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Perspectives on the simulation of protein–surface interactions using empirical force field methods

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ABSTRACT

Protein–surface interactions are of fundamental importance for a broad range of applications in the fields of biomaterials and biotechnology. Present experimental methods are limited in their ability to provide a comprehensive depiction of these interactions at the atomistic level. In contrast, empirical force field based simulation methods inherently provide the ability to predict and visualize protein–surface interactions with full atomistic detail. These methods, however, must be carefully developed, validated, and properly applied before confidence can be placed in results from the simulations. In this perspectives paper, I provide an overview of the critical aspects that I consider being of greatest importance for the development of these methods, with a focus on the research that my combined experimental and molecular simulation groups have conducted over the past decade to address these issues. These critical issues include the tuning of interfacial force field parameters to accurately represent the thermodynamics of interfacial behavior, adequate sampling of these types of complex molecular systems to generate results that can be comparable with experimental data, and the generation of experimental data that can be used for simulation results evaluation and validation.

1. Introduction

The ability to understand and predict the interactions between proteins with material surfaces (either physically adsorbed or covalently linked) represents long-standing challenges in the fields of biomaterials and biotechnology. The behavior of proteins on material surfaces is of critical importance for numerous applications. These include the biocompatibility of materials when implanted in the body and for the function of substrates for tissue engineering, regenerative medicine, drug delivery, and bioseparations [1–8]. Protein–surface interactions also underlie the performance of biosensors, bioanalytical systems, and bioreactors as well as for the development of technologies for biodefense [9–12]. The continued growth of subfields such as nanobiotechnology and biomolecular engineering pushes the need for this understanding down to the submolecular and atomic levels in order to tap into the extreme versatility of proteins and their respective bioactive functionality. While much has been learned over the past several decades through the creative efforts of numerous research groups, the understanding of protein interactions with surfaces at the level of detail necessary to actually predict and control protein orientation, conformation, and bioactivity remains an elusive but still highly sought after goal.

The folding of a polypeptide chain into its native-state protein structure can be represented by what is referred to as the protein's folding funnel (Fig. 1a) [13–15]. This representation of the folding process depicts the relative free energy of the protein vs. its conformational state for the protein free-floating in physiological solution. The conformation of the protein that provides the minimum free energy state represents the protein's stable native-state structure. However, when a protein comes in contact with a material surface, the functional groups of the surface apply additional forces on the protein as well as causing a thermodynamic shift in the solvated state along the contacting surfaces of both the protein and the adsorbent material. These combined effects can substantially alter the shape of the folding funnel in a manner such that the native-state conformation of the protein no longer represents the lowest free energy state of the overall system. When this happens, the protein's conformation will change in a manner to cause the protein to undergo unfolding (or perhaps better thought of as 'refolding'), toward a new low free energy state for the overall protein–surface–solvent system, as depicted in Fig. 1b. As will be addressed below, this phenomenon adds substantial additional complexity to the challenge of understanding and accurately predicting protein–surface interactions.

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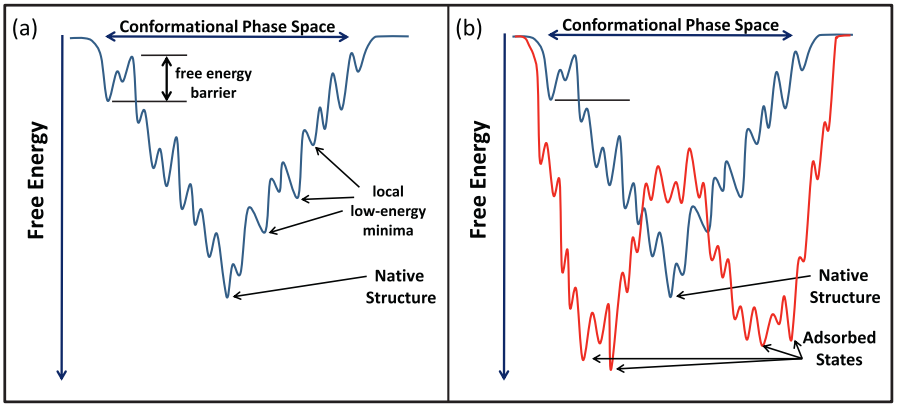

Fig. 1. (a) Protein folding funnel for a protein in aqueous solution illustrating the free energy of the system as a function of the conformational state of the protein. Multiple local low-energy wells exist separated by free energy barriers, with the global low-energy state representing the native-state structure of the protein. (b) When a protein adsorbs to a surface, additional free energy contributions influence the system due to protein–surface interactions and corresponding changes in the hydration state of the protein and the surface. These combined effects cause the free energy profile to shift such that the native state of the protein is no longer the global low free energy state. The multiple low-energy adsorbed states represent different adsorbed orientations of the protein on the surface.

Protein–surface interactions have been widely studied and characterized over the past several decades in an effort to understand and control protein adsorption behavior. Methods were primarily initially developed to simply measure the amount of protein adsorbed to a surface, their competitive nature, and Vroman effects leading to the displacement of one adsorbed protein with another using techniques such as radiolabeling [16,17], surface plasmon resonance spectroscopy (SPR) [18], quartz crystal microbalance [17], and Fourier transform infrared (FTIR) spectroscopy [19,20]. Subsequently, more sophisticated experimental methods have been developed to obtain structural information regarding a protein's adsorbed orientation and conformation. These methods include circular dichroism spectropolarimetry (CD) to measure adsorption-induced changes in secondary structure [21,22], a combination of NEXAFS/SFG/ToF-SIMS to obtain information on adsorbed orientation and structure [16], FTIR for secondary structure [19], and amino-acid labeling/mass spectrometry (AAL/MS) to probe orientation and changes in tertiary structure [23,24]. These methods, however, are still very limited in their ability to provide complete residue-level detail of a protein's orientation and conformational behavior on a surface. Thus additional methods are still needed to provide a more complete depiction of protein adsorption behavior.

Empirical force field-based molecular modeling has the potential to meet this need with the inherent ability to predict molecular interactions with full atomistic detail. However, as an empirical approach, these methods must first be carefully developed and validated for specific applications. Other fields have actively taken on this challenge with great success to the point where molecular simulation methods are considered to be an indispensable resource for research and development. For example, the biophysics community has developed force field parameters and methods to represent and predict protein folding behavior in aqueous solution and when interacting with cell membranes [25,26], and the pharmaceutical field has developed force field parameters and methods for drug design [27,28]. These types of methods have similar potential for representing and predicting the interactions between peptides and proteins with material surfaces. However, this potential can only be realized if methods are developed to meet the specific needs of this type of application [29–31].

In this perspectives paper, my objective is to provide an overview of the critical issues that have to be addressed in order for simulation methods to be developed to accurately simulate protein–surface interactions. I would like to emphasize two important points regarding this overall objective. Firstly, I will not cover the closely related field of peptide–surface interactions except as it directly relates to providing information in support of the simulation of protein–surface interactions. Readers should refer to the many excellent papers that have been published in that specific area of research, which primarily focus on the atomistic-level interactions and conformational behavior between specifically sequenced peptides and various material surfaces [32–48]. Secondly, I specifically use the phrase, 'accurately simulate' because simulations can easily be conducted in a manner that gives completely erroneous and misleading results; often without any means to assess the reality of the predicted behavior. The real challenge for the simulation of protein–surface interactions is to develop methods that will accurately represent the behavior of a designated molecular system, and to have the ability to quantitatively verify that the results realistically represent actual system behavior. In the following sections, I present the attempts that I have made with both my experimental and computational research groups to provide this capability.

2. Methods

2.1. Overview of critical issues for empirical force field molecular simulation

In order to understand the specific issues that must be addressed for the development of empirical force field methods for the simulation of protein adsorption behavior, it is important to first understand some of the basic principles that are used for conducting this type of molecular simulation.

Two of the most important requirements that must be met to provide the ability to accurately represent molecular behavior using empirical force field methods are: (1) to have an appropriate force field equation and set of force field parameters to properly represent the interactions between the atoms contained within a given molecular system, and (2) to provide sufficient 'sampling' of the configurational states of the system to obtain a statistically representative depiction of the system's behavior.

2.1.1. Force field parameterization

The force field used in an all-atom empirical force field simulation is an analytical expression that accounts for the potential energy (PE) contributions of each type of atomic level interaction in a given molecular system as a function of the relative position of the atoms with respect to one another [49]. The force field type typically used for the simulation of biomolecules is called a Class I