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A thermodynamic study of peptides binding to carbon nanotubes based on a hydrophobic-polar lattice model using Monte Carlo simulations

Y Cheng[1,2], G R Liu[2,3], Z R Li[3], C Lu[1] and D Mi[4]

[1] Institute of High Performance Computing (IHPC), Singapore 117528, Singapore
[2] Centre for Advanced Computations in Engineering Science (ACES), Department of Mechanical Engineering, National University of Singapore, 9 Engineering Drive 1, Singapore 117576, Singapore
[3] The Singapore-MIT Alliance (SMA), E4-04-10, 4 Engineering Drive 3, Singapore 117576, Singapore
[4] Department of Physics, Dalian Maritime University, Dalian 116026, People's Republic of China

E-mail: chengy@ihpc.a-star.edu.sg, mpeliugr@nus.edu.sg, smalzr@nus.edu.sg, luchun@ihpc.a-star.edu.sg and mid@newmail.dlmu.edu.cn

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Abstract

Carbon nanotubes (CNTs) are outstanding novel materials that have great potential for a variety of chemical and biomedical applications. However, the mechanism of their interactions with biomaterials is still not fully understood, and more insightful research work is needed. In this work, we use the 2D hydrophobic-polar lattice model and the Monte Carlo simulation method to study the interactions between model peptides and CNTs. The energy parameters of the coarse-grained lattice model are qualitatively determined based on experimental data and molecular dynamics simulation results. Our model is capable of reproducing the essential phenomena of peptides folding in bulk water and binding to CNTs, as well as providing new insights into the thermodynamics and conformational properties of peptides interacting with nanotubes. The results suggest that both the internal energy and the peptide conformational entropy contribute to the binding process. Upon binding to the CNTs, peptides generally unfold into their denatured structures before they reach the lowest-accessible energy states of the system. Temperature has a significant influence on the adsorption process.

(Some figures in this article are in colour only in the electronic version)

1. Introduction

The broad application of carbon nanotubes (CNTs) in biomedicine is hindered by their hydrophobic properties [1]. Therefore experimental efforts have been made by functionalizing CNTs with biological materials to make CNTs soluble or capable of being applied in various forms such as bio-sensors, gene and drug delivery [1–5]. As an alternative approach, simulations have been critical in revealing the properties that are not accessible to experiments [6]. In our earlier work [7, 8], we studied self-insertion of peptides into single-walled carbon nanotubes (SWCNTs) and binding of peptides to the outer surface of the SWCNTs using molecular dynamics (MD) simulations based on an atomic model. The energetic and conformational analysis suggested that the hydrophobicity of peptides was correlated with their affinities for CNTs, and the van der Waals interaction played a dominant role in the interactions between peptides and CNTs.

However, MD simulation of the all-atom models is currently only suitable for simulating folding behaviours of short peptides in a relatively short time scale (typically nanoseconds). Such an approach is not applicable to the study of the whole folding process which is typically in the order of microseconds to seconds. In order to characterize the properties of peptides binding to CNTs over a longer time scale, Monte Carlo (MC) simulation of a coarse-grained hydrophobic-polar (HP) lattice model is performed.

Despite its simplicity, the HP lattice model is capable of capturing the most essential mechanism of protein folding such as hydrophobic effect and multi-stage folding kinetics [9]. Furthermore, the full conformational spaces of protein folding can be enumerated exhaustively and insights into the nature of free energy landscapes can be obtained. Therefore the model has been successfully used to explore kinetics and thermodynamics of protein folding in bulk solvent [9–15] or adsorption of protein to various surfaces [16–18].

While the HP model is most intuitively defined in 3D to mimic the physical phenomenon of protein folding, it is arguable whether a 3D model is more realistic than a 2D model for current computationally feasible sizes. For example, in order to represent the appropriate surface-interior ratios of protein molecule, 16–20 monomers in two dimensions can reproduce a chain of 154 monomers in three dimensions [12]. The latter case is obviously beyond the scope of exact enumeration. A chain with 27 monomers is a feasible size in three dimensions, but unfortunately there is only one interior residue in a maximally compact conformation. Therefore the 2D lattice model is a feasible model while the exact enumeration of all the configurations is possible. It was also suggested that the ideal number of monomers for the 2D lattice model is about 16–20 [12].

In this paper, we extend the previous work to study the mechanism of peptides binding to CNTs using the HP lattice model and the MC simulation method. The exact enumeration of all the possible conformations of peptides has been carried out on 2D lattices with a chain length of 16 monomers. In order to simulate the peptide–CNT interactions, we introduce a model wall with an energetically favourable potential to monomers on the peptide. The hydrophobicity of the CNT is incorporated into the existing HP lattice paradigm and the interaction parameters between model peptide monomers and the CNT monomers can be qualitatively determined based on experimental data and MD simulation results. The model is validated by qualitatively agreeing with experimental observations and simulation results of the high-resolution model, and provides further insight that is crucial for the design of nanotube-based devices and drug delivery systems.

2. Methods

2.1. The all-atom model using the MD simulation method

In order to qualitatively develop the peptide–CNT interaction energy parameters of the HP lattice model, intensive MD simulations have been carried out. There are two major steps involved in the estimation of the binding free energy of each amino acid to the CNT. Firstly, we carry out MD simulations in explicit solvent to obtain the equilibrium structure of the amino acid, the CNT and the amino acid–CNT complex separately. Secondly, water molecules are removed from the equilibrated structure and the energy calculation is performed in implicit solvent using the molecular mechanics-generalized Born surface area (MM-GBSA) method. The binding free energy is then calculated as the energy difference between the complex and the individual systems. A more detailed description on the implementation of the free energy estimation is provided in [8].

2.1.1. MD simulations of the system in different states. The Amber 7 software package is used to perform MD calculations [19]. Simulations are carried out separately for single amino acid, the SWCNT and the amino acid-SWCNT complex. The initial structures of the amino acids and a (6, 6) type SWCNT are constructed using the LEAP model in the Amber 7 package. Initially the amino acid and the CNT are in direct contact with no water molecules between them to form a peptide–SWCNT complex. Each of the three objects is solvated in TIP3P explicit solvent [20] with periodic boundary conditions applied. These systems correspond to the bound and the unbound states.

The MD simulations are conducted as follows. A local minimum energy configuration is obtained by 20 000 cycles of the conjugate gradient energy method. The system is then equilibrated for 100 ps with constant volume and constant temperature (NVT) ensembles. This is followed by 400 ps of constant pressure and constant temperature (NPT) ensembles [21]. A time step of 1 fs is used for integration. Both the root mean square deviations (RMSDs) of the backbone atoms on the amino acids and the energetic fluctuation are traced to ensure the convergence of the MD simulation.

2.1.2. Calculations of binding free energy using the MM-GBSA method. Water molecules are removed from the final structures of each system in explicit solvent simulation. The MM-GBSA method [22] is then applied to calculate the binding free energy, for 10 ps of equilibration and 20 ps of data collection period. The GBSA method considers the solvent as continuum medium, and therefore the electrostatic contributions from solvent molecules are efficiently estimated.

As shown in equation (1), the binding free energy between an amino acid and a SWCNT is estimated by the difference between the absolute free energies of the complex in implicit solvent ($G^{s}_{complex}$), and that of the sum of the SWCNT (G^{s}_{cnt}), and the amino acid (G^{s}_{aa}) solvated in implicit water:

$$\Delta G = G^{s}_{complex} - (G^{s}_{cnt} + G^{s}_{aa}) \quad (1)$$

For each system representing the solvated molecules and the surrounding solvent, the free energy is calculated from the solute's gas-phased molecular mechanics energy E_{MM}, and the solvation-induced free energy G_{sol}, which is expressed as $G^{s} = E_{MM} + G_{sol} \cdot E_{MM}$ is computed as the sum of the internal energy $E_{internal}$, the van der Waals interaction energy E_{vdw} and the electrostatic energy E_{ele}. The internal energy includes the bond stretching potential E_{bond}, the angle bending energy E_{angle} and the torsion energy $E_{torsion}$, while the contribution of the solvation free energy, G_{sol}, takes into account both polar G_{pol} and nonpolar G_{nonpol} terms.

2.2. The HP lattice model using the MC method

2.2.1. The 2D HP lattice model for protein analysis. First proposed by Dill and Lau [9], the HP model is based on the assumption that the hydrophobic interaction is the dominant

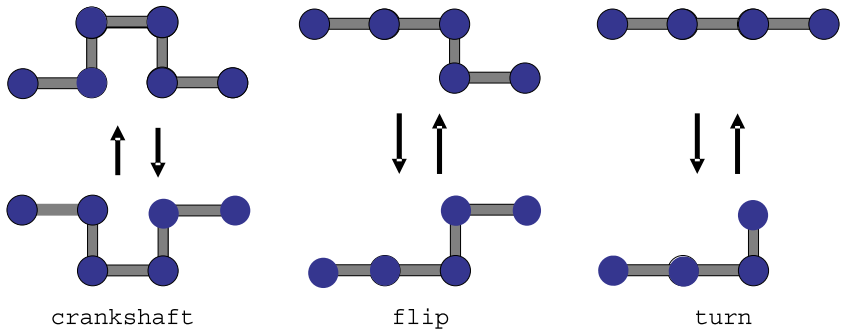

Figure 1. The Verdier–Stockmayer moves allowed for peptide conformational transition.

force in protein folding. Each monomer on the protein is represented by either of the two types, hydrophobic (H) or polar (P).

In a 2D lattice model, the structure of a protein is modelled as linked beads. Each protein chain contains N monomers which are connected through $N-1$ links. In this work $N = 16$ is adopted, which is an ideal length for studying the 2D HP lattice model [12]. The protein chain is placed on the nodes of a Cartesian coordinate grid. All connecting vectors move parallel to either the x- or the y-axis with a self-avoiding configuration. The lattice spaces which are not occupied by the chain monomers are assumed to be solvent units.

The presence of a CNT surface is introduced into the simulation by modelling a straight wall on the lattice space. Although the structure of the CNT is 3D, it is the inner surface or the outer surface of the SWCNT that acts as a most useful part when interacting with peptides. Each bead along the wall represents a segment of the CNT. We refer to such beads as type 'C'. The wall is regarded as a rigid boundary, where no monomer can go through it.

The potential energy of a lattice chain containing N monomers is defined as the sum of the interaction energies between all the contact pairs of the system. In the case of a peptide chain solvated in bulk water, the two elements which are adjacent in coordinate but not directly connected are defined as one contact pair. If both elements are hydrophobic, it is called a native contact. For each contact pair (i, j), a corresponding variable $\gamma_S(A_i, A_j)$ is counted to the interaction potential energy between the two monomers. The parameters $\gamma_S(H, H)$, $\gamma_S(H, P)$ and $\gamma_S(P, P)$ are determined according to the relative affinities between these element types. We adopt the energy parameters $\gamma_S(H, H) = -2\varepsilon$, $\gamma_S(H, P) = -\varepsilon$ and $\gamma_S(P, P) = 0$ in this model in which $\varepsilon > 0$ and 2ε is the free energy required to unfold one 'H–H' contact. The advantage of this set of parameters is that compact conformations of peptides in water can be obtained [13].

The interaction energies between the CNT and the peptide monomers are counted only when the monomers are in direct contact with type 'C' monomers. In other cases, the interaction energy is zero. The energy parameters $\gamma_S(H, C)$ and $\gamma_S(P, C)$ are discussed in section 3.2.2 based on both experimental and MD simulation results.

Therefore the total energy (E) of a system is calculated as $E = \sum_{(i,j)}^{N_K} \gamma_S(A_i, A_j)$, where N_k denotes the total number of contact pairs in a certain peptide structure, including those between pairs of monomers on the peptide and also monomers on the CNT.

2.2.2. MC simulations of peptide–CNT interactions. As shown in figure 1, the peptide undergoes three types of allowable Verdier–Stockmayer moves (crankshaft, flip and turn) [23]. The MC simulation of the lattice structures follows the Metropolis algorithm [24]. At each MC cycle, a single movement is randomly selected for a randomly chosen segment of the peptide, and the energy of the newly generated system is evaluated. If the energy of the new system is found to be equal to or less than that of the original conformation, the configuration is updated and a new cycle starts. If the new conformation results in an increase in system energy, the Boltzmann factor, $P = \mathrm{e}^{-\Delta E/k_\mathrm{B}T}$ is compared with a random number r generated between 0 and 1. The quantity k_B is the Boltzmann constant, with the dimensionless unit of $k_\mathrm{B} = 1$ and T is the temperature. $k_\mathrm{B}T$ has the same dimension as ε. If $P > r$, the new configuration is accepted; otherwise, the previous configuration is retained. This weighted method allows both energy-favourable and unfavourable movements to take place during the simulation.

2.2.3. Calculations of thermodynamics for peptide–CNT binding process. The thermodynamic quantities of the model peptides binding to CNTs are calculated using a canonical ensemble. The partition function of the system, Z, is expressed by means of sampling all the possible configurations of the peptide chain in each energy state:

$$Z = \sum_x \exp[-E(x)/k_\mathrm{B}T] = \sum_{E_i} \Omega(E_i) \exp(-E_i/k_\mathrm{B}T), \tag{2}$$

where $\Omega(E_i)$ is the density of states with energy E_i. In this case, E_i is determined by both the 'H–H' and 'H–P' interaction energy within the lattice chain and the neighbouring 'H–C' and 'P–C' interactions between the peptide monomers and the 'C' type monomers.

The probability (ρ_M) that the system is in its native (lowest-accessible energy) state E_M is expressed as

$$\rho_M(T) = \frac{\exp(-E_M/k_\mathrm{B}T)\Omega(E_M)}{Z}. \tag{3}$$

It should be noticed that the peptide may adopt several different conformations in the lowest-accessible energy state and this

energy state may be degenerated. The probability that the system is in the denatured (non-lowest energy) states is

$$\rho_U = 1 - \rho_M.$$

For a system at equilibrium, the ratio of probabilities ρ_M–ρ_U yields the equilibrium constant K_{MU}

$$K_{MU} = \frac{[U]}{[M]} = \frac{\rho_U}{\rho_M}, \tag{4}$$

where $[M]$ and $[U]$ are the concentrations of the systems, corresponding to the lowest and the non-lowest energy states, respectively. Furthermore, the free energy change can be calculated as

$$\Delta G_{MU} = G_U - G_M = -k_B T \ln K_{MU}. \tag{5}$$

The internal energy U is calculated as the ensemble averaged energy E

$$U = \langle E \rangle = \sum_i \rho_i(E_i) E_i, \tag{6}$$

where $\rho_i(E)$ is the probability that the energy of the system is E_i. Different energy states are enumerated and the corresponding probabilities are calculated through the partition function.

$$\rho_i(E_i) = \frac{\exp(-E_i/k_B T)\Omega(E_i)}{Z}. \tag{7}$$

The Helmholtz free energy of the system, A, could be calculated as $A = \langle A \rangle = -k_B T \ln Z$. Since the CNT surface is stationary, the conformational entropy of the model peptide is the entropy of the whole system, which is determined through the standard thermodynamic equation, $S = (U - A)/T$.

3. Results and discussion

3.1. Thermal unfolding of model peptide

In this section, the thermal unfolding behaviour of a randomly selected 16-monomer model peptide with the sequence HPPHHHPPHPPHHPPH is investigated. This model peptide (named peptide I) contains eight hydrophobic residues and can fold into a unique native conformation with seven 'H–H' contacts.

We simulate the thermal unfolding of peptide I at different temperatures over 5×10^6 iterations. Here the dimensionless temperature T^* is employed, which is in units of ε/k_B. It is observed that at low temperature, the most probable state for the peptide is its native state, while at high temperature, the denatured conformations are more populated. We can describe the denaturation in terms of the unfolding free energy change ΔG_{MU}. For example, as illustrated in table 1, at the temperature $T^* = 0.2$, the corresponding free energy change $\Delta G_{MU} = G_U - G_M \gg 0$, indicating a stable native structure. On the other hand, at the temperature $T^* = 1.6$, $\Delta G_{MU} < 0$, which shows that at higher temperature, the probability of finding the model peptide in the native state decreases drastically, and hence a denatured structure is preferred by the model peptide.

Table 1. Thermodynamic quantities of sequence I in bulk water at different temperatures. In the table T^* is the dimensionless temperature, U is the internal energy, ΔG_{MU} is the standard free energy change, S is the conformational entropy of the peptide, A is the Helmholtz free energy and ρ_M is the probability that the system lies in the lowest-accessible energy of the system. The energy unit is ε.

T^*	U (ε)	ΔG_{MU} (ε)	$T * S$ (ε)	A (ε)	ρ_M
0.2	−14.0	+∞	0.0	−14.0	1.00
0.8	−12.2	−0.3	3.9	−16.1	0.40
1.6	−6.2	−5.1	12.9	−19.1	0.04

In this simulation, the temperature acts as a thermodynamic property which controls the folding behaviour of the model peptide chain. The higher temperature induces the unfolding and therefore influences other macroscopic properties of the peptide. It is assumed that the Gibbs free energy difference between the native and the unfolded states is zero at the mid-transition temperature. For peptide I, at the temperature $T^* \approx 0.7$, $\rho_M \approx 0.5$ and $\Delta G_{MU} = 0$, we observe a phase transition state where the peptide exists both in the folded and the unfolded states. This temperature is often defined as the protein folding temperature [11]. We have tested the dynamic process of peptide folding in bulk solvent and binding to CNTs at varied temperatures, including those below and above the folding temperature.

3.2. Thermodynamics of peptides binding to CNTs

3.2.1. The MD simulation results and experimental proofs to determine energy parameters. The stability of both energetic and structural trajectories of the systems throughout the MD simulation in explicit solvent is analysed before the free energy is evaluated. The RMSDs of the backbone atoms of the amino acid and the standard deviations of the energies are recorded. We observe that the structures of the amino acids change without wild oscillation and the potential energies converge within the simulation time.

At the stage of free energy calculation using the MM-GBSA method, the average free energy and their standard deviations during the data collection period are provided in the appendix. The binding free energy ΔG reflects the free energy difference between the two defined states. The lower value of ΔG indicates that the residue has a stronger binding affinity for the CNT. The standard errors are also analysed to trace the stability of energy perturbation.

The calculation results indicate that the binding free energies vary with different amino acids. In order to qualitatively derive the interaction parameters for the HP model, the occurrence of each amino acid in proteins w_i [25] and their estimated free energy ΔG_i are utilized to evaluate the average binding free energy for both the hydrophobic group and the hydrophilic group.

According to the Kyte–Doolittle (K–D) hydropathy scale [26], each amino acid has been assigned a value indicating its relative hydrophilicity and hydrophobicity. We classify the 20 amino acids into two groups based on this scale. The amino acids with positive values (including ILE, VAL, LEU, PHE, CYS, MET, ALA) are considered

hydrophobic (H) and the others with negative values are classified into hydrophilic (P) groups. For the hydrophobic group, the average binding free energy is

$$\overline{\Delta G}_H = \sum_1^{n_h} \Delta G_i w_i \Big/ \sum_1^{n_h} w_i = -5.63\,\mathrm{kcal\,mol^{-1}},$$

and $\overline{\Delta G}_P = \sum_1^{n_p} \Delta G_i w_i / \sum_1^{n_p} w_i = -3.97\,\mathrm{kcal\,mol^{-1}}$ for the hydrophilic group, where $n_h = 7$ and $n_p = 13$ and the values of w_i are extracted from [25].

These results imply that both hydrophobic and hydrophilic amino acids have affinities for CNTs and generally the binding of hydrophobic amino acid is stronger. In addition, experimental studies have shown that both hydrophobic and hydrophilic peptides may spontaneously bind to CNTs while hydrophobic peptides indeed have stronger affinities for CNTs than hydrophilic ones [4]. Therefore, our MD simulation results are also consistent with experimental results.

3.2.2. The selection criteria for the interaction energy parameters and the binding mechanism. Based on the experimental observations and the energetic analysis of the atomic model, we qualitatively develop the interaction energy parameters for the HP lattice model according to the following assumptions: the binding affinity of CNTs for hydrophobic residues should be stronger than for hydrophilic ones, which implies $\gamma_S(H, C) < \gamma_S(P, C)$. In addition, both hydrophobic and hydrophilic amino acids have affinities for CNTs, which implies that $\gamma_S(P, C) < 0$ and $\gamma_S(H, C) < 0$.

Based on relative values of $\gamma_S(H, H) = -2\varepsilon$, $\gamma_S(H, P) = -\varepsilon$ and $\gamma_S(P, P) = 0$, several parameter sets may be acceptable if they satisfy the criteria. We repeat the simulations of representative peptide binding to the CNT using the same setups and experimental conditions except for the interaction parameters. Although the average system energy and the accessible structures of the peptide are parameter dependent, the binding mechanisms are qualitatively the same for these acceptable parameter sets. The thermodynamic quantities of peptide I binding to the CNT using preliminary parameters at representative temperatures over 5×10^6 MC runs are listed in table 2.

As shown in table 2, both the internal energy and the peptide conformational entropy contribute to the Helmholtz energy. The internal energy is composed of two terms: the intra-molecular interaction within the peptide and the peptide–CNT interaction. The selection of the parameters affects not only the absolute value of internal energy, but also the balance between the internal energy and the entropy. For example, at $T^* = 1.6$, the contribution of the internal energy U is -39.4ε, when $\gamma_S(H, C) = -4\varepsilon$ and $\gamma_S(P, C) = -3\varepsilon$. As the parameters are set as $\gamma_S(H, C) = -5\varepsilon$, $\gamma_S(P, C) = -4\varepsilon$, U decreases to -51.7ε. The ratio of U to the Helmholtz free energy also enlarges.

Such an observation is reasonable because if both 'H' and 'P' types of elements have a strong affinity for the CNT, the intra-molecular interaction, which stabilizes the compact structure of the peptide, becomes relatively weak. The strong binding affinity of the peptide to the CNT induces the conformational change of the peptide. Both the internal energy and the entropy would then be affected by this strength of affinity.

Table 2. Thermodynamic properties of sequence I binding to the CNT using different parameters at $T^* = 1.6$. In the table E_M is the lowest-accessible potential energy, other parameters can be referred to in table 1.

$\gamma_S(H, C)$ $\gamma_S(P, C)$ (ε)	E_M (ε)	U (ε)	ΔG_{MU} (ε)	T^*S (ε)	A (ε)	ρ_M
$-4, -3$	-42.0	-39.4	0.3	3.6	-43.0	0.54
$-5, -4$	-53.0	-51.7	1.5	1.8	-53.5	0.72

In addition to the parameters listed in table 2, we have also taken into account other values of $\gamma_S(H, C)$ and $\gamma_S(P, C)$. If the interaction between 'H–C' and 'P–C' types of monomers is considered weak, for example $\gamma_S(H, C) = -2\varepsilon$, $\gamma_S(P, C) = -\varepsilon$, or $\gamma_S(H, C) = -\varepsilon$, $\gamma_S(P, C) = 0$, the entire peptide weakly binds to the surface of the CNT. Such an observation is not consistent with the experimental and MD simulation results. Therefore we do not list the data for discussion. It may be inferred that choosing $\gamma_S(H, C) < \gamma_S(H, H)$ is also essential.

3.2.3. Conformational changes of peptide chain binding to CNT surface. Based on the developed parameters, the conformational changes of peptides upon binding are simulated and captured. In order to make the discussion more general, we introduce the second model peptide, namely peptide II. Compared with peptide I, peptide II possesses more hydrophilic monomers, and has no unique native structure.

At the beginning of each simulation, the model peptide is positioned partly in contact with the model CNT in their compact conformation, as shown in figure 2(*a*). The vertical line on the left side of the model peptide represents the CNT surface.

A typical binding process is discussed on peptide I with preliminary parameters of $\gamma_S(H, C) = -5\varepsilon$, $\gamma_S(P, C) = -4\varepsilon$. Since the local energy barriers can be against the attempts that the chain unfolds into conformational trajectories leading to the lowest-accessible energy, the model peptide binds reversibly at energies well above the energy minimum at an early stage of the binding process.

At a later stage of the adsorption, the chain is irreversibly bound to the surface, at least within the duration of the simulation. As shown in figure 2(*b*), it is found that the peptide unfolds at the interface, and the adsorption is essentially irreversible. Some native contacts may also be retained due to the internal attractions between peptide residues. The similar configuration at equilibrium was also observed through the MD simulations of the atomic model [8]. The corresponding system potential energy decreases to a lower average value, and fluctuates between low energy states.

The conformational change of peptide I is further illustrated in figure 3. The number of monomers in the first and the fourth layers adjacent to the CNT surface is plotted against the MC simulation cycles. In the first layer, the number of

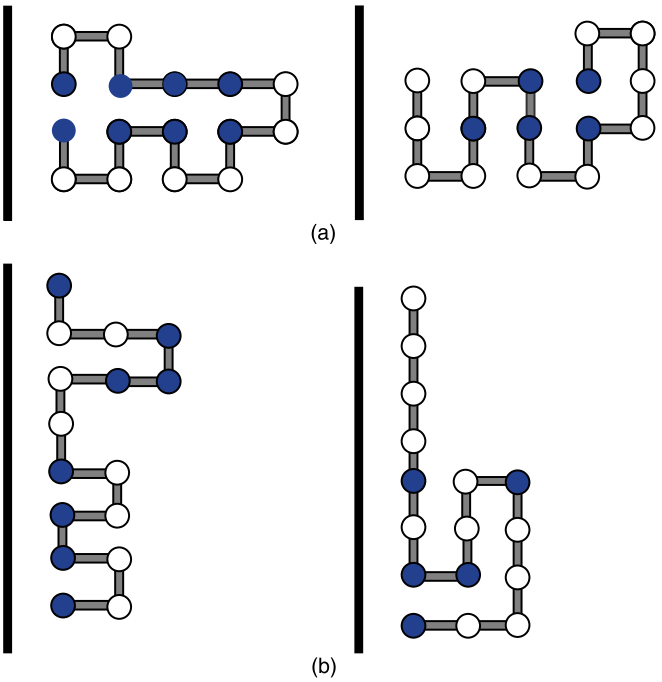

Figure 2. (*a*) Initial structures of peptide sequence I (left) and sequence II (right) interacting with the model CNT surface. Peptide sequence I has eight hydrophobic residues and sequence II possesses five. The filled cycles represent hydrophobic monomers while unfilled ones represent the polar elements. (*b*) Representative conformations of sequence I (left) and sequence II (right) binding to CNT surface at $T^* = 1.6$. The peptide–CNT interaction energy parameters are $\gamma_S(H, C) = -5\varepsilon$ and $\gamma_S(P, C) = -4\varepsilon$.

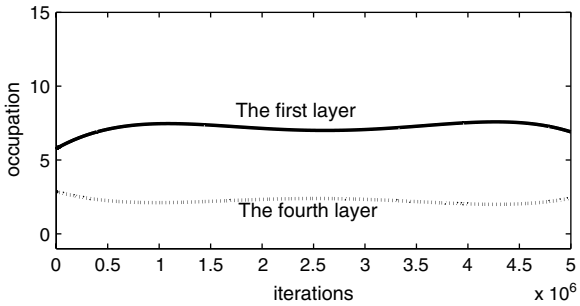

Figure 3. Averaged number of monomers in the first and the fourth layers adjacent to the CNT surface against the MC cycles for peptide I at $T^* = 1.6$ (fitted using fourth order polynomials).

monomers on the peptide increases drastically, indicating the adsorption of the peptide. In contrast, in the layers which are farther away from the wall, for example, the fourth one, the number of monomers decreases, and the denaturation of the peptide is observed. It is also observed that the average number of hydrophobic contacts for peptide I in bulk water is more than that of the peptide binding to the CNT surface at the same temperature, indicating a change of peptide properties upon binding.

Temperature is a crucial factor that affects the behaviour of peptides binding to CNTs. For example, at $T^* = 0.8$, peptide I is trapped at its local minimum over the course of MC simulation. The monomer numbers in the first and the fourth layers do not change significantly at $T^* = 0.8$, showing that the peptide largely maintains its initial conformation at low temperature, and the binding is reversible. On the other hand, at $T^* = 1.6$, the peptide is found denatured and bound to the CNT irreversibly. Further investigations reveal that the lowest-accessible energy state for peptide I is $E_M = -32.0\varepsilon$ at $T^* = 0.8$, but $E_M = -53.0\varepsilon$ at $T^* = 1.6$. Increasing the temperature may facilitate the adoption of previously inaccessible low energy states of the peptide–CNT system.

4. Concluding remarks

In this work, the coarse-grained HP lattice model is employed to study the interaction between peptides and CNTs. Using the dynamic MC simulations, this HP lattice model can reproduce the dynamic behaviours of peptides folding in bulk water, as well as peptides binding to the CNT surface.

The interaction parameters between the CNT monomers and two types of monomers on the model peptide are developed based on the relevant experimental data and MD simulation results. To the best of our knowledge, this is the first time that such a set of preliminary parameters has been developed to study peptides binding to the CNT. The simulation results imply that the suggested parameters here are acceptable and can qualitatively reflect the mechanisms of the binding process.

Since all the possible configurations of the system are enumerated, thermodynamics and conformational change of peptides binding to CNTs can be explored. The analysis of the thermodynamic quantities suggests that both the internal energy and the peptide conformational entropy contribute to the binding process. Upon binding to the CNT, peptides generally unfold into their denatured states to reach the low energy states of the system. In order to access the low energy levels, the peptide has to escape from local energy minima and the average number of native contacts may decrease. Temperature has a significant influence on the behaviour of the peptide binding to the CNT. The model developed in this paper elucidates the interaction mechanism between peptides and CNTs.

The simple models used in this paper are low-resolution representations of peptides and nanotubes. The coarse-grained HP lattice model mainly concerns the most important driving force of protein folding—the hydrophobic interactions; it does not always reflect the specific real proteins. Therefore, although the simple model here can address the general features of peptides binding to CNTs, it could not provide the particular descriptions of the corresponding processes, such as the atomic detail and the geometric accuracy. In this way, the conclusions from our work are only approximate, qualitative and revelatory. Further work will be undertaken to study the coarse-grained model using more complicated monomer alphabets and more detailed contact energies [27].

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Table A1. Binding free energies and the standard deviations estimated using the MM–GBSA method.

Amino acid	The amino-acid SWCNT complex ($G^s_{complex}$)		Amino acid (G^s_{aa})		
	Mean	Std dev	Mean	Std dev	ΔG
Ile	1584.591	8.2012	−62.4168	1.7384	−6.5813
Val	1559.739	9.7484	−89.0848	1.7052	−4.7658
Leu	1565.049	10.427	−81.4391	1.8871	−7.1018
Phe	1598.538	8.5823	−48.4989	1.7332	−6.5523
Cys	1596.942	9.0752	−53.5529	1.429	−3.0945
Met	1586.07	9.1196	−59.2105	1.9881	−8.3093
Ala	1596.049	8.4567	−54.1631	1.7447	−3.3771
Gly	1573.276	10.1111	−76.9428	1.0023	−3.3711
Thr	1552.899	9.1481	−97.6639	2.1033	−3.0267
Ser	1570.769	8.7619	−80.4642	1.4295	−2.3565
Trp	1601.97	9.2565	−43.6792	2.9699	−7.9406
Tyr	1571.817	9.3792	−75.6519	1.8876	−6.1211
Pro	1594.68	8.6813	−55.662	1.8604	−3.2473
His	1605.269	9.9353	−42.3449	2.2036	−5.9758
Glu	1623.309	8.8987	−25.4096	1.9013	−4.8712
Asn	1515.04	7.7544	−133.307	1.5842	−5.243
Gln	1536.462	8.6544	−114.396	1.9972	−2.7319
Asp	1613.098	10.0269	−34.2139	1.5893	−6.2779
Lys	1570.113	10.2352	−81.9991	2.2068	−1.4772
Arg	1400.151	8.9225	−248.73	2.5351	−4.7084

Appendix

Binding free energies and the standard deviations estimated using the MM–GBSA method are listed in table A1. The energy unit in this table is kcal mol^{-1}. The free energy of the SWCNT for all the twenty systems is $G^s_{cnt} = 1653.5895$ kcal mol^{-1} and the standard deviation is 8.7468 kcal mol^{-1}. The binding free energy is estimated as $\Delta G = G^s_{complex} - (G^s_{cnt} + G^s_{aa})$. The lower value of ΔG correlates with a stronger binding affinity.

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