Sivaprakash Arul* et al.
(IJITR) INTERNATIONAL JOURNAL OF INNOVATIVE TECHNOLOGY AND RESEARCH
Volume No.4, Issue No.2, February - March 2016, 2824 – 2828.

Molecular Simulations of Organic-Inorganic Interface

SIVAPRAKASH ARUL
Department of Biotechnology
KV College of Engineering and Technology
Tamilnadu, India

Abstract: **Recent interest in biomolecule adsorption tomaterial surface has grown rapidly, but little is understood at this time regarding specific recognition happens and how to design surfaces to control protein adsorption behavior. Molecular dynamics simulation methods have enormous potential to address this problem by providing an approach to directly investigate the adsorption behavior of biomolecules at the atomic level. The simulation methods should be accurately applied to get meaningful data and the crucial parameters are validated force field, solvation effects, and sampling. In this short review, I address each one and the future directions of this field.**

KeyWords: **Molecular Dynamics, Protein Adsorption, Simulations and Materials Surface**

I. INTRODUCTION

Adsorption of biomolecules to material surfaces is of great importance in the many scientific fields because of its role in determining cellular responses to implanted materials and substrates for tissue engineering and regenerative medicine[1-3]. Cells do not have receptors for materials such as metals, polymers or ceramics, and thus lack respond to chemically stable material surfaces, but when a material is exposed to a protein-containing solution, proteins rapidly adsorb onto the surface that drive cellular response. The effects of adsorption of proteins in an active state is critical importance in many other applications, such as the development and optimization of surfaces for biosensors,[4] nanoparticles,[4-7]biocatalysis,[8-10] bioanalytical systems for diagnostics and detection[11], and bioseparations[10].

Protein adsorption behavior has been intensively studied over the past several decades. A lot of knowledge has been learned from these efforts, but the detailed understanding of the molecular mechanisms underlying protein adsorption behavior and how to control it is still lacking, which means that the design of surfaces for biomedical and biotechnology applications can, at best, only be approached by educated trial-and-error methods. Due to several variables involved for surface design is so enormously large e.g., morphology of the material surface, types of functional groups present, their spatial distribution, the chance of finding optimal conditions to control protein adsorption behavior by a trial-and-error approach for a given application is infinitesimally small. Given this situation, it is clear that new approaches are needed to help understand biomolecule adsorption behavior at the molecular level, so that this understanding can then be applied to guide surface design to directly control these types of interactions.

One of the most direct methods of addressing interactions at the molecular level is through molecular simulation. Molecular simulations have very little impact at the interaction of biomaterial at this time, but widely used in other areas such as understanding of protein folding[12], protein-protein[13], protein-ligand interactions[14]. Similar potential application of molecular simulation methods is to help to understand biomolecule-material interface behavior. However, as with other areas of application, molecular simulation methods cannot just be borrowed, but must be carefully and specifically developed, validated, and applied for this particular application.

Here, I help to provide direction for the biomaterial field as it takes on the challenge of developing molecular simulation methods for its own applications. The specific objectives of this article are: 1 to provide a general introduction to molecular simulation methods for the biomaterials, 2 to highlight the key factors and problems, and 3 to present approaches to address the adsorption behavior that will provide meaningful results.

II. MOLECULAR SIMULATION METHODS

Computational methods examine structural, chemical, and physical properties underlying interactions between the inorganics and organic molecules.These three classes are quantum mechanical, all-atom empirical force field methods, and coarse-grained methods. Quantum mechanical calculations enable the analysis of the geometry of molecules, conformers, and clusters of moleculeswith a focus on electron density, orbital geometry, chemical reactions, and transition states, whereas molecular dynamics and monte carlo simulations reveals structure, conformations, binding energy.

Quantum mechanical methods utilize various means to approximately solve the Schrödinger equation to calculate the properties of a molecular system using electrons as the fundamental particles under consideration[15]. These types of calculations can be highly accurate and require no fitted parameters, but they are also extremely computationally expensive. It is mainly used to develop parametrization for the all-atom empirical force field methods.

All-atom empirical force field methods do not address the behavior of electrons, but rather treat individual atoms as the fundamental unit and use an empirically fit force field equation to calculate the amount of energy involved in atom-atom interactions based on the configuration of the atoms and their state of bonding. Force field methods are commonly used for MM and MD simulations. Because these calculations are much less rigorous than QM calculations, all-atom empirical force fields can be relatively easily used to model the behavior of systems with tens of thousands of atoms, and when used for MD simulations, can relatively easily simulate time frames for tens of nanoseconds. Now molecular dynamics methods are used to address the behaviorof peptide-surface interaction[16, 17] and protein-surface interactions for small proteins.

The third type of molecular simulation, coarse-grained methods, treats groups of atoms as the fundamental unit in the system, with a force field equation then used to define energy contributions as a function of the configuration with respect to one another and their connectivity with one another. Generally these methods treat solvation effects implicitly by using some type of mean-field approximation. Both of these types of approximations greatly reduce the computational cost of the system, thus enabling system size, conformational searching, and time scales to be greatly expanded, with this advantage coming at a cost of decreased accuracy

III. FORCE FIELD PARAMETERIZATION

The reliability of an all-atom empirical force field method, whether it be MM, or MD, is the parametrization of the force field. The force field equation is actually a relationship that describes how the potential energy of the system changes as a function of the positions of the atoms for a given state of atomic bonding. It is called a force field equation because when differentiated with respect to a spatial coordinate, the resulting expression provides the forces acting on each atom as a function of their relative positions. These atomic forces are used in MM calculations to determine how the arrangement of atoms in the system can be adjusted to minimize its energy, and in MD simulations to determine how atoms should move over a given time step of the simulation.

The parameters of an empirical force field are empirically determined for a given set of atoms for a designated type of application. There are primarily two types of empirical force fields that are used for molecular simulations, which are referred to as class I force fields e.g, AMBER, CHARMM, OPLS, GROMOS and class II force fields e.g., MM2, CVFF, PCFF, and COMPASS[18]. Both force field one and two have parameters that represent potential energy contributions for bonded interactions in the form ofseparate terms for covalent bond stretching, bond bending, and bond rotation, and nonbonded interactions in the form of both electrostatic and Lennard-Jones interactions

Recent changes in the force-field development made this field more familiar and interesting. Feng. et. al studied the absorption energies of natural amino acids on gold with modified force field parameters (fig.1)[19].

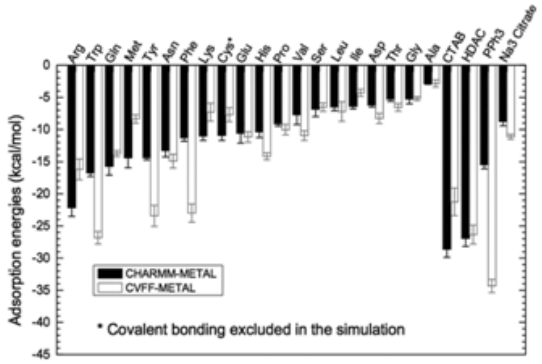

Fig. 1 Computed adsorption energies of the natural amino acids on gold(111) surfaces in solution using CHARMM-INTERFACE and the CVFF-INTERFACE force field. Reproduced with permission from[19]

The exciting aspect of the development of an empirical force field for amino acid residue-surface interactions is the fact that all proteins are essentially composed of the same set of 20 naturally occurring amino acids, and a very large number of polymers are composed of the same basic set of functional groups. Thus, once a set of force field parameters is validated for these types of amino acid–polymer functional group interactions, this same parameter set should be able to be applied to accurately simulate the adsorption behavior of any protein on any polymer containing similar types of functional groups, with capabilities then only limited by the power of the computational resources that are available. Similarly, the approach can be also applied in the metals and semi-metals [20].

While this should provide a very promising approach to help understand and predict protein-surface interactions, there are other key aspects of a molecular simulation such as solvation effects and system sampling.

IV. SOLVATION EFFECTS

During the process of biomolecule adsorption, the water molecules and salt ions in solution helps to mimic the natural reaction. Without the involvement of solvation, simulation cannot be accurate. As such, it is essential that solvation effects be accurately represented in any molecular simulation of peptide-surface or protein-surface interactions. A simulation composed of only a peptide and a surface, without the presence of solvent molecules or the representation of solvation effects, represents molecular behavior under vacuum conditions, which has little to do with processes that occur in aqueous solution and it is not accurate.

The most direct and accurate way of including solvation effects in an all-atom empirical force field simulation, is to include the molecules of the solvent explicitly using a water model that was specifically designed to be used with the selected force field along with the appropriate concentration of salt ions. For Ex. SPC[21], SPC/E, TIP3P[22], TIP4P, TIP 5P, and polarizable water[23]. The benefit of the use of explicit solvation in a simulation of peptide adsorption is that the water molecules are then able to specifically interact with the functional groups of both the amino acid residues of the peptide and the adsorbent surface, with these interactions being in direct competition with the interactions between the water molecules themselves and the amino acid functional groups with those of the adsorbent surface.

At this time, none of the implicit solvation methods have been validated for peptide- surface interaction, and results from their use should be met with healthy skepticism until they can be demonstrated to provide realistic peptide adsorption behavior.

V. SAMPLING

Next important critical issue that must be addressed in any molecular simulation is the issue of sampling. Discussion of this issue will primarily be restricted to MD simulations, although sampling problems are equally of concern when using MC methods. To appreciate the importance of this, it must be realized that a conventional MD simulation typically represents the behavior of a single molecule over a simulated time scale of tens of nanoseconds, while an experimental measurement represents an ensemble average of the behavior of billions of molecules over time spans of milliseconds and longer. This situation raises the obvious question of how can the results of a MD simulation possibly be compared to an experimental measurement? The answer to this question is that MD simulation results can indeed be compared to experimental results if the simulated system is appropriately represented and sufficiently sampled.

One of the main problems with this, however, is that it is often difficult to achieve the necessary degree of sampling. As a complicating factor related to this problem, systemsinvolving the behavior of complex molecular structures, suchas a peptide or a protein adsorbing on a surface, generallyexhibit a very rough potential energy surface, which representsthe relationship between the potential energy as a functionof the coordinates of the system, also referred to as theconfigurational phase space. This potential energy surfacetypically has numerous local low-energy positions that areseparated from one another by relatively high potential energybarriers. To overcome this type of problem, advanced sampling methods can be employed that introduce an artificial driving force into the simulation that enables the system to escape from designated low-energy positions and more fully explore the entire phase space of the system.

To address this sampling issue, either mostly wide and well developed methods including relica exchange molecular dynamics of number of conformations of the peptide starting conformation is necessary, but all these methods require significant development.

VI. FUTURE DIRECTIONS

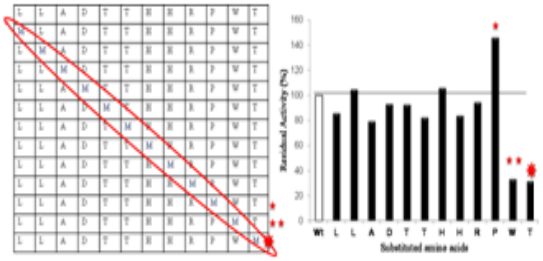

Fig-2:Mutated peptides studied computationally to understand interaction pattern. Reproduced with permission from [17]

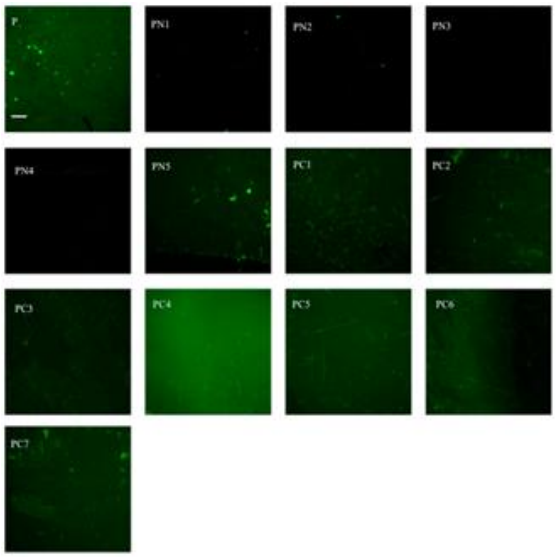

Fig-3:Engineered peptides for greater adhesion to substrate. Reproduced with permission from [24]

New methods and algorithms in the computational chemistry field are continually being developed and refined to improve the capabilities of molecular simulation. Others working on the force-field development in combination with quantum mechanical calculations. Substantial engineering effect is going on from the simulation understanding. Researchers try to mutate a peptide computationally and study the interaction towards material surface (fig.2) [17]. In other scenario, engineered high affinity from the knowledge of simulations (fig.3) [24]. Molecular simulations started to give breakthrough in the field of biomaterials, but it needs more research input.

VII. CONCLUSIONS

Molecular simulation is a rapidly continue to advance in computation power and algorithm development to further improve the way that computational resources are used also continues to progress at a rapid pace. Current computational resources maybe insufficient at this time to enable simulations to be conducted to predict the competitive adsorption behavior of large proteins on biomaterials surfaces to form an equilibrated adsorbed protein layer, and to predict the interactions of membrane-bound cell receptors with this adsorbed protein layer, it is highly likely that within a decade or two that these types of systems will be able to be readily handled. These prospects, coupled with the rapidly developing field of nanotechnology, hold promise for the eventual development of the capabilities of actually being able to proactively design surfaces at the atomic level to specifically control the manner that proteins adsorb, thus controlling surface bioactivity and subsequent cellular response for a broad range of applications in biotechnology and biomedical engineering.

VIII. REFERENCES

[1]. W.B. Tsai, J.M. Grunkemeier, C.D. McFarland, T.A. Horbett, Platelet adhesion to polystyrene-based surfaces preadsorbed with plasmas selectively depleted in fibrinogen, fibronectin, vitronectin, or von Willebrand's factor, J Biomed Mater Res, 60 (2002) 348-359.

[2]. D.G. Castner, B.D. Ratner, Biomedical surface science: Foundations to frontiers, Surface Science, 500 (2002) 28-60.

[3]. V. Hlady, J. Buijs, Protein adsorption on solid surfaces, Current Opinion in Biotechnology, 7 (1996) 72-77.

[4]. S.J. Geelhood, T.A. Horbett, W.K. Ward, M.D. Wood, M.J. Quinn, Passivating protein coatings for implantable glucose sensors: evaluation of protein retention, J Biomed Mater Res B Appl Biomater, 81 (2007) 251-260.

[5]. I. Lynch, K.A. Dawson, Protein-nanoparticle interactions, Nano Today, 3 (2008) 40-47.

[6]. C.-W. Hung, T.R.P. Holoman, P. Kofinas, W.E. Bentley, Towards oriented assembly of proteins onto magnetic nanoparticles, Biochemical Engineering Journal, 38 (2008) 164-170.

[7]. J.B. Hall, M.A. Dobrovolskaia, A.K. Patri, S.E. McNeil, Characterization of nanoparticles for therapeutics, Nanomedicine (Lond), 2 (2007) 789-803.

[8]. M. Hartmann, Ordered mesoporous materials for bioadsorption and biocatalysis, Chemistry of Materials, 17 (2005) 4577-4593.

[9]. Q.X. Mu, W. Liu, Y.H. Xing, H.Y. Zhou, Z.W. Li, Y. Zhang, L.H. Ji, F. Wang, Z.K. Si, B. Zhang, B. Yan, Protein binding by functionalized multiwalled carbon nanotubes is governed by the surface chemistry of both parties and the nanotube diameter, Journal of Physical Chemistry C, 112 (2008) 3300-3307.

[10]. Huang-Hao Yang, Shu-Qiong Zhang, Xiao-Lan Chen, Zhi-Xia Zhuang, a. Jin-Gou Xu, X.-R. Wang, Magnetite-Containing Spherical Silica Nanoparticles for Biocatalysis and Bioseparations, (2004).

[11]. S. Sanchez, M. Pumera, E. Fabregas, Carbon nanotube/polysulfone screen-printed electrochemical immunosensor, Biosens Bioelectron, 23 (2007) 332-340.

[12]. D.A. Beck, V. Daggett, Methods for molecular dynamics simulations of protein folding/unfolding in solution, Methods, 34 (2004) 112-120.

[13]. I. Halperin, B. Ma, H. Wolfson, R. Nussinov, Principles of docking: An overview of search algorithms and a guide to scoring functions, Proteins, 47 (2002) 409-443.

[14]. I. Muegge, Selection criteria for drug-like compounds, Med Res Rev, 23 (2003) 302-321.

[15]. S.K. Ramakrishnan, M. Martin, T. Cloitre, L. Firlej, C. Gergely, Design rules for metal binding biomolecules: understanding of amino acid adsorption on platinum crystallographic facets from density functional calculations, Physical chemistry chemical physics : PCCP, 17 (2015) 4193-4198.

[16]. S.K. Ramakrishnan, E. Estephan, M. Martin, T. Cloitre, C. Gergely, Probing the mechanism of material specific peptides for optical biosensors, Bio-Mems and Medical Microdevices, 8765 (2013).

[17]. S.K. Ramakrishnan, M. Martin, T. Cloitre, L. Firlej, C. Gergely, Molecular mechanism of selective binding of peptides to silicon surface, J Chem Inf Model, 54 (2014) 2117-2126.

[18]. S.W. Bunte, H. Sun, Molecular modeling of energetic materials: The parameterization and validation of nitrate esters in the COMPASS force field, Journal of Physical Chemistry B, 104 (2000) 2477-2489.

[19]. J. Feng, R.B. Pandey, R.J. Berry, B.L. Farmer, R.R. Naik, H. Heinz, Adsorption mechanism of single amino acid and surfactant molecules to Au {111} surfaces in aqueous solution: design rules for metal-binding molecules, Soft Matter, 7 (2011) 2113-2120.

[20]. S.K. Ramakrishnan, M. Martin, T. Cloitre, L. Firlej, F.J. Cuisinier, C. Gergely, Insights on the facet specific adsorption of amino acids and peptides toward platinum, J Chem Inf Model, 53 (2013) 3273-3279.

[21]. A. Glattli, X. Daura, W.F. van Gunsteren, Derivation of an improved simple point charge model for liquid water: SPC/A and SPC/L., Journal of Chemical Physics. 6/8/2002, 116 (2002) 9811.

[22]. P.M. and, L. Nilsson*, Structure and Dynamics of the TIP3P, SPC, and SPC/E Water Models at 298 K, (2001).

[23]. S.J.S. Steven W. Rick, Joel S. Bader, B.J. Berne, Fluctuating charge force fields for aqueous solutions, Volumes 65–66 (1995) 31–40.

[24]. S.K. Ramakrishnan, S. Jebors, M. Martin, T. Cloitre, V. Agarwal, A. Mehdi, J. Martinez, G. Subra, C. Gergely, Engineered Adhesion Peptides for Improved Silicon Adsorption, Langmuir : the ACS journal of surfaces and colloids, 31 (2015) 11868-11874.

