Protein Simulations in Confined Environments

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Abstract

Materials surfaces mimic cell like architecture and proteins can be encapsulated by these material surfaces (e.g. a porous glass or gold). Depending on the number and types of surface interactions, this confine environment could destroy the protein or help it maintain its bioactivity. We developed computer models and simulation tools for the understanding of surface-protein interaction at the atomistic levels. At the molecular level, molecular dynamics simulations are very powerful, but the high computational cost of molecular simulations is a drawback. A viable alternative method to study protein-surface interactions is the coarse-grained molecular simulations of simplified models, such as elastic network model. At the atomic interaction level, we used ab initio simulations to calculate the potential between surface and protein atoms.

Introduction

Understanding the structure and function relationships for proteins and biomolecular assemblies is one of the challenges in the post-genomic era. Simulations and predictions of processes at the molecular level will advance computational biology research and speed up our understanding of molecular biology. At the molecular level, molecular dynamics (MD) simulations are very powerful. The high computational cost of MD simulations, however, is a drawback and new techniques are needed to overcome this problem. Intuitively, simulations should be developed in an environment of experimental validation, or they do not engender confidence in their predictive power.

Molecular dynamics (MD) simulations of proteins can provide atomic details of motional phenomena. Binding in a variety of different receptor-ligand systems appears to be well modeled by molecular dynamics and continuum models.[1] Several experimental results agree well with computational binding constants (e.g., inhibitor binding to cAMP-dependent protein kinase[2] and asparagines binding to aspartyl-tRNA synthetase).[3] On the other hand, fully atomistic MD simulations with explicit solvents have limitations, such as empirical force fields, inefficient sampling of conformations, and high computational cost. A viable alternative method to study surface-protein interactions is the coarse-grained MD simulations of simplified models.[4-8]

In this paper, we combined coarse-grained molecular dynamics simulations with ab initio calculations to study gold-protein interactions. We obtained interaction constants for five amino acids on a <111> gold surface.

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Elastic Network Model

Our method, which is now known as the Gaussian Network Model (GNM), models fluctuations of proteins. The GNM method is very successful in describing the dynamic characteristics of proteins.[4,5,7] Comparison with experiments shows that slow and fast modes of proteins are associated, respectively, with function and stability.[5] Results from GNM calculations were found to be in excellent agreement with x-ray crystallographic temperature factors (also called Debye-Waller or B-factors).[5,7] The GNM is based on the following postulate: In folded proteins, residues undergo gaussianly distributed fluctuations around their mean positions, due to harmonic potentials between all "contacting" residues. No residue specificity need be invoked as a first order approximation. Instead, the inter-residue potentials are all represented by the same single-parameter harmonic potential. The fluctuations of residues are controlled by a harmonic potential and α-carbons being used as representative sites for residues. The dynamic characteristics of the molecule are fully described in this model by the so-called Kirchhoff matrix of contacts. Two residues are defined to be in contact if the distance between their α-carbons is less than a cut off radius of 7 Å. A first test of the validity of the GNM is to compare the predicted fluctuations of residues with those observed in experiments (Debye-Waller or B-factors).

Results

In our study, interactions of five amino acids with <111> gold surface are simulated using GNM. Figure 1 shows the illustrations of ALA, GLY and VAL residues interacting with gold surface.

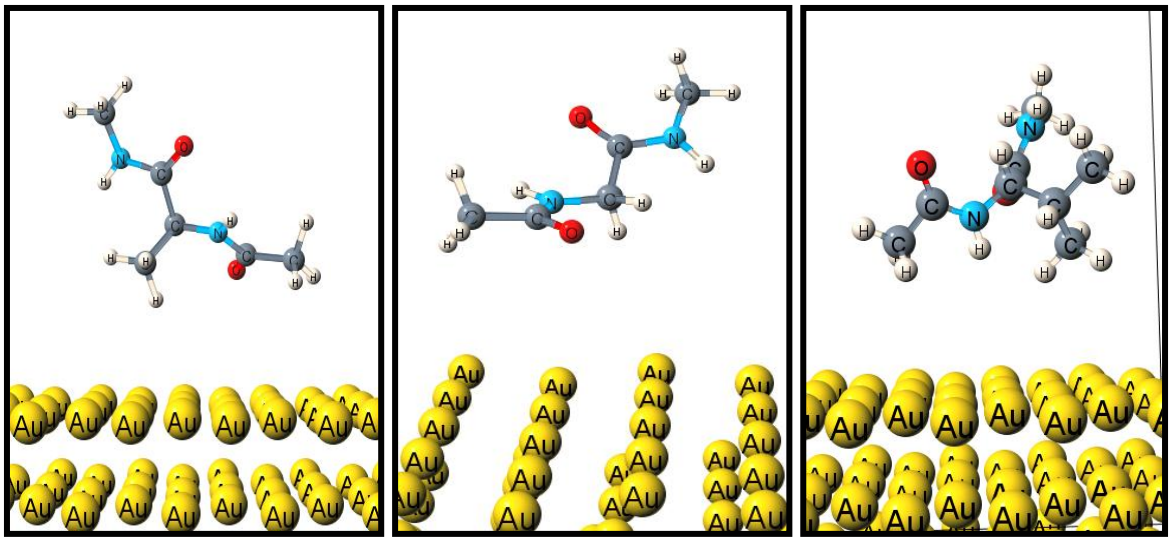

Figure 1. Illustrations of protein residue-gold surface interactions.

Our elastic network model assumes a protein molecule as a chain of α–carbon atoms being the representative sites for corresponding residues. Figure 2 shows the case for a single protein residue.

Interaction of each protein residue with gold surface is expressed with a single system parameter, γ. Resembling a spring-mass system, a residue fluctuates with a mean value of ΔR, while assumed as being connected to the gold surface. A valid "connection" between a residue and material surface requires the value of R_{cut} being smaller than the interaction cutoff radius of 10Å, where R_{cut} is the distance between the α–carbon atom of residue and nearest gold atom on surface. Each kind of residue has a different ΔR value, and the interaction parameter γ varies for each amino acid.

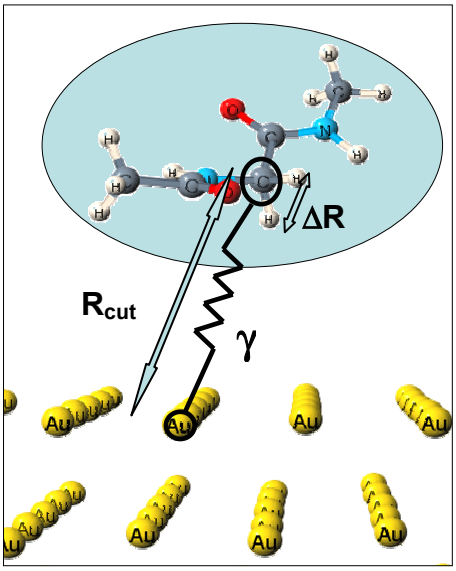

Figure 2. Representation of elastic network model for a single residue.

Since a unified atom model of amino acid has six degrees of freedom in its three dimensional environment, the free energy values of an amino acid-gold surface system are obtained for different orientations. Using VASP ab initio molecular dynamics package, the graphs in Figure 3 are obtained. It is clear that there are specific orientations for an amino acid molecule where the free energy of the system is minimized. These orientations refer to specific angular or translational positions of the protein with respect to the gold surface.

The system interaction parameter γ can be obtained once a specific region of orientations (i.e. providing the minimum free energy for the system) is determined for calculations. γ value for each amino acid-gold system is calculated by using conjugate gradient minimization with Chi-square analysis:

$$X^2(\gamma) = \sum_i \left(\tilde{E}_i - f(\gamma)_i\right)^2 \qquad (1)$$

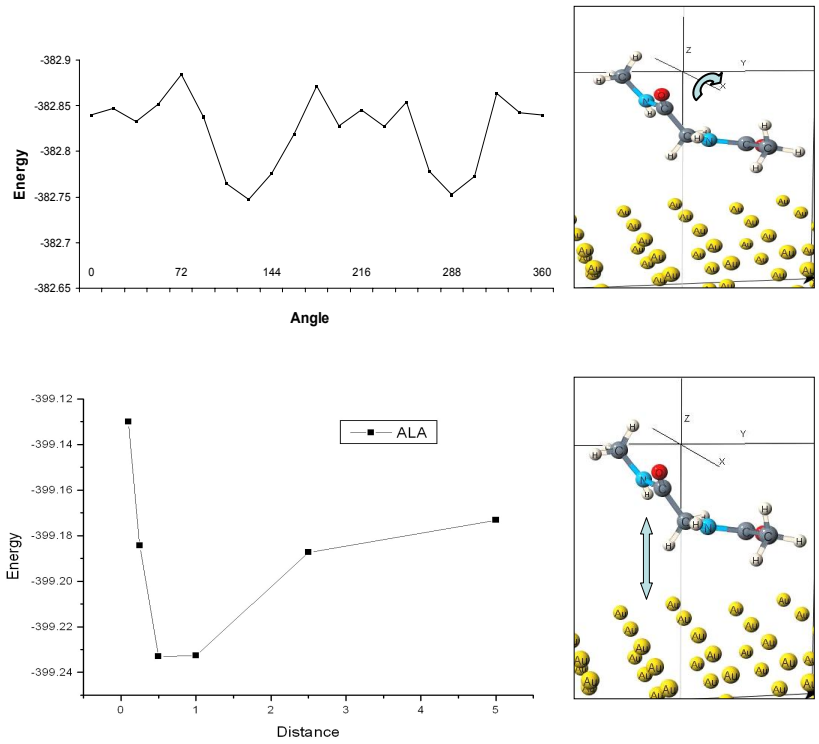

Figure 3. Energy graphs of an amino acid-gold surface system for angular and translational orientations of amino acids with respect to the surface.

Equation 1 was minimized with a single parameter equation by using the ab-initio energy values (E), and the values obtained by our elastic network model represented with function f (f is given by a harmonic potential in the form of $1/2\gamma\Delta R^2$). Since γ is unknown, the function X^2 is minimized by using conjugate gradient method. In the end, the interaction parameter γ for a specific protein-gold surface system is obtained. Table 1 shows a table of γ values for some residue-gold surface systems.

Table 1. Interaction constants for five amino acid simulated on gold surfaces.

	Au Surface (kcal/mol.Å^2)
γ_{ALA}	25
γ_{GLY}	21
γ_{VAL}	26
γ_{ILE}	27
γ_{LEU}	31

Conclusion:

Based on computational studies that are described here, we are developing a new coarse grained approach to understand and predict the binding mechanism of biological assemblies to confined spaces such as gold surfaces. We obtained interaction constants for five amino acids on a <111> gold surface (~25 kcal/(mol $Å^2$)).

We have previously showed that the force constant of protein-protein interactions is 1.0 ± 0.5 kcal/(mol $Å^2$), assuming an interaction cutoff distance of 7 Å.[4] Assuming a Debye temperature (T_D=170K) for gold and the mass of gold (mAu = 197 AMU), the equivalent interaction constant for gold-gold interactions will be given by $K=mAu\ (k_B\ T_D\ /\ \hbar\ )^2$ where k_B is the Boltzmann constant and ħ is the reduced Planck constant. As a result, the force constant of gold-gold interactions is 240 kcal/(mol $Å^2$). We conclude that a force constant of 25 kcal/(mol $Å^2$) is a reasonable estimate for amino acid-gold interactions. As a future work, we will calculate the system interaction parameters for various material surfaces (e.g. polymer, ceramic) and protein molecules.

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