Dynamic Properties of Protein-Like Heteropolymers: A Computer Simulation Study

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Summary: A simple model of a single polypeptide chain was used in the computer simulation. The units in a model polypeptide were located at α-carbons and embedded in a very flexible [310] lattice. The force field that mimics polymer-polymer and polymer-solvent interactions contained a long-range contact potential between the residues as well as local preferences in forming helical structures. The chain consisted of two types of residues: hydrophilic and hydrophobic. The classic Metropolis simulation algorithm was used. Monte Carlo simulations were carried out for helical sequences of residues and for various temperature conditions. It was shown that the formation of secondary structures in the chain under consideration had an influence on local short-time dynamic properties. The analysis of the autocorrelation functions enables one to identify the presence of secondary structures. The analysis of the formation of polymer-polymer and polymer-solvent contacts in ordered structures was also made.

Keywords: coil-to-globule transition; helical proteins; lattice models; Monte Carlo method; protein folding

Introduction

The structure of a polypeptide chain in solution has been a subject of intensive studies for many years.[1-2] The formation of secondary structures like α-helices and its stability in different solvent conditions is one of important problems here. It appeared that simplified and naive models could give an insight into the behavior of complex systems of biomolecules.[3-7] The introduction of a limited number of simple interaction potentials as well as a simplified sequence of a chain (primary structure) can help in answering the fundamental questions concerning the structure of globular proteins.[3,4] Even the simplest models of polypeptide chains cannot be solved analytically without making further simplified assumptions and, therefore, computer simulation seems to be a proper tool here. It was already shown that simulations of simple models without specific interactions could reproduce an "all-or-none" folding transition.[3,4,8] Here we present some initial data of simulation results concerning the dynamics of a model polypeptide chain.

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The Model and the Method

Amino acid residues in the model chain were represented by α-carbons only.[5] The chain was built on a flexible [310] lattice with a coordination number $z = 90$. A polypeptide chain can be constructed on this lattice with an accuracy of 0.6-0.7 Å with respect to real one, assuming that the lattice unit was chosen to be 1.22 Å. The chains under consideration consisted of two kinds of residues: hydrophilic (H) and hydrophilic (P). The chain was built of typical helical septets -HHPPHPP-.[3,4,9] Two kinds of interactions were introduced into the model. A pair of non-bonded amino acid residues interacted with a simple contact potential. This potential consisted of a short-distance repulsive part and long-distance V_{ij} part:

$$V_{ij} = \begin{cases} \varepsilon_{rep} \text{ for } r_{ij} < 3 \\ \varepsilon_a \text{ for } 3 \le r_{ij} \le 5 \end{cases} \quad (1)$$

where r_{ij} is a distance between a pair of non-bonded residues. Similarly to our previous works[4-6] we have chosen $\varepsilon_{rep} = 5$ in this model. The finite repulsion instead of commonly used infinite one was chosen in order to help the chain make some local rearrangements. The attractive part of the potential ε_a took values which were different for each type of a contact: $\varepsilon_{HH} = -2$, $\varepsilon_{PP} = -1$, $\varepsilon_{HP} = 0$ for a pair hydrophobic, hydrophobic-hydrophilic and a pair of hydrophilic residues, respectively.

It was previously shown[3] that long-distance attractive forces could not generate higher number of helical states. Hence, we introduced some local preferences in forming the helical states to the model. A helical state can be identified by a configuration of vectors connecting three consecutive residues ν_{i-1}, ν_i, ν_{i+1}:

$$r^{*2}_{i-1,i+2} = (\mathbf{v}_{i-1} + \mathbf{v}_i + \mathbf{v}_{i-1})^2 \cdot \text{sign}((\mathbf{v}_{i-1} \times \mathbf{v}_i) \cdot \mathbf{v}_{i+1}) \quad (2)$$

In this study the local potential ε_{loc} took values 0 and –8.[4]

The classic Metropolis simulation algorithm was used. In this algorithm the chain underwent a series of local micromodifications of its conformation.[3-4] These motions were: one-residue motion, two-residue motion and end reorientations. The new probe conformation of a chain was accepted according to the Metropolis criterion, i.e. with the probability proportional to its Boltzmann's factor. The model chain underwent an equilibrium annealing from temperatures corresponding to a random coil state transition to a dense packed globule. The temperature T is a factor that scales interaction potentials.

Results and Discussion

The analysis of contacts formed between a pair of residues (HH, HP and PP) can be made by means of contact maps, which represent the contacts present in the final conformation of a simulation trajectory.

Figures 1-3 present contacts maps for the chain with $N = 60$ residues at different temperatures and for different values of helical potential. One can observe in Fig. 1 that for a fully flexible chain ($\varepsilon_{loc} = 0$) at good solvent conditions ($T = 4$), the contacts are observed mainly along the chain contour. The contacts between the residues which are distant along the chain contour are rare. The annealing of this chain leads to a dense collapsed globule.[3,5] In such a globule, at temperature $T = 1$ (Fig. 2) the number of contacts between residues is considerably higher. One can also notice that the pattern partially resembles that characteristic of helical proteins. The contacts are predominantly of the HH type. The introduction of a strong local potential ($\varepsilon_{loc} = -8$) almost does not change the properties of the chain at high temperatures but the number of helical states is higher. But at temperature $T = 1$ the structure of the chain is quite different: the number of helical states approaches 80 %.[5]

One can observe in Fig. 3 that the pattern is more helical but the number of contacts is lower compared to the previous case. This can be explained by the fact that the presence of longer helices does not allow forming dense-packed structures, which blocks the proximity of large number of residues.[5] Fig. 4 presents the average frequency of contacts for the case shown in Fig. 3. A comparison of both maps implies that the helical structures are very unstable. This instability is apparently caused by the lack of specific interactions.[10]

The dynamic behavior of secondary structures can be studied by means of the autocorrelation functions.[4,6] We calculated the single bead autocorrelation function

$$g(\Delta t) = \left\langle [\mathbf{r}_i(t + \Delta t) - \mathbf{r}_i(t)]^2 \right\rangle \qquad (3)$$

where $\boldsymbol{r}_i$ are coordinates of the i^{th} polymer bead at times t and $t+\Delta t$.

Figures 5-7 present function g(t) versus the residue number i. At high temperature (Figure 5) the dynamics of the chain is Rouse-like. At low temperatures for the flexible chain ($\varepsilon_{loc} = 0$), the motion of the chain is highly hindered (Fig. 6). The parts of the chain that strongly interact (with high number of HH contacts) practically do not move (Fig. 7). The introduction of a strong helical potential ($\varepsilon_{loc} = -8$) also friezes parts of the chain because of the formation of secondary structures (helices).

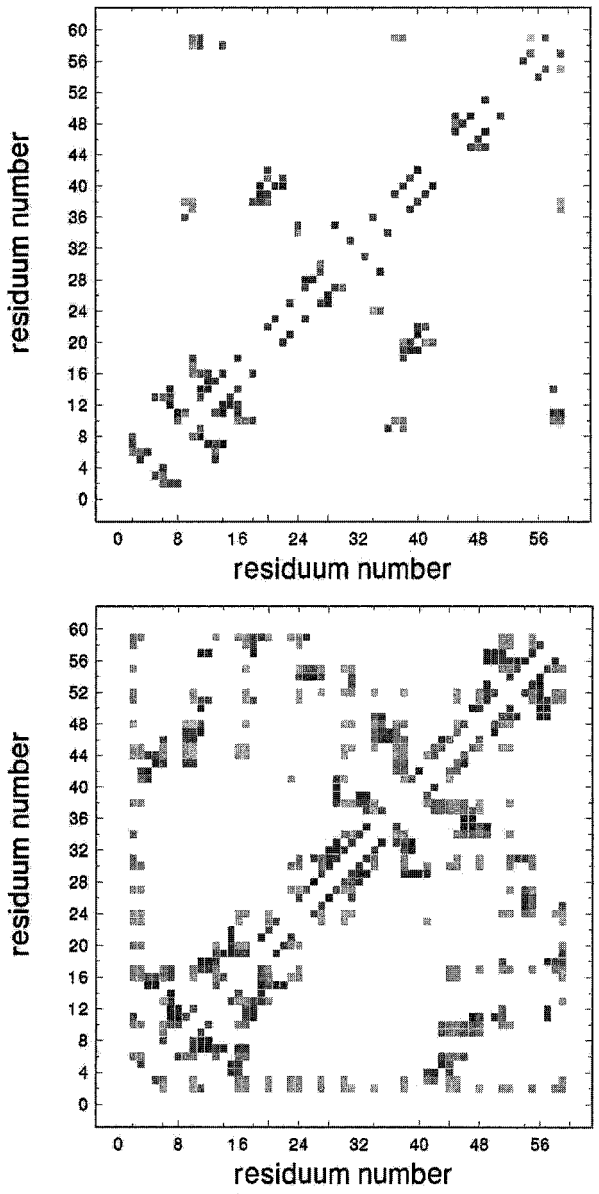

Fig. 1-2. Contact map of a chain with $N = 60$ residues with no local potential $\varepsilon_{loc} = 0$. The darkest squares correspond to PP contact, intermediate to HP contact and the lightest to HH contact respectively. Temperature $T = 4$ (top) and $T = 1$ (bottom).

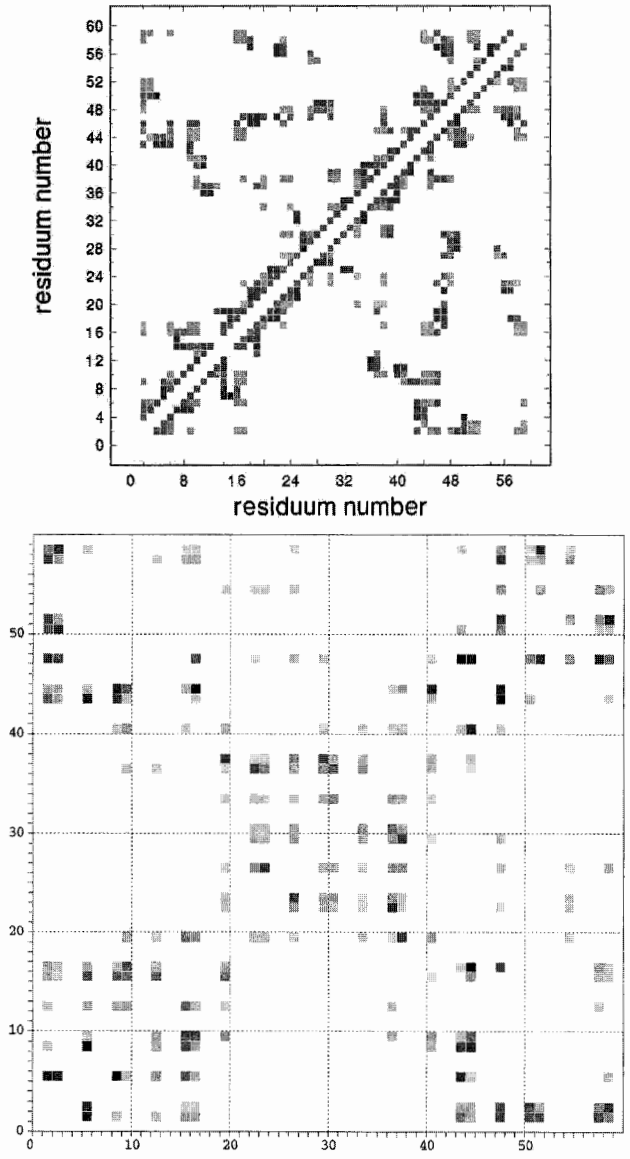

Fig. 3-4. Contact map of a chain with $N = 60$ residues with strong local potential $\varepsilon_{loc} = -8$ at temperature (see Fig.1-2) and $T = 1$ (bottom). The frequency of contacts (bottom). The intensity of gray is proportional to the lifetime of a contact.

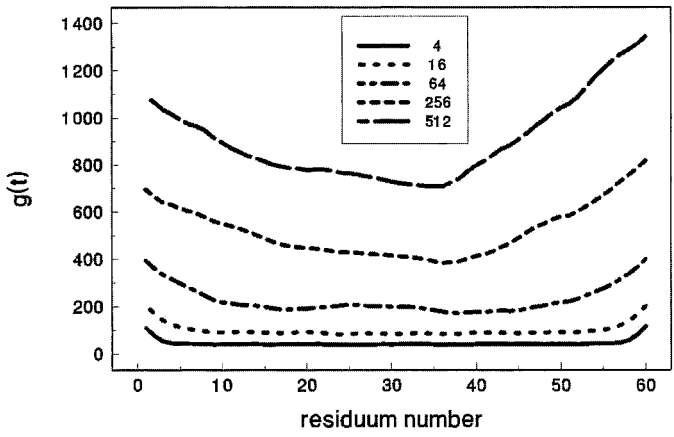

Fig. 5. Autocorrelation function of a single bead as a function of the residue number. The case of a chain with $N = 60$ residues at temperature $T = 4$ with no local potential $\varepsilon_{loc} = 0$. The numbers given in inset correspond to Δt in Eq.(3).

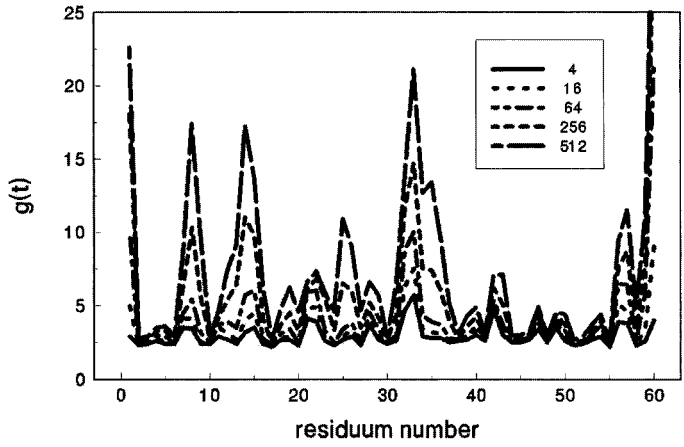

Fig. 6. Autocorrelation function of a single bead as a function of the residue number. The case of a chain with $N = 60$ residues at the temperature $T = 1$ with no local potential $\varepsilon_{loc} = 0$ (for the inset see Fig.5).

Figures 8-9 present final chain conformations that correspond to the contact maps discussed above. The secondary structures (helices) are emphasized in these figures by use the ribbon-type plot. One can notice that at low temperature long helices were formed while at high temperatures only few helical states can be observed. The positions of helices in the low-

temperature chain correspond to minima on the autocorrelation function plot (Fig.7), which means that the helical structures are less mobile. The main conclusion is that the analysis of the dynamics of the molecule can be used as an identification tool that shows the structure of the chain.

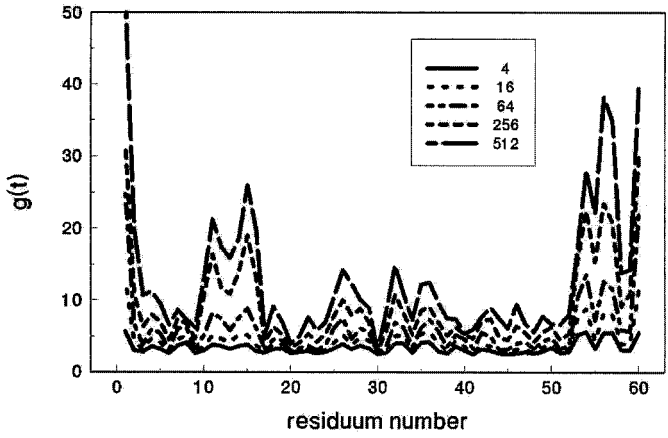

Fig. 7. Autocorrelation function of a single bead as a function of the residue number. The case of a chain with $N = 60$ residues at the temperature $T = 1$ with the local potential $\varepsilon_{loc} = -8$ (for the inset see Fig.5).

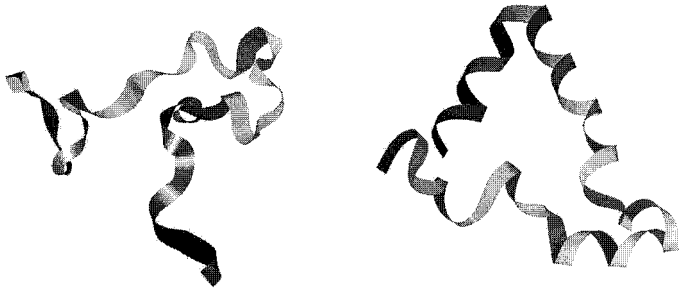

Fig. 8-9. A typical conformation of the chain with $N = 60$ residues and local potential $\varepsilon_{loc} = -8$. Temperature $T = 4$ (left) and $T = 1$ (right).

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