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Identification of peptide adsorbates for strong nanoparticle–nanoparticle binding by lattice protein simulations

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ABSTRACT

Nanoparticles with short peptides adsorbed to their surfaces often assemble into interesting structures when suspended solution. In this paper, the interaction between a peptide adsorbed to a surface and another peptide adsorbed to an opposing surface is studied using the lattice protein model. It is found that the interaction strength between the two peptides generally increases as the hydrophobicity of peptides increases. Moreover, there is a preference for hydrophobic amino acids to be neighboring hydrophilic amino acids in cases which yield strong peptide–peptide interactions. These results provide insights for tailoring the strength of nanoparticle–nanoparticle binding by engineering of peptide adsorbates.

1. Introduction

Metal and inorganic nanoparticles have received extensive attention as possible building blocks for novel nanotechnologies [1]. While nanoparticles usually assemble into amorphous coagulates when suspended in solution [2], nanoparticles with organic molecules or short (∼10-mer) peptides adsorbed to their surfaces often assemble into structures with interesting shapes and properties [2–7]. The result of this assembly depends on which parts of the nanoparticle surface the adsorption takes place [6], the molecular structure and surface selectivity of the adsorbate [8,9], the experimental conditions (temperature, pressure, pH, and solvent) under which the assembly process is performed [10], and the strength of the interaction between molecules adsorbed to opposing nanoparticle surfaces. By analogy with chemical bonding between atoms, it is possible to speak of the connection formed between two nanoparticles *via* surface-adsorbed peptides as a 'nanoparticle–nanoparticle bond'. However, while the fundamentals of chemical bonding are well-understood, the general principles that connect the chemical composition of the adsorbate molecules with the strength of the nanoparticle–nanoparticle bond remain unknown.

This paper considers the interaction between two short peptides adsorbed to two opposing surfaces as a model for the nanoparticle–nanoparticle bond described above. While this exact situation does not appear to have been studied in the literature, peptide adsorption to a single surface has been investigated thoroughly, especially from the point-of-view of biomedical applications [11–17]. It is now well-accepted that peptides adsorbed to surfaces have quite a different equilibrium structure than peptides in the gas- or liquid phase [14,18,19] and the kinetics of this adsorption process has been characterized with rate equations for a variety of cases [14,16,17]. The adsorption strength is also highly dependent on the amino acid sequence of the peptide [8]. These studies are proceeding toward a microscopic understanding of surface-adsorbed and confined peptides, however there remains the outstanding practical problem of identifying peptide sequences to achieve a strong nanoparticle–nanoparticle bond.

In this paper, the interaction between two peptides adsorbed to opposing surfaces is considered from the point-of-view of the lattice protein model (Fig. 1) [20]. We investigate how the amino acid sequence of the peptide affects the strength of the nanoparticle–nanoparticle bond, as measured by the interaction strength between the two peptides. The lattice protein model is an early model for protein folding [21,22] and continues to be used extensively to study protein physics [23–28]. This model treats the peptide as a string of beads, where each bead is a single amino acid. The beads reside on vertices of a cubic lattice, and

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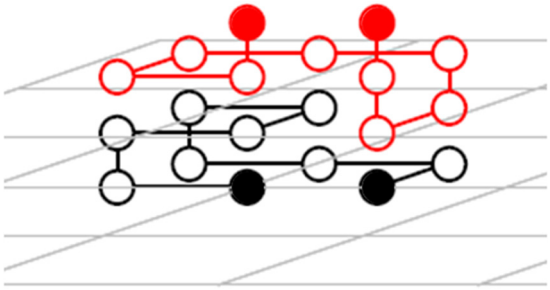

Fig. 1. Lattice protein model for the nanoparticle–nanoparticle bond. The gray grid represents the lower surface. The upper-surface is not shown. The two filled black beads are fixed to the lower surface, and the two filled red beads are fixed to the upper-surface.

only interactions between beads on adjacent sites of the cubic lattice contribute to the total energy of peptide. The lattice protein model is obviously inappropriate for predicting the detailed conformation of real peptides, however it is surprisingly successful at correlating the equilibrium stability with peptide amino acid sequence [29]. The lattice protein model has been used to study adsorption of single peptides to single surfaces [30] and between surfaces [31]. With the availability of detailed atomistic molecular dynamics (MD) simulations and quantum chemical calculations, it may seem unnecessary to resort to the lattice protein model at all. On the other hand, atomistic MD simulations are only useful with a force field which accounts for both the metal surface–amino acid and amino acid–amino acid interactions with the same level of accuracy. Such force fields are only just starting to appear in the literature and are restricted to specific metal surfaces [32–35]. In contrast, surface-amino acid interactions can be incorporated into the lattice protein model as a set of free parameters, which provides generality in the kind of surfaces that can be studied. This fact, as well as the relative computational efficiency of scanning large libraries of peptide sequences with the lattice protein model, makes the lattice protein model a very reasonable approach for identifying optimal peptides for strong nanoparticle–nanoparticle bonding. We will consider a special case where the terminal amino acids of the peptides are immobile and in direct contact with their respective surfaces. The situation might be relevant to the case of cysteine-terminated peptides adsorbed to gold nanoparticles [36].

Via Monte Carlo simulations on an extensive library of randomly generated, 10-mer peptides, we find that in general the strength of the nanoparticle–nanoparticle bond (as measured by the peptide–peptide interaction energy) tends to increase as the fraction of hydrophobic amino acids in the peptide increases, and tends to decrease as the fraction of hydrophilic amino acids in the peptide increases. These trends become more dramatic as the hydrophilicity of the surface increases. These results resemble the general rule-of-thumb that isolated peptides in aqueous environments tend to fold in such a way that their hydrophobic amino acids are buried within the core of the folded protein and can interact with each other [37,38]. Unexpectedly, we find that in peptides which lead to strong nanoparticle–nanoparticle bonding, hydrophobic amino acids are often neighboring hydrophilic or mildly hydrophobic amino acids. This may facilitate the interaction between the two peptides by preventing the peptides from 'folding into themselves' and not interacting with each other. This preference for hydrophobic–hydrophilic pairing becomes weaker as the surface hydrophilicity increases, but nonetheless still appears important in peptides which yield strong nanoparticle–nanoparticle bonding. These results therefore provide, for the first time, a starting point for tuning the strength of the nanoparticle–nanoparticle bond by careful engineering of the peptide surface adsorbates.

This paper is organized as follows. Section 2 describes the lattice protein model and the Monte Carlo simulation technique utilized here to calculate the interaction strength between the two peptides. Section 3 presents our main results and a detailed discussion, and conclusions are left for Section 4.

2. Methods

We consider two lattice proteins adsorbed to two opposing surfaces (Fig. 1). Each protein is modeled as a string of beads, where each bead represents an amino acid [20–22]. The beads occupy vertices of a cubic lattice and are labeled as 1, 2,..., where the numbering starts at one of the terminal residues. Henceforth we will refer to these beads as amino acids. The lower (upper) surface is denoted by S_1 (S_2), and the peptide adsorbed to S_1 (S_2) is denoted by P_1 (P_2). All configurations of the model must satisfy the following two conditions: the two terminal amino acids of P_1 (P_2) are always fixed to S_1 (S_2); no two amino acids may occupy the same vertex of the lattice; and no amino acid may reside at vertices below S_1 or at vertices above S_2. The first condition is expected to be satisfied for the case of cysteine-terminated peptides adsorbed to gold surfaces [36]. Consider some configuration for the model σ that satisfies these conditions and let $P_k(\sigma)$ denote peptide k when the model is in this configuration. The energy of configuration σ is defined as

$$\varepsilon(\sigma) = \sum_{\{i\sim j: i,j\in P_1(\sigma)\}} \varepsilon_{ij} + \sum_{\{i\sim j: i,j\in P_2(\sigma)\}} \varepsilon_{ij} + \sum_{\{i\sim j: i\in P_1(\sigma), j\in P_2(\sigma)\}} \varepsilon_{ij} + \sum_{\{i\sim S_1\}} u_i + \sum_{\{i\sim S_2\}} u_i \quad (1)$$

where the notation $\{i\sim j : i,\ j\in P_m(\sigma)\}$ denotes all pairs (of non-covalently bonded) amino acids which are contained in peptide $P_m(\sigma)$ and reside at adjacent vertices on the cubic lattice, $\{i\sim j : i\in P_m(\sigma),\ j\in P_n(\sigma)\}$ denotes all pairs of amino acids which reside at adjacent vertices on the cubic lattice such that amino acid i is contained in peptide $P_m(\sigma)$ and amino acid j is contained in peptide $P_m(\sigma)$, and $\{i\sim S_k\}$ denotes all amino acids that are adjacent to surface S_k. In Eq. (1), ε_{ij} is the interaction energy between amino acids i and j, and u_i is the interaction energy between amino acid i and the surface. Note that the interaction between amino acids which are covalently bonded does not contribute to Eq. (1). The probability that configuration σ occurs at equilibrium is

$$g(\sigma) \propto \exp\left(\frac{-\varepsilon(\sigma)}{k_B T}\right) \quad (2)$$

where k_B is the Boltzmann constant and T the temperature. The normalizer constant (partition function) in Eq. (2) is assumed to be unknown. The task of this paper is to estimate the *peptide–peptide interaction energy*, defined as

$$E_{\text{int}} = \langle \varepsilon_{\text{int}}(\sigma) \rangle, \quad (3)$$

where

$$\varepsilon_{\text{int}}(\sigma) = \sum_{\{i\sim j: i\in P_1(\sigma), j\in P_2(\sigma)\}} \varepsilon_{ij} \quad (4)$$

is the protein–protein interaction energy when the model is in configuration σ, and the angular brackets denotes an average with respect to the probability distribution $g(\sigma)$ in Eq. (2).

In this paper, we estimate (3) *via* MCMC sampling with the Metropolis-Hastings algorithm. For an introduction to this technique, the reader is referred to literature sources [39,40]. In order to scan the configuration space of the model during the MCMC sampling, we employ *shift transformations*. An individual shift transformation on amino acid l of peptide k in the direction x,