Using the order parameter vector of a chain conformation $\{\sigma_i\}$, $\mathbf{S}(\{\sigma_i\}) = [N_{NB}(\{\sigma_i\}), N_h(\{\sigma_i\}), N_c(\{\sigma_i\})]$, where N_{HB}, N_h, and N_c denote the number of hydrogen bonds, h residues, and contacts, respectively, and the corresponding control parameter vector $\mathbf{K} = [\beta E_{HB}, -\Delta S(h), \beta k]$, with $\beta = (k_B T)^{-1}$, we obtain a free energy of the conformation $\{\sigma_i\}$,

$$\beta F(\{\sigma_i\}) = \mathbf{K} \cdot \mathbf{S}(\{\sigma_i\}) . \tag{1}$$

The role of F is equivalent to that of a Hamiltonian in other models.

This model has a coil-dominated high-temperature phase and a helix-dominated low-temperature phase. For $k \geq 0$ the low-temperature phase is a single helix spanning the whole system, and the change from coil to helix is not accompanied by a phase transition [10,11]. For $k < 0$, however, the low-temperature phase is multihelical, with neighboring helices stabilizing each other via tertiary interactions, and the transition between the coil and the multihelical phases is first order.

The multihelical phase consists of several subphases characterized by different numbers of helices. These subphases are separated from each other and from the coil phase by significant barriers in F, a feature that leads to long relaxation times at the transition point as well as to a slow, glasslike relaxation within the multihelical phase [8]. The existence of these subphases indicates that, in addition to the order parameters that enter the Hamiltonian, Eq. (1), the number of helices of a conformation $\{\sigma_i\}$, $N_{hel}(\{\sigma_i\})$, is an additional relevant order parameter; see also Fig. 1.

To investigate the behavior of this system at and around its phase transition point we generated order parameter histograms, $n_K(\mathbf{S})$, from MC simulations for parameter sets $\mathbf{K}$ corresponding to the coil and the multihelical phase for various values of L. For $L = 40$, additional simulations close to the phase transition point were performed for a check of the method. We provide the respective parameters and histogram properties for that length in Table I.

With the use of MHM [1], the relative probability to find the system at parameter set $\mathbf{K}$ in a state with order parameter $\mathbf{S}$, $P_K(\mathbf{S})$, can be approximated from histograms obtained at the parameter sets $\mathbf{K}_i$, $i = 1, \ldots, M$, by

$$P_K(\mathbf{S}) = \frac{\sum_{i=1}^{M} g_i^{-1} n_i(\mathbf{S}) \exp[-\mathbf{K} \cdot \mathbf{S}]}{\sum_{j=1}^{M} g_j^{-1} N_j \exp[-\mathbf{K}_j \cdot \mathbf{S} + f(\mathbf{K}_j)]} . \tag{2}$$

Here, $N_i = \sum_{\mathbf{S}} n_i(\mathbf{S})$, and $g_i = 1 + 2\tau_i$ renormalizes the size of the histogram to take correlation effects into account, with τ_i being the correlation time of the simulation i. By $f(\mathbf{K})$ we denote the free energy of the system at parameter set $\mathbf{K}$, $\exp[-f(\mathbf{K})] = Z(\mathbf{K}) = \sum_{\mathbf{S}} P_K(\mathbf{S})$, which is determined only up to an additive constant.

We have argued above that, using Eq. (2), histograms of the coil and the multihelical phase (histograms 1 and 3 of Table I) suffice to reconstruct the first-order phase transition. However, this requires the knowledge of the free energy difference between these histograms. Applying Bennett's ARM [6] to the model studied here leads to the equation

$$\Delta f_{ij} = \ln \frac{\langle \mathscr{F}[\mathbf{S} \cdot (\mathbf{K}_i - \mathbf{K}_j) + C] \rangle_i}{\langle \mathscr{F}[\mathbf{S} \cdot (\mathbf{K}_j - \mathbf{K}_i) - C] \rangle_j} + C , \tag{3}$$

TABLE I. Histograms, $L = 40$.

	β ($|E_{HB}|^{-1}$)	Size (10^6 MC steps)	Phase	Correlation time (MC steps)
		Histograms, $\Delta S(h)/k_B = -3.57$		
1	2.66	10	random coil	5
2	3.43	600	mixed	10^6
3	3.96	50	multihelical	330
		Auxiliary histograms, $\Delta S(h)/k_B = -0.57$		
1a	0.16	10	random coil	0.5
2a	1.16	50	mixed	30
3a	1.56	20	multihelical	12
		Subphase histograms, $\Delta S(h)/k_B = -3.57$		
3.2	3.96	5	$N_{hel} = 2$	22
3.3	3.96	5	$N_{hel} = 3$	15
3.4	3.96	5	$N_{hel} = 4$	10
3.5	3.96	5	$N_{hel} = 5$	10

where $\Delta f_{ij} = f(\mathbf{K}_i) - f(\mathbf{K}_j)$, and $C = \ln(Z_j N_i / Z_i N_j)$ has to be determined self-consistently. $\mathcal{F}(x) = 1/[1 + \exp(x)]$ is the Fermi function, and $\langle x \rangle_i$ denotes the average of x with respect to histogram i. To apply Eq. (3), the two histograms in question have to overlap at least partially, which is not the case for the single-phase histograms 1 and 3. Bennett has already pointed out the possibility of obtaining free energy differences for disjoint histograms by performing additional simulations for intermediate parameter sets so as to form an overlapping chain of histograms. However, a simulation near the critical point is not feasible in general.

In our model we can exploit the property that, by changing the parameter $\Delta S(h)$ to less negative values, systems are obtained that exhibit significantly shorter relaxation times and a more gradual transition. For such systems, equilibrated histograms can be generated for the separate phases *and* in the transition region (see Table I) at a much smaller expense of computation time than for the original system. With the use of such auxiliary histograms, a sequence of mutually overlapping histograms can be formed to join the single-phase histograms of the original system. This allows the determination of Δf_{31} between the disjoint histograms 1 and 3 of Table I by repeated application of Eq. (3), as illustrated in detail in Table II. For comparison, the value of Δf_{31} determined using histogram 2 of Table I as the intermediate histogram is also given in Table II. Both values agree closely. However, the expected error for the latter value is significantly larger because of the long relaxation time for the simulation near the critical point.

It was already noted that the multihelical phase is also characterized by long relaxation times, here due to infrequent switches between various coexisting *subphases* characterized by different helix numbers. These relaxation times become prohibitively long, particularly for systems with larger sizes (we have studied systems up to $L = 200$). With minor modifications, it is also possible to apply the principles we used to reconstruct the histogram at the phase transition for a reconstruction of histograms *within* the multihelical phase. Histograms for helical subphases with a constraint in helix number N_{hel} can be generated with much smaller computational effort than for the full histogram; see Table I. They are obtained simply by introducing an infinite energy barrier for all steps that attempt to change the helix number during the simulations.

TABLE II. Δf, $L = 40$, according to Eq. (3). Root mean square deviation (RMSD) according to Bennett [6].

Histograms	Δf	RMSD
1/2	-1.627	0.12
2/3	-22.886	33×10^{-2}
Σ:1/3	-24.513	0.12
1/1a	-9.501	5×10^{-3}
1a/2a	-3.828	5×10^{-4}
2a/3a	-14.742	4×10^{-4}
3a/3	3.569	2×10^{-3}
Σ:1/3	-24.502	5.4×10^{-3}

In direct analogy to the multiple-histogram equation, Eq. (2), it is possible to combine several subphase histograms $n_i^a(\mathbf{S})$ with identical helix number $N_{\text{hel}} = a$, obtained at various parameter sets $\mathbf{K}_i$, $i = 1, \ldots, M$. The relative probability *within this subphase* of a system state $\mathbf{S}$ (with $N_{\text{hel}} = a$), at parameter set $\mathbf{K}$, is approximated by

$$P_{\mathbf{K}}^a(\mathbf{S}) = \frac{\displaystyle\sum_{i=1}^{M} (g_i^a)^{-1} n_i^a(\mathbf{S}) \exp[-\mathbf{K} \cdot \mathbf{S}]}{\displaystyle\sum_{j=1}^{M} (g_j^a)^{-1} N_j^a \exp[-\mathbf{K}_j \cdot \mathbf{S} + f^a(\mathbf{K}_j)]} . \quad (4)$$

Here, the sum in the denominator ranges only over subphase histograms with $N_{\text{el}} = a$. We note that the free energies $f^a(\mathbf{K}_j)$ in Eq. (4) have now to be calculated with respect to subphase histograms with $N_{\text{hel}} = a$ only.

These subphases histograms can now be combined, again using ideas of the MHM. Following the arguments in Ref. [1], and using the property that the subphases fully partition the order parameter space into *disjoint* patches, one arrives at

$$P_{\mathbf{K}}(\mathbf{S}) = \sum_a p_{\mathbf{K}}^a P_{\mathbf{K}}^a(\mathbf{S}) \quad (5)$$

for the combined histogram. Given a full histogram of an auxiliary system at some convenient parameter value $\mathbf{K}'$, one obtains for the relative contribution of subphase a, $p_{\mathbf{K}}^a$ in Eq. (5),

$$p_{\mathbf{K}}^a = p_{\mathbf{K}'}^a \exp[f^a(\mathbf{K}) - f^a(\mathbf{K}')] , \quad (6)$$

where $p_{\mathbf{K}'}^a$ is given by $p_{\mathbf{K}'}^a = \sum_{\mathbf{S}} n_{\mathbf{K}'}^a(\mathbf{S}) / \sum_{\mathbf{S}} n_{\mathbf{K}'}(\mathbf{S})$.

Using the methods described we have investigated the first-order transition of our model. Contrary to other approaches [12], we choose the fluctuations of the specific energy $e = (N_{\text{HB}} E_{\text{HB}} + N_c k)/L$, i.e., $e_2 = \langle (e - \langle e \rangle)^2 \rangle$, as the observable to monitor the transition [13]. For first-order transitions the peak of this function assumes a finite nonzero value in the thermodynamic limit, which is given by $e_{2,\text{max}} = (\Delta e)^2/4$, where Δe is the specific latent heat. Figure 2 shows the behavior of e_2 for various values of the system size. For $L = 40$ the curves deriving from histogram 2, from the combination of histograms 1 and 3, and from 1 together with 3.2 to 3.5, respectively, all coin-
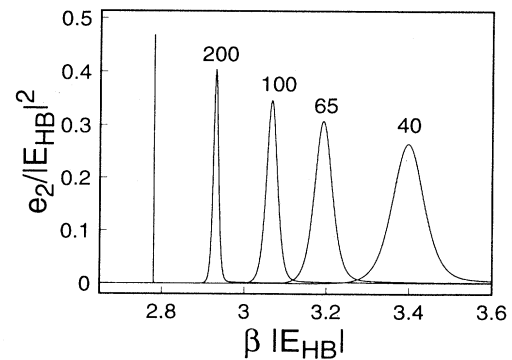

FIG. 2. Fluctuations in specific energy, $e_2 = \langle (e - \langle e \rangle)^2 \rangle$, vs β for L as indicated; also shown is the extrapolation for $L \to \infty$.

cide, thereby confirming our approach. For the longer systems, subphase histograms for the helical phase were used invariably. Included in the figure is the extrapolated function for infinite system size, corresponding to a latent heat of $\Delta e = 1.37 E_{HB}$ and a transition at $\beta = 2.78 E_{HB}$.

In closing, we will briefly discuss why other methods proposed for obtaining simulation results for first-order phase transitions fail in our system. Because of the high dimensionality of the order parameter space and the complicated phase structure (compare Fig. 1), the straightforward identification of a—possibly small number—of transition states in order parameter space, necessary for a successful application of the multicanonical method [2], is impossible. In addition, the states corresponding to the individual phases occupy only an extremely small part of the order parameter space. By raising the temperature, as in the entropic sampling [3] and simulated tempering [5] methods, not only the transition states but also an enormous number of "uninteresting" states would become accessible. To suppress these states at higher temperatures, a prohibitively large number of parameters (of the order of 10^6 for $L = 100$) would have to be optimized.

The microcanonical ensemble approach promoted by Hüller and co-workers [13,14] or cluster dynamics approaches [4,15] are also not applicable in our case.

We believe that the approach presented here offers possibilities for investigating model systems in parameter regimes where relaxation times are too long to allow equilibrated MC simulations, such as at strong first-order transitions or at glass transitions and within the glass phase. A prerequisite for the successful application of the method is the existence of a detour in control parameter space with a more gradual transition, i.e., much shorter relaxation times, so that the necessary free energy differences can be determined. To apply the subphase method, Eqs. (4) to (6), there has to be an order parameter set that allows one to identify subphases unambiguously.

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