Modeling two-state cooperativity in protein folding

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Abstract

A protein model with the pairwise interaction energies varying as local environment changes, i.e., including some kinds of collective effect between the contacts, is proposed. Lattice Monte Carlo simulations on the thermodynamical characteristics and free energy profile show a well-defined two-state behavior and cooperativity of folding for such a model. As a comparison, related simulations for the usual Gō model, where the interaction energies are independent of the local conformations, are also made. Our results indicate that the evolution of interactions during the folding process plays an important role in the two-state cooperativity in protein folding.

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Due to the developments of experimental methods and theoretical models, many achievements of protein folding have been made recently [1]. A protein can fold itself to its uniquely well-defined native structure in a biologically short time, regardless of the huge number of possible conformations, showing a highly cooperatively kinetic behavior. It is now clear that the cooperativity of folding may result from the backbone hydrogen bonding, sidechain packing and hydrophobic interactions, among them the hydrophobic interactions are believed to be the dominant driving force for folding [2]. For many small single-domain proteins or lattice proteinlike models, there is a two-state behavior between the unfolded states and the folded native one [3,4]. Recently, Chan and Kaya [5] indicated that according to the calorimetric criterion, which is widely used in experiments as a condition for two-state folding, popular lattice models, e.g., two-letter HP and 20-letter MJ models, are far from two-state models. This may be due to some flawed assumptions in the potential functions used in these models. Lattice models usually use statistical potential functions extracted from the pairing frequencies of 20 kinds of amino acids in databases of protein structures [6]. Although these knowledge-based potentials may be a good approximation to the relative strength of interactions between the residues in the native state, they provide no information about how the interactions evolve during the folding. For computational convenience, a common assumption in lattice models is that the interactions are additive, and they are the same during the folding as in the native state. This means that the interaction energies are conformation-independent. Clearly this is not relevant to the experimental situation [7]. In fact, as Dill pointed out [8], the thermodynamic additivity principle which is widely used in chemistry may be unsuitable in biochemistry. Some recent experiments also indicated that the transition state is an expanded version of the native state, where the majority of interactions are partially formed [9], and their strengths are different from those in the native state (with $\Phi < 1$). That is, these interactions depend on the conformations [7], especially the local structures around the contacts as emphasized recently in Ref. [10]. Previously, the non-additivity was built in a lattice model for packing effects [11]; and the hydrophobic force depending on the local density of peptide atoms was also taken into account in an off-lattice
model [12]. Studies on these models show that the introduction of the non-additivity is significant, but the two-state cooperativity of these models is not checked, and the effects of the non-additivity on thermodynamics and kinetics of folding need to be further studied.

In this paper, we develop a refined Gō model where the pairwise interaction energies vary as the local environment changes, i.e., some kinds of collective effects between contacts are introduced. Our purpose here is to study the two-state cooperativity of protein folding and its physical origin with such a model. Our results give a general picture about how the conformation-dependent interactions affect the folding kinetics, which is consistent with the phenomenological explanation based on experimental results.

We model a polypeptide chain as a self-avoiding chain on a cubic lattice. A contact is formed if two residues are space adjacent but not sequence adjacent. If two residues form a contact as the same as in the native state, we call this contact a native contact, otherwise a non-native contact. Following the Gō model [13], only native contacts are considered to contribute to the total energy. Different from the Gō model, we assume that the interaction energies between residues are conformation-dependent, and vary with changes of the local environment. To achieve this, we introduce a parameter $S$ to describe the degree for a residue being ordered relative to the native state. For the $i$-th residue in a certain conformation, its degree of order $S_i$ is defined as

$$S_i = \frac{z_i}{z_i^{nat}},$$

where $z_i$ is the number of native contacts in this conformation, $z_i^{nat}$ is the number of contacts formed in the native state. Obviously, $S_i$ varies between 0 (the $i$-th residue being fully disordered) and 1 (being fully ordered). Thus, the interaction energy between residues $i$ and $j$, $B_{ij}=-(S_i+S_j)\varepsilon/2$ is defined, where $S_i$ and $S_j$ are the degrees of order for residues $i$ and $j$, respectively. $\varepsilon$ is the unit of energy and is set to be 1 in this work. The total energy of the conformation then is $E = \sum_{i<j} \Delta_{ij} B_{ij}$, where $\Delta$ is unity when residues $i$ and $j$ form a native contact, and zero otherwise. Here, a contact formed between residues $i$ and $j$ may have different energies in different conformations, i.e., $B_{ij}$ may change from one conformation to
another (for the Gō model, one always has $B_{ij} = -\varepsilon$). In general, a contact formed between residues $i$ and $j$ will stabilize, to some extent, other contacts that residue $i$ or $j$ formed with other residues. On the contrary, its breakage may destabilize those contacts as well. Therefore, the introduction of the degree of order for a residue into the potential function reflects the cooperativity between the residues. Although the correlation distance is small, only one lattice unit, the many-body effects are obviously included in our model. Figure 1 shows such a collective effect. The interaction energies of contact A-B (or B-C) are different when the other contact is present or not present. Clearly, the energy of state $I_3$ is lower than the sum of that of states $I_1$ and $I_2$, indicating the interaction non-additivity. Each contact is stabilized by the other contact due to the collective effect. Note that in this paper our model is called Gō+ model to distinguish from the Gō model.

Now let us present the Monte Carlo simulations on the thermodynamic and kinetic features for both models. The mean first passage time (MFPT), as a common measure of folding rate, is calculated by an average of the first passage time (FPT) over 1000 runs. Each run begins with a random conformation, and ends when the native state is reached for the first time. The FPT is the Monte Carlo steps (MCS) consumed in a run.

Generally, as the temperature $T$ decreases, the population of the native state, $P_N$, increases from zero to about unity. The degree of sharpness of changes in $P_N$, similar to the “rapidity” in Ref. [14], is a measure of the cooperativity of the folding reaction. Figure 2 shows the population $P_N$ and the specific heat $C_v$ versus temperature $T$ for a 36-mer chain for both models. $P_N$ is defined as $P_N = e^{-E_N/T} / \sum E \Omega(E)e^{-E/T}$, where $\Omega(E)$ is the density of states for energy $E$, $E_N$ is the energy of the native state. $\Omega(E)$ is calculated with the Monte Carlo histogram method [15]. From Fig.2 we can see that the folding transition for our Gō+ model is much sharper than that of the Gō model, i.e., a sharper change in $P_N$. There is also a single peak in $C_v$ curve, but it is narrower than that of the Gō model. For our Gō+ model, the maximum of $C_v$ occurs at a temperature nearly the midpoint temperature of transition with $P_N=1/2$, i.e., the difference between these two temperatures is quite small. This is consistent with recent studies on naturally occurring proteins [14,16], implying
a good cooperativity of folding in this model. Differently, such a temperature difference is
large for the Gō model (see Fig. 2), indicating that the folding of the Gō model is much less
cooperative than that of the Gō+ model. Since the sharpness is only a qualitative descrip-
tion for the transition, we further calculate the equilibrium energy distribution at the folding
transition temperature, $T_f$. Figure 3 shows such distributions for both models. Clearly our
Gō+ model shows a good bimodal behavior, and the denatured-state energy is distributed in
a narrow region [see Fig. 3(a)]. This means clearly a two-state folding and there is basically
no intermediate states at equilibrium. Differently, for the Gō model as shown in Fig. 3(b),
there are many intermediate states and the bimodal behavior is not so significant as that in
Fig. 3(a). Thus for the Gō model the folding is not of a two-state. This is in agreement with
Chan and Kaya’s argument [5].

In experiments, a well-established criterion for two-state folding is that the van’t Hoff
enthalpy $\Delta H_{vH}$ around the transition midpoint is equal, or very close, to the calorimetric
enthalpy $\Delta H_{cal}$ of the entire transition. In this work, we calculate the ratio $\Delta H_{vH}/\Delta H_{cal}$ as
suggested in Ref. [3] (here, the definition of $\Delta H_{vH}/\Delta H_{cal}$ is equal to $(k_2)^2$ in Ref. [3]), and
list the results in Table I. From Table I, we can clearly see the difference between the Gō
model and our Gō+ model. The Gō model, which is considered as a model with minimal
energetic frustrations, does not meet the calorimetric two-state criterion and gives out the
value of $\Delta H_{vH}/\Delta H_{cal}$ far from 1. Nevertheless, our model satisfies the criterion quite well
(for real proteins, the value of $\Delta H_{vH}/\Delta H_{cal}$ is 0.96±0.03 [17]). This, again, implies the
two-state folding and the good cooperativity of our Gō+ model.

Physically, the high cooperativity of our model may result from the narrow distribution of
the denatured states and the high population of the native state at the folding temperature
(see also Figs. 2 and 3). In our model, the energy spectrum relating to various conformations
is redistributed, comparing with that of the Gō model, due to the collective effect between
interactions. As a result, the energies of non-native conformations are moved to higher
energy levels and a larger energy gap is left between the non-native conformations and the
native one (for the two models, the energies of the native state are the same). The large
energy gap makes the native state particularly stable, which is believed to be a necessary condition for cooperative folding [18]. This may be the physical origin of the two-state cooperativity. It can be further explained from the viewpoint of the free energy profile. For our Gō+ model, as shown in Fig.4, the free energy profiles have broad activation barriers. The broad activation barriers can account for the large movement of transition state caused by mutation or temperature changes, and are considered as a common feature of the two-state folding [19]. Our numerical results are surprisingly consistent with a phenomenological speculation for the existence of such a free energy profile in Ref. [19]. It should be noted that the broad activation barriers are consistent with the narrow distribution of the denatured states.

Now let us make a comparison of the foldability based on the plots of the MFPT versus $P_N$ for both models. Note that we use $P_N$ instead of the commonly used temperature $T$ in the horizontal axis in Fig.5. This is because that an identical condition should be taken for the comparison. In lattice simulations, the temperature has an arbitrary unit and also has no direct relationship with the real temperature. The comparison between two different models at the same temperature may make no sense. Nevertheless, at an identical condition with the same $P_N$, the differences in the foldability can be well-defined. This is similar to other conditions used previously [20]. From Fig. 5, we can see that the MFPT for our Gō+ model shows a slow decrease as $P_N$ increases, it reaches a minimum at $P_N \approx 0.93$, and then it increases. For the Gō model, there is also a minimum but at $P_N \approx 0.71$. It is clearly that when the native state is stable (say, $P_N \geq 0.9$), our Gō+ model folds significantly fast, i.e., the MFPT is smaller with one or two orders of magnitude than that of the Gō model. Physically, this can be explained as follows. From Eq.(1) we can easily see that the energy gain of forming a contact is usually smaller for our Gō+ model than that for the Gō model. At high temperatures, entropic contribution is dominant to the free energy barrier, and the loss of entropy is always undercompensated by the energy gain, thus the Gō+ model folds slower for its smaller energy gain. Whereas at low temperatures, folding is nearly a downhill process, and the loss of entropy is always overcompensated by the energy gain.
Therefore, for the Gō+ model, it is easier to escape from kinetic traps, and the folding is faster. Finally, we note that for the two models the pathways of reaching the transition state from the denatured state are different. Due to the high cooperativity in our Gō+ model, a good core, the assembly of non-polar residues, is formed much earlier at low temperatures than that in the Gō model. Detailed kinetic results will be reported elsewhere. We also note that similar results are obtained for different chain sizes.

In conclusion, our Gō+ model, with many-body interactions depending on the local structures included, exhibits a good two-state folding behavior. Our results suggest that the evolution of interactions during the folding plays an important role in the two-state cooperativity in protein folding. We give a possible way how the interactions evolve in the folding, which may capture some essential features of the two-state folding. We expect further study could provide new insights into the mechanism of protein folding.

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REFERENCES

[1] K.A. Dill and H.S. Chan, Nat. Struct. Biol. 4, 10, (1997); D. Baker, Nature (London) 405, 39, (2000); W.A. Eaton et al., Annu. Rev. Biophys. Biomol. Struct. 29, 327, (2000); J.N. Onuchic, L.-S. Zaida, and P.G. Wolynes, Annu. Rev. Phys. Chem. 48, 525, (1997); C.M. Dobson and M. Karplus, Curr. Opin. Struct. Biol. 9, 92, (1999); J. Wang and W. Wang, Nat. Struct. Biol. 6, 1033, (1999).

[2] J.M. Sorenson and T. Head-Gordon, Fold. Des. 3, 523, (1998).

[3] S.E. Jackson, Fold. Des. 3, R81, (1998).

[4] H.S. Chan, S. Bromberg, and K.A. Dill, Phil. Trans. R. Soc. Lond. B 348, 61, (1995); D.K. Klimov and D. Thirumalai, Fold. Des. 3, 127, (1998);

[5] H.S. Chan, Proteins 40, 543, (2000); H. Kaya and H.S. Chan, Proteins 40, 637, (2000); H. Kaya and H.S. Chan, Phys. Rev. Lett. 85, 4823, (2000);

[6] S. Miyazawa and R.L. Jernigan, Macromolecules 18, 534, (1985); A. Koliski, A. Godzik, and J. Skolnick, J. Chem. Phys. 98, 7420, (1993).

[7] A.R. Fersht et al., Proc. Natl. Acad. Sci. USA 91, 10426, (1994); R.L. Baldwin, Nature (London) 369, 183, (1994).

[8] K.A. Dill, J. Biol. Chem. 272, 701, (1997).

[9] D.E. Otzen et al., Proc. Natl. Acad. Sci. USA 91, 10422, (1994); F. Chiti et al., Nat. Struct. Biol. 6, 1005, (1999); J.C. Martinez and L. Serrano, ibid. 6, 1010, (1999); D.S. Riddle et al., ibid. 6, 1016, (1999).

[10] J.R. Banavar and A. Maritan, Proteins 42, 433, (2001).

[11] C.J. Camacho and D. Thirumalai, Proc. Natl. Acad. Sci. USA 90, 6369, (1993).

[12] S. Takada, Z. Luthey-Schulten, and P.G. Wolynes, J. Chem. Phys. 110, 11616, (1999).
[13] N. Gō, Annu. Rev. Biophys. Bioeng. 12, 183, (1983).

[14] F. Cecconi et al., cond-matt/0101229.

[15] A.M. Ferrenberg and R.H. Swendsen, Phys. Rev. Lett. 63, 1195, (1989); N.D. Socci and J.N. Onuchic, J. Chem. Phys. 103, 4732, (1995).

[16] C. Micheletti et al., Phys. Rev. Lett. 82, 3372, (1999).

[17] P.L. Privalov, Adv. Protein Chem. 33, 167, (1979).

[18] A. Sali, E.I. Shakhnovich, and M. Karplus, Nature (London) 369, 248, (1994).

[19] M. Oliveberg et al., J. Mol. Biol. 277, 933, (1998); D.E. Otzen et al., Biochemistry 38, 6499, (1999); M. Oliveberg, Acc. Chem. Res. 31, 765, (1998).

[20] V.I. Abkevich, A.V. Gutin, and E.I. Shakhnovich, J. Mol. Biol. 252, 460, (1995); D.K. Klimov and D. Thirumalai, Proteins 26, 411, (1996).

[21] J. Lee, Phys. Rev. Lett. 71, 211, (1993); M.H. Hao and H.A. Scheraga, J. Phys. Chem. 98, 4940, (1994).
Table I: The ratios of $\Delta H_{vH} / \Delta H_{cal}$ for the Gō model and our Gō+ model, respectively. Ten sequences are calculated for each chain size.
FIG. 1: Schematic illustration of collective effect between two interactions. From a state $I_0$ with three unstructured residues, the chain can be settled in a state $I_1$ (or $I_2$) with a contact A-B (or B-C) and an equilibrium constant $K_1$ (or $K_2$). A state $I_3$ with two contacts A-B and B-C can be reached from state $I_1$ or $I_2$, but with different equilibrium constants $K_2\gamma$ or $K_1\gamma$. In state $I_3$, each interaction is stronger by a factor $\gamma$ due to the existence of the other contact.

FIG. 2: Population $P_N$ and specific heat $C_v$ varying with the temperature $T$ for a 36-mer chain.

FIG. 3: The energy distribution for the same 36-mer used in Fig.2, using (a) Gō+ potential and (b) Gō potential at respective folding transition temperature, $T_f$.

FIG. 4: The free energy profile $F(E) = E - TS(E)$ of our Gō+ model at different temperatures, where entropy $S(E)$ is calculated by using entropy sampling Monte Carlo method [21]. Here U, N and TS denote the unfolded state, native state and transition state, respectively. Note that the free energy profile at high temperature is overall shifted so that the unfolded states are overlapped.

FIG. 5: MFPT versus $P_N$ for a 36-mer chain.
Figure 1
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Figure 2
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Figure 3
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Figure 4
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Figure 5
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| Chain size | $\triangle H_{\text{str}}/\triangle H_{\text{cal}}$ Go model | $\triangle H_{\text{str}}/\triangle H_{\text{cal}}$ Go+ model |
|------------|----------------------------------------------------------|----------------------------------------------------------|
| 27-mer     | 0.62±0.01                                                | 0.91±0.01                                                |
| 36-mer     | 0.60±0.01                                                | 0.91±0.01                                                |
| 48-mer     | 0.74±0.01                                                | 0.95±0.01                                                |