Molecular Dynamics Simulation of the Bio-adhesion in Molecular Motors

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Abstract—**Molecular dynamics (MD) simulation is employed to study the bio-adhesion in F1 ATP molecular motor. Histidine-peptide is widely used as linkage in micro systems because of its strong binding strength to metals. This paper focuses on the adhesion between a synthetic peptide containing 6×His-tag (Gly-Gly-Lys-Gly-Gly-Lys-Gly-Gly-His-His-His-His-His-His) and metal substrate, which is used to define the position of the F1 ATP molecular motor on the metal substrate. It is shown that the binding strength between histidine and nickel substrate is the strongest, while that of copper is smaller and that of gold substrate is the smallest. From the result of simulation, we find that the stability of adhesion between histidine and the metal substate result of the ringed structure in histidine.**

Keywords- *Molecular dynamics (MD); molecular motor; bio-adhesion; CHARMM*

I. INTRODUCTION

For the realization of the construction of nanomechanical devices, it is necessary to integrate the molecules into highly functional systems. So the controlling of the molecular movement plays a very important role. The early examples of controlled molecular movement involved sterically hindered molecules [1-2]. In recent years, research is steadily shifting its emphasis from systems controlled in solutions to those in confined environments such as surfaces or Langmuir-Blodgett films [3]. A next logical step in the development of machinery to be used for nanotechnological devices is to organize these molecular components on surfaces by some linkages. Histidine is often synthesized into peptide to be used as linkage molecules in nanoelectromechanical systems (NEMS).

Histidines were used to specifically attach, as well as precisely position and orient, biological molecules on nickel, copper and gold substrates created using electron beam lithography [4]. In order to integrate biomolecular motors into NEMS, procedures for the specific attachment, positioning, and orientation of these motors is essential. Therefore, the objective of this simulation was to evaluate the binding of biological molecules to nanofabricated substrates. Montemagno and Bachand [4] have carried out the experiment to test the binding strength of the biological molecules to three substrates (i.e., gold, copper, and nickel). In this paper, we perform molecular

dynamics (MD) simulation to model the adhesion between a synthetic peptide and three different metal substrates without considering the possible chemical interaction between them. Therefore, we gain an insight into the mechanism of the adhesion between histidine-peptide and metal substrate to a certain extent.

MD simulations are based upon numerical solvents of the classical Newtonian equations of motion in which the force exerted on each atom is given by the negative gradient of the potential energy function with respect to the position of the atom [5]. CHARMM [6] (Chemistry at HARvard Macromolecular Mechanics) is a highly regarded and widely used simulation package. Given the CHARMM calculated empirical energy field, MD simulations are performed by classical mechanics in which the equations of motion derived from Newton's second law are solved for all atoms in the molecule.

In this simulation, CHARMM is both a force field engine and a force field itself. The force field engine uses an empirical energy function to describe the forces on atoms in a molecule. We peeled the synthetic peptide form three metal substrates respectively, and the curve of force vs. extension was obtained. We found that the binding strength is different for peptide adhesion to different metal substrate. The adhesion between the histidine-peptide and nickel substrate is the strongest among the three kinds of metal. And the high binding strength comes from the ringed molecular structure in histidine.

II. METHODS

A. Topology and Parameters

A synthetic peptide containing a 6×His-tag (Gly-Gly-Lys-Gly-Gly-Lys -Gly-Gly-His-His-His-His-His-His) (Fig. 1) was used to fix motor on the metal substrate [4]. For the peptide, the standard amino acid residue topology and parameters [6] based on CHARMM 27 all-atom parameters [7] are used. For metals, however, as metal substrates are not composed of biomolecules, the topology and parameters are not directly viable in the standard CHARMM amino acid residue topology and parameters. We prepare these relevant parts for metals for use in CHARMM. We consider that there is no chemical interaction between the peptide and metal substrate. The metal atoms are treated as uncharged Lennard-Jones particles with parameters in Table 1 [8]. Because the metal atoms are always fixed, we subsequently just care about

the bond length and bond angle between the metals atoms but bond energy which is set to zero in the simulation.

Therefore, there are just van der waals interactions between peptide and metal substrate. The non-bond interactions are based on Lennard-Jones 12-6 potential:

$$U(r_{ij}) = 4\varepsilon \left[\left(\frac{\sigma}{r_{ij}} \right)^{12} - \left(\frac{\sigma}{r_{ij}} \right)^6 \right],$$

where ε is a parameter that depends on the types of the two atoms involved in the interaction and r_{ij} is the separation of the two atoms. The parameter σ gives the radius of the minimum in the potential and ε is a scaling parameter for the strength of the interaction. The metal Lennard-Jones parameters are given in Table 1. The carbon-carbon bond length of 1.42 Å and bond angle of 120° are maintained by a Morse bond, a harmonic cosine angle, and a cosine torsional potential. Geometry average is taken as combination rules for setting Lennard-Jones interaction parameters between metal atoms and amino acid atoms.

Table.1. Lennard-Jones Parameters of nickel, copper and gold [8].

| Metals	ε / k_B (deg.)	σ (Å)
Nickel	6030	2.282
Copper	4750	2.338
Gold	5123	2.637

B. Setup of Solvated System

The synthetic peptide contains 14 amino acid residues including 6 Glys, 2 Lyses, 6 Hises. Three-layer metal substrate is generated with each layer containing 338 atoms with metal lattice constants in Table 2. Depending on the dimension of peptide and metal substrate, the molecular system is solvated in a periodic 40×40×90 Å box with pre-equilibrated TIP3 water molecules as solvent [9]. To neutralize the electrical charge of the system, tow CL^- counterions per phosphate group is included. Each CL^- ion is placed randomly in the solvent box. Water molecules that are closer than 1.6 Å form any atom of the solute molecule or counterion are deleted.

Table. 2. Lattice constants and atomic weight of the three metals used in simulation.

Metals	Lattice constant (nm)	Atomic weight
Nickel	0.352	58.710
Copper	0.361	63.546
Gold	0.408	196.967

C. Dynamics Simulation Methodology

All the molecular dynamics simulations are done by employing the code CHARMM 28b1 [6]. During the simulation, leapfrog algorithm [10] is used for integrating the Newton's equation of motion for each atom, with a time step of 1 fs. Periodic boundary conditions using image conventions are applied in calculating the nonbonded interactions. With a nonbond cutoff 12 Å, the nonbonded pair list is updated every 10 steps, and the nonbonded interaction energies and forces are smoothly shifted to zero at 10 Å. The relative dielectric constant 1.0 for electrostatic calculations is used. As initial configurations, peptide is placed on the surface of metal with a mean distance about 6 Å. Then the system is equilibrated for 200 ps at 300 K. The temperature is checked every 100 steps, and adjusted by scaling velocities only if the average temperature of the system is outside the range 300±10 K. Thus the average temperature is maintained at 300 K. The size of the water box is kept fixed during the simulation, making it effectively under a constant NVT system. To simulate the peeling process of peptide from metal substrate, a dummy atom and the algorithm of constant velocity dynamics are used in the simulation. The dummy atom is linked with the end of the peptide far from the histidine by the constraint function NOE and pulled in the designed direction at a constant velocity. The force constant we used for NOE is $K = 8$ kcal/mol/Å². With the direction of peeling perpendicular to the substrate, pulling rates are selected as 0. 1 Å/ps. During the peeling, the metal substrate is fixed so that the peeling of the peptide is realized.
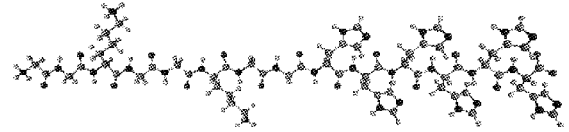
Synthetic pepetide sequence:

Gly-Gly-Lys-Gly-Gly-Lys-Gly-Gly-His-His-His-His-His-His

Fig. 1. The topology structure of the synthetic pepetide before equilibrium viewed by VMD.

III. RESULTS

We have simulated the interaction of synthetic peptide with nickel, copper, gold substrates respectively in water solvent at 300 K. Fig. 1 shows the molecule structure of the synthetic peptide before equilibrium and Fig. 2 is the peptide after equilibrium in water. It is clearly seen form it that the six histidines align together at one end of the peptide. The peptide adhesion to the metal substrate after equilibrium shows in Fig. 3, in which the vdW force is the key force between the synthetic peptide and metal substrate. All the images of MD results are manipulated by the software VMD [11].

On the basis of above simulations, the peeling process of peptide form metal substrate is simulated. Fig. 4 shows the process of peeling the synthetic peptide from substrate. During the peeling process, the end far from the histidines is pulled at a

constant velocity (v=0.1 Å/ps) with the direction perpendicular to the substrate. Together with the typical force profile (Fig. 5), we can see that the pulling forces on different metal substrate are different.
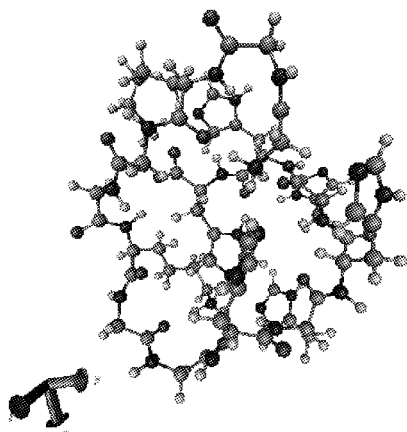

Fig. 2. Topology structure of the synthetic pepetide after equilibrium.
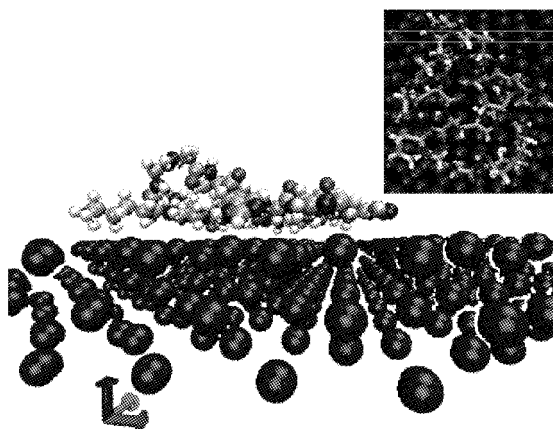

Fig. 3. The synthetic pepetide adhesion to metal substrate viewed form different angle.

parallel to the substrate (Fig. 3), so the area of interaction becomes bigger which leads to intensive and stable adhesion.
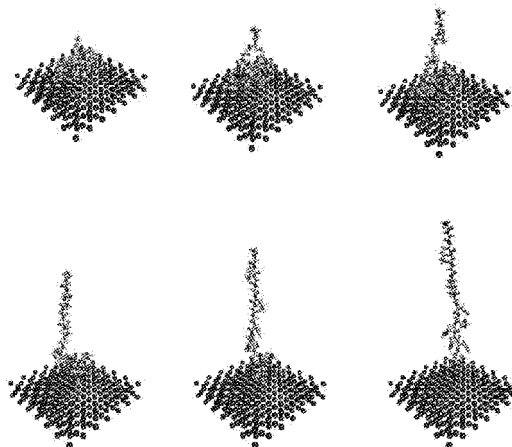

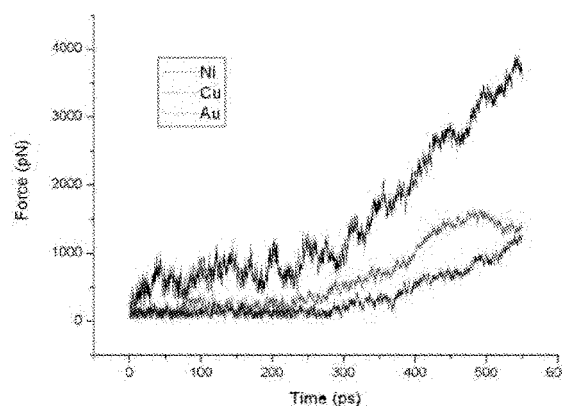Fig. 4. Peeling the synthetic peptide from metal substrate.

Fig. 5. Peel off force of the synthetic peptide adhesion to three metal substrates.

IV. CONCLUSION

In conclusion, we employed MD simulation to model the adsorption of a synthetic peptide on three metal substrates and the peeling process of synthetic peptide from these substrates. On the basis of MD simulation, we obtain the critical peel-off force of peptide from metal substrates. The adhesion between synthetic peptide and nickel substrate is the most intensive, and that of copper substrate is a little smaller, while for gold substrate it is the smallest. When histidine adhesive to the substrate, the ringed structure in it always tries to become

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