How the All-Atom Simulation and the Ising-Based Theory Reconcile with Each Other on the Helix-Coil Transition

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Abstract. In this report, we addressed a somewhat basic question about how the two extreme models, the all-atom model and the Ising-based model, can be consistent with each other regarding the polypeptide helix-coil transition. Comparisons of several physical properties were made between the results of the all-atom simulations and those of the Ising-based theories. From the equilibrium point of view, the two models were found to exhibit a qualitatively similar trend, which is significant considering the extreme difference in precision between the two models. On the other hand, from the kinetic viewpoint, there appeared a difference in relaxation behavior between the two models; i.e., so-called stretched exponential relaxation was observed in the all-atom simulation whereas the kinetic Ising model showed simple exponential relaxation. A plausible source of the observed difference is briefly discussed.

Key words: Glauber dynamics, Helix-coil transition, Ising model, kinetics, molecular dynamics simulation, relaxation, statistical mechanics, stretched exponential

The helix-coil transition was one of the most active subjects in the early stage of biophysics and has been studied since late 1950s. Soon after the discovery of the reversible helix-coil transition exhibited by a polypeptide, a simple theoretical models based on the Ising model were proposed to describe the phenomenon both for equilibrium [1] and non-equilibrium regimes [2,3], and the Ising-based theories seem to have been working successfully as the framework of this phenomenon for 40 years. In contrast to the long history of the Ising-based theories, it is only recently that we were able to employ another theoretical model, i.e., the so-called all-atom model used in computer simulations. On reflection, the Ising-based model and the all-atom model represent the extremes in terms of model precision. Nonetheless they must represent the same phenomenon. Therefore a natural question arises concerning how well the Ising-based theory can account for the all-atom simulation. We directed our interest of this study to this somewhat basic yet unsettled question.

The system we studied here is the same as reported in the previous molecular dynamics (MD) study of the helix-coil transition [4]: 15-residue polyalanine chain represented by the all-atom model [5] following the Nosé-Hoover-chain dynamics (numerically integrated with 1 fs time-step) without interaction cutoff and explicit solvents. In the all-atom model, the state of each residue was classified into two, the helix and the coil states, according to whether or not the α -helical hydrogen bond was formed. The time course of the MD simulation provided both the equilibrium and the kinetic properties to be studied here. On the other hand, as the other extreme model, we employed the Zimm-Bragg (Z-B) model which is one of the most popular Ising-based models [6]. In the Z-B model, each residue is assumed to adopt two possible states (helix/coil), and only the nearest neighbor interaction is considered, hence any equilibrium property can be calculated only by two statistical factors called the growth factor s and the nucleation factor σ (chain length n is treated as constant in this study). As to the temporal evolution of the system, while the equation of motion is naturally presumed in the all-atom model, a transition rule must be somehow provided in the Ising model to make the system evolve. The transition rule proposed by Glauber [2] has been the basis of the kinetic study of the Ising model, and our kinetic study also conformed to the Glauber rule, by which the 11-spin Ising chain was allowed to make stochastic state transitions. Note that other transition rules proposed in the direct context of the helix-coil transition are essentially similar to the Glauber rule, but are far more entangled mathematically [3, 7–9]. In this way, from both perspectives of statistical mechanics and kinetics, the comparisons between the all-atom model and the Ising-based model were made.

We first investigate the characteristics of equilibrium helix-coil transition. In Figure 1a, temperature-dependent helix ratio is presented. The helix ratio resulting from the MD simulation demonstrated that the polypeptide underwent transition from the α -helix to the random-coil as temperature increased. The Z-B theoretical curve that best-fits the MD data is also provided in the figure (solid line). Obviously the best-fit curve coincided well with the MD data, indicating the capability of the Z-B model in representing the transition curve exhibited by a realistic polypeptide model. However, a sign of caution is also included in this figure concerning the reliability of the best-fit parameter. Besides the best-fit result ($\sigma = 0.01$), another Z-B fitting curve calculated under the condition of no nearest neighbor interaction (i.e., $\sigma = 1$) is included in Figure 1a. This alternative fitting curve yielded a relatively good fitting result, which implies that the obtained best-fit parameter is not robust because even a small data error would significantly affect it. The robustness of the resulting parameter sets is further discussed elsewhere utilizing the chi-square landscape [10]. While the helix ratio represents the first moment of equilibrium distribution, the specific heat shown in Figure 1b concerns the second moment of the distribution. As shown in Figure 1b, the specific heat showed a peak at about the transition temperature, and a good agreement between the two models was again recognizable. Note that the additional Z-B fitting curve calculated under

Figure 1. Helix ratio and specific heat as a function of temperature. Helix ratio is the fractional number of the helix-residues found in the chain. Specific heat was calculated using the mean square fluctuation of energy, and the base line was set at $(3N - 6) k_B$. Solid line represents the Z-B theoretical curve that best-fits the MD data. The Z-B theoretical values were evaluated numerically at each temperature of the MD data point, and then were subjected to the non-linear least-squares procedure using Levenburg-Marquardt algorithm (cf. Reference [10]). Dotted line represents an alternative Z-B fitting curve calculated under the constraint of no nearest neighbor interaction ($\sigma = 1$) for the purpose of comparison. Error bars are drawn at the 95% confidence level.

the constraint of $\sigma = 1$ (dotted line) corresponds to the Schottky-type specific heat and is more distinguishable from the best-fit curve ($\sigma = 0.05$) compared to the helix ratio case in Figure 1a.

Meanwhile, we just mention the helix-stabilizing factor that can be addressed only by the all-atom model. We focused on the electrostatic interaction and examined its influence on the helix stability by conducting further MD simulations using larger dielectric constants. In Figure 2, transition curves for three cases ($\epsilon = 2, 4, 8$) are presented. We first note that the MD data and the Z-B best-fit curve coincided well for each case, indicating the capability of the Z-B model again. The figure further shows that the helix stability was lowered as ϵ was enlarged hence the electrostatic interaction was weakened. Interestingly the transition temperature T_m decreased in the manner that $T_m(\epsilon) = c_1 \cdot \epsilon^{-1} + c_2$ where c_1 and c_2 are constants (see the inset). This relation can be rationalized assuming that $T_m \approx \Delta H / \Delta S$ and $\Delta H \approx \Delta H_e \cdot \epsilon^{-1} + \Delta H_{ne}$ where Δ means the difference between the helix and coil states and H_e and H_{ne} represent electrostatic and non-electrostatic enthalpy contributions at $\epsilon = 1$, respectively. Such a significant influence of the electrostatic interaction on the helix stability is understandable when we bring to mind that the electrostatic interaction plays an important role for the hydrogen bond formation. In explicit solvents, the electrostatic interaction was also found to be one of the dominant helix-stabilizing factors [11].

Figure 2. Dielectric-constant dependence of transition curves. Three series of MD simulations were performed using larger dielectric constants ($\epsilon = 2, 4, 8$). Solid line represents the Z-B theoretical curve that best-fits each MD data series. The top right inset shows dielectric-constant dependence of the transition temperature, T_m , at which helix ratio becomes one-half (horizontal broken line). For the fitting curve in the inset, refer to the text.

Figure 3. Temporal evolution of the helix ratio observed at about the transition temperature. A part of long-time trajectory is displayed as an example of dynamical helix-coil transition. (a) Molecular dynamics trajectory of the 15-residue polyalanine. (b) Monte Carlo trajectory of the 11-spin Ising chain to which the Glauber transition rule [2] was applied with the unit rate of k . Detailed conditions of the MC simulation will be presented elsewhere [14].

In contrast to the equilibrium helix-coil transition shown above, Figure 3 illustrates kinetic helix-coil transition that was observable in the time course of the system order parameter (helix ratio) at about the transition temperature. As shown in both Figures 3a and b, the chain exhibited a number of transitions between the mostly helix state and the mostly coil state, showing some amount of cooperativity [4]. Note that the time course of the Ising model was obtained by Monte Carlo

Figure 4. Auto-correlation functions calculated from the trajectories of the helix ratio. Notice that the vertical axes are in log-scale. (a) Auto-correlation for the all-atom model. The line represents the stretched exponential function, $\exp[-(t/\tau)^\beta]$, that best-fits the MD data with $\beta \approx 0.5$. (b) Auto-correlation for the Ising model. For comparison, auto-correlation of cyclic chain is included along with the rigorous analytical form, $\exp[-2(1-\gamma)kt]$, where $\gamma = (1-\sigma)/(1+\sigma) = 0.895$ [2, 13].

simulation using the Glauber transition rule [2]. To extract further characteristics from the time courses exhibited by the two models and to make a comparison between them, we analyzed the trajectories by means of the auto-correlation function as presented in Figure 4. Auto-correlation function is the time-domain counterpart of power-spectral-density function that was utilized in the previous study [4]. As shown in Figure 4a, the auto-correlation function of the all-atom model was roughly represented by a so-called stretched exponential function that is an empirical relaxation form frequently observed in protein relaxation dynamics [12]. This kind of auto-correlation with a long-time tail is consistent with the so-called $1/f$ type power-spectral-density function demonstrated in the previous study [4]. Contrasting with the stretched exponential auto-correlation observed in the all-atom model, the auto-correlation function of the Ising model presented in Figure 4b showed a simple exponential form. For the purpose of comparison, auto-correlation function for the cyclic chain case is also included in Figure 4b, where the rigorous solution is available [2]. (Rigorous solutions are available only for a few special cases [2, 13], and hence numerical approach becomes important.) The relaxation time for the cyclic chain is closely related to the above-mentioned nucleation parameter σ (see the figure caption). Comparison between the open and the cyclic chains shows that the end-effect only decreased the relaxation time, keeping the exponential form almost unchanged. It is important to note that the exponential relaxation of order parameter observed in the Ising model is not peculiar to the Glauber transition rule, but is common in other transition rule [9]. Thus, contrary

to the equilibrium case, the kinetic (or relaxation) characteristics were found to differ between the two models.

Following are some concluding remarks of this report. We showed that the all-atom model and the Ising-based model coincided with each other in respect to the equilibrium properties, even though a care was required about the reliability of the obtained best-fit parameters. Taking into account the extreme simplicity of the Ising-based model, the observed agreement is significant because it implies that the assumption made in the model is proven essential to describe the equilibrium helix-coil transition of a realistic polypeptide model. Of course, some quantitative differences, which were not taken up in this report, actually arose between the two models when we paid attention to the details [10]. With regards to the kinetic property, on the other hand, we showed a disagreement between the two models in their relaxation behaviors of the order parameter. This disagreement suggests that the Glauber transition rule is too simple to retain the anomalous kinetics exhibited by the all-atom model. In the realistic polypeptide model, it would be unreasonable to suppose that the state transition of a residue is determined only by the states of the nearest neighboring residues, as is assumed in the kinetic Ising models. The state transition of a residue in the realistic polypeptide model, instead, may be regarded as crossing over an energy-barrier the height of which is widely distributed. The distributed energy-barrier represents the situation where a single residue-state transition is composed of a variety of microscopic transitions going along different paths with different barrier heights, and is essentially the same idea as proposed in the protein relaxation dynamics studies [12]. Indeed, Monte Carlo simulation using a modified Glauber rule, with the distributed energy-barrier incorporated, was found to reproduce the relaxation behavior of the all-atom model. The study in this line will be reported elsewhere [14].

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