

## Further understanding of the biased diffusion for peptide adsorption on uncharged solid surfaces that strongly interact with water molecules



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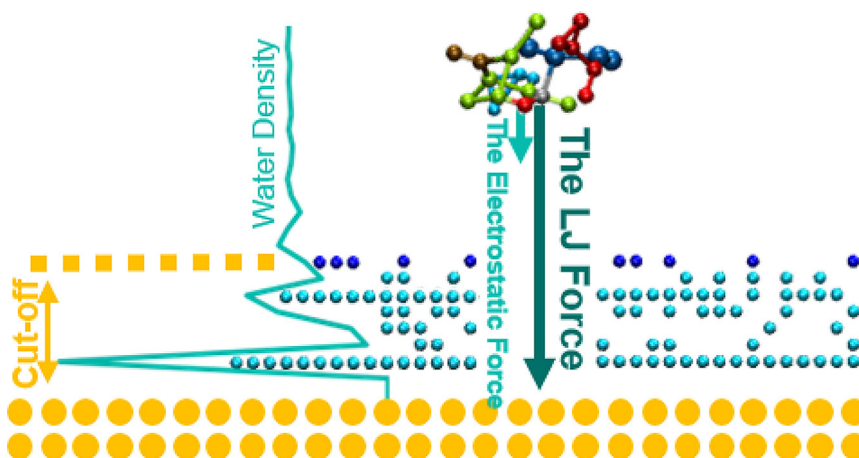
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### HIGHLIGHTS

- Aggregated water layers on uncharged solid surface promote peptide adsorption.
- Biased diffusion is mainly attributed to the LJ force via quantitative analyses.
- The 'net' LJ force is one order of magnitude bigger than the electrostatic force.

### GRAPHICAL ABSTRACT



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### ABSTRACT

Molecular-level understanding of protein adsorption on uncharged solid surfaces has been a challenge due to experimental limitations. Recent computational efforts have demonstrated that the adsorption process starts from a biased diffusion phase, where the peptide or protein tends to move towards the solid surface from a position beyond the interaction range that the surface can reach. The strong interactions between the solid surface and the water molecules adjacent or near it would establish well-oriented water molecular 'layers', which are said to bring the 'net' electrostatic interactions hence exhibiting longer distance attractions. In this work, the peptide adsorption process has been investigated by resorting to a unique mesoscale modeling approach. Here, quantitative analyses on the adsorption of an A3 peptide on uncharged solid surfaces that strongly interact with water have revealed that, different from previous reports, the biased diffusion could be mainly attributed to the Lennard-Jones (LJ) forces, whose 'net' value could reach one order of magnitude

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bigger than the 'net' electrostatic force originated from the aggregated water 'layers' close to the surface. In addition to offering the new understanding of the adsorption mechanisms, promising applications of the current method for large systems beyond a single peptide are also discussed.

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## 1. Introduction

Proteins, as the leading actors within a cell, are very important for all lives on earth. They build our bodies [1], transmit and receive signals [2] and play an important role in human immune response [3]. Furthermore, as an important nutrition source [4], proteins are utilized to produce a wide variety of products, especially in the dairy [5,6], bakery [7], and meat industries [8]. Protein aggregation and deposition, a commonly observed phenomenon, however, could lead to challenging problems for the industry, such as energy waste [9–11] and bio-safety [12,13]. The structures of protein chains have been studied for decades [14] and it is well known that changing pH [15,16], ion strength with extra  $\text{Ca}^{2+}$  and  $\text{S}^{2-}$  ion *etc.* [17], surface chemistry with different kinds of polymers [18] under different fluid conditions, such as impinging jet flow [19] and the turbulent flow [20] in industrial heat-exchanger *etc.*, would influence the adsorption process. Experimental studies demonstrated that acidic amino acid residues have strong affinity towards the surface and probably can offer a major contribution to the adsorption [21]. Since it's very difficult to obtain dynamic and localized experimental data, whether the protein deposit originates from the discrete unfold protein [17,22] or the aggregated mixture [23] is unclear. Our fundamental understandings of protein adsorption mechanisms are far from completion.

Computer simulations of protein adsorption have also been carried out in the past years. Molecular scale simulations of protein adsorption have also been carried out in the past years and interaction potentials between different parts in a peptide and the surface have been identified [24–26]. However, most of the past efforts focused on the lock-down phase, and only limited investigations can be identified for the phases before locking down, which should be critical for us to understand what are key factors leading to protein diffusion towards the surface. Through analyzing peptide structure evolution during the adsorption process, Yu classified the roles of individual residues in a peptide chain as effective anchoring residues, dynamic anchoring points, and flexible peptide backbone [27]. Meanwhile, Yu innovatively divided the whole adsorption process into four consecutive regimes: diffusion (i.e., the movement of a peptide chain towards the surface), anchoring (i.e., the touch-down of the peptide on the surface), crawling (i.e., the duration between the first anchoring and first stable bond formation) and binding (i.e., the forming of the first stable bond) [27]. Penna further defined a three-phase process: the bias diffusion phase (i.e., the movement of a peptide from the bulk to the interface), the anchoring phase (i.e., the engagement of a peptide atom in a sustained way with the second aggregated water layer) and the lock-down phase (i.e., the engagement of a peptide atom in a sustained way with the first aggregated water layer) [28].

Penna *et al.* confirmed the biased diffusion of a peptide towards a strongly interacting surface based on over 240 independent molecular dynamics (MD) simulations [28]. This biased nature allows peptides located initially outside the interaction range (that a surface can reach) to move favorably towards the surface. This phenomenon was attributed to two major factors: (1) in part, the aggregation of the water molecules adjacent to the solid surface, and (2) more importantly, the orientational ordering of the water adjacent to the solid surface led to the charged layers that in effect

brought the long-range electrostatic interaction into play between the peptide and the solid surface. However, they didn't quantify the electrostatic forces resulting from the charged layers. Furthermore, without quantitative comparisons with other effective forces, the claim of the dominant effect of electrostatic interactions on biased diffusion becomes questionable.

In this work, we develop simulation models and quantitative analysis methods that hopefully can answer the following important scientific questions in the study of peptide adsorption on a strongly 'water' interacting uncharged solid surface: (1) Will water molecules adjacent to the surface reorganize themselves to form aggregated layers? (2) Will the surface be endowed with charged layers? (3) If biased diffusion does exist, what are the dominant forces leading to this interesting phenomenon?

We combine the MARTINI force field [29–32] and Bond-Fluctuation model [33–35] (BF model) while neglecting some degrees of freedom to achieve our goal. MARTINI force field [29–32] was initially designed for Coarse-Grained (CG) simulations of lipid systems, and then it was extended to the study of protein adsorption on graphite, chitin, and collagenous tissues *etc.* BF model [33–35] is a promising lattice model that uses bond vectors instead of bonded interactions for efficient simulations of polymer systems with satisfactory accuracy. This model has been successfully used to simulate a variety of polymer systems including the DNA and nanostructured networks. Beyond the study of the adsorption of a short peptide chain, the CG hybrid model will hopefully investigate much larger adsorption systems in the future that may involve multiple protein chains, which is of great scientific and practical significance.

## 2. Modeling and simulation methodology

A CG lattice Monte Carlo (LMC) model is developed to investigate peptide/protein adsorption on strongly interacting surfaces. A simulation box of  $7.50 \times 7.50 \times 7.50 \text{ nm}^3$  is created first with periodic boundary conditions imposed in *x* and *y* direction (Fig. 1). In the *z* direction, the bottom part is 1.2 nm height solid surface beads and the top part is 1.2 nm height, where is over 3 nm away from the peptide, unmovable water beads for the stabilization of the bulk water. The box is divided into cubic cells of  $0.125 \times 0.125 \times 0.125 \text{ nm}^3$  in size. Every cell can only contain one bead. Within the simulation box (see Fig. 1), 2314 water beads (the relative density of bulk water could maintain at 1 according to the preliminary experiment) are placed on top of 5400 substrate beads. The peptide in the system is a well-accepted gold-binding A3 peptide chain with 25 amino acid beads [36] (i.e., AYSSGAPMPPF shown in Fig. 2). All simulations are carried out at 298 K and 1 atm. The solution is kept at the neutral condition, i.e., pH = 7.

### 2.1. Coarse graining and system setup

The four-to-one map utilized in the MARTINI model has been adopted in this work to coarse grain the amino acid residues and water molecules [30–32]. As shown in Fig. 3, the red bead at the center of a cell is the neutral part that interacts with other beads through the LJ potential. The orange site indicates the location of the

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