A SimBioMa Workshop

Challenges in Modelling the Interface Between Biomolecules and Inorganic Surfaces

18–20 March 2009, Schloss Waldthausen, Mainz, Germany

Organised by Tiffany Walsh and Mike Allen, University of Warwick, U.K., and Wolfgang Paul, University of Mainz, Germany. Supported by the European Science Foundation and the Engineering and Physical Sciences Research Council.

Summary

This workshop brought together 5 experimentalists and 35 computer simulators to discuss current problems in the simulation of the interface between biomolecules, especially peptides and proteins, and inorganic surfaces. There were 31 residential and 9 local participants. ESF funding was used to support the accommodation and subsistence of the participants, and the meeting was additionally supported from a UK EPSRC grant to cover the remaining accommodation and subsistence costs, plus travel for participants coming from outside Europe.

The oral presentations covered experimental determination of genetically-engineered peptide adsorption and possible applications in nanotechnology (Sarikaya, Tamerler, Oren) as well as biominerals (Perry), adsorption on semiconductors (Goede), and the influence of intrinsically disordered proteins (Evans); Monte Carlo simulations using very simple lattice-based and off-lattice models (Janke, Hsu, Taylor, Bachmann); atomistic simulations of adsorption and adhesion (Kubiak, Sushko, Notman, Langel, Köppen, Kokh, Walsh, Yang, Vila Verde); and electronic structure calculations for biomolecules on surfaces (Delle Site, Ugliengo, Corno, Corni).

A dozen posters were presented, covering adsorption of small molecules and biomolecules on minerals (Cooke, Freeman), electronic structure calculations on organic molecules in clays (Geatches), enzyme reactions (Palma), nucleation and growth of crystals (Harding), water layers at metals (Ghiringelli), self assembly (Martsinovich, Meskine), phase behaviour of polymers and peptides near surfaces (Swetnam, Möddel), entanglement in polymer globules (Reith) and surface-molecule force-field development (Tomasio).

The discussions between participants included the following points.

- The importance of surface relaxation and the water layers near the surface in accommodating adsorbed biomolecules.
- The enormous range of simulation techniques required to understand, simultaneously, large-scale effects such as aggregation and cooperativity in the adsorption process, alongside specific quantum chemistry and interaction energetics, giving possibly high selectivity.
- The importance of proper experimental characterization of surfaces, particularly in situations that represent what happens *in vivo*, and the transfer of this knowledge to the simulation.

It was generally remarked that this is a rapidly evolving field, and the workshop provided a useful opportunity for the interaction of experts in widely differing simulation techniques, plus a better understanding of how experiment and simulation may be related. A suggestion to hold a similar workshop in about two years was strongly supported.

Scientific Content and Discussion

Oral Presentations

Modeling and Simulation of Peptide Adsorption at Silicon Substrates
Michael ***Bachmann***, University of Leipzig
Our multicanonical Monte Carlo simulations of a novel hybrid peptide-substrate model revealed the correspondence between proline mutation and binding affinity to a clean silicon substrate. After the synthesis of theoretically suggested amino-acid sequences with different binding behaviour, subsequent atomic-force microscopy experiments confirmed the relevance of the selective mutations upon adhesion.

Simulating the interaction of peptides and gold surfaces in water
Stefano ***Corni***, University of Modena
We performed density functional theory and classical molecular dynamics simulations of the interactions between peptides and the Au(111) surface in explicit water. The interplay between the gold-water and the gold-peptide interactions will be discussed, as well as the related capability of the peptides to displace water from the gold surface.

Hydroxyapatite surfaces in interaction with biomolecules: from H_2O to amino acids
Marta ***Corno***, Albert Rimola and Piero Ugliengo, University of Torino
B3LYP periodic simulations of the adsorption processes of different molecules (H_2O, CO, HCOOH, glycine and some other amino acids) on 001 and 010 hydroxyapatite surfaces have been carried out by means of the quantum-mechanical CRYSTAL06 code. Results are compared to experimental data (microcalorimetric and IR spectroscopic measurements). For amino acids, the stability of different forms of interaction, neutral vs zwitterionic, as well as H_2O role in the interaction will be presented.

Large molecules near metal surfaces: a density functional-based bridging-scale approach
Luigi ***Delle Site***, MPI for Polymer Research, Mainz
We present a hierarchical quantum-classical scale-bridging approach for modeling and simulating large molecules in bulk and in solution, on inorganic (metal) surfaces. Some examples include the study of the adsorption of oligopeptides on a Pt(111) in solution. Also, for a future perspective, the basic idea of an adaptive resolution simulation technique for studying such problems is presented.

IDP sequences: preferred tools for bio-inspired inorganic materials
John Spencer ***Evans***, New York University
Intrinsically disordered proteins (IDPs) are characterized by an almost complete lack of folded structure and an extended conformation with high intramolecular flexibility and little secondary structure. This talk will present examples of biomineral-associated IDP sequences as well as inorganic interaction bacterial and phage display sequences. We conclude that the sequence and structural features encoded within the IDP genomes may lead to inorganic interaction and materials/nanotechnological applications.

Mid-infrared spectroscopy of thin amino-acid and peptide layers on semiconductors
Karsten ***Goede***, Marius Grundmann, University of Leipzig
We have employed FTIR spectroscopy to detect thin layers of several amino acids and 12-mer peptides on semiconductor substrates in the mid-infrared (MIR) and also the far-infrared (FIR). While it is known that these peptides are largely unfolded in watery solution, there are indications that the approach of an attractive substrate by a peptide molecule might stabilise its folded conformations. Another central finding is the nearly complete absence of water within these amino-acid and peptide layers.

Adsorption of multi-block and random copolymer on a solid surface
Hsiao-Ping ***Hsu***, University of Mainz
The adsorption of a single multi-block AB-copolymer on a solid planar substrate is investigated by means of an off-lattice bead-spring model, lattice computer simulations using PERM, and scaling analysis. We discuss how the critical adsorption energy and the fraction of adsorbed monomers depend on the block length of sticking monomers and on the total length of the polymer chains. The findings of both methods are fully consistent and in good agreement with theoretical predictions.

Aggregation and Crystallization of Semiflexible Polymers
Wolfhard ***Janke***, Michael Bachmann, University of Leipzig
Christoph Junghans, MPI for Polymer Research, Mainz
By means of multicanonical computer simulations, we investigate thermodynamic properties of the aggregation of interacting semiflexible polymers, using a mesoscopic bead-stick model. In aggregation the constituents experience strong structural fluctuations, similar to peptides in coupled folding-binding cluster formation processes. In contrast to a recently studied related proteinlike hydrophobic-polar heteropolymer model, aggregation and crystallization are separate processes here.

Brownian dynamic simulation of protein adsorption on metal surfaces
D. B. ***Kokh***, B. Huang, R. C. Wade, P. J. Winn, EML Research, Heidelberg
Our approach is designed to treat large molecules in continuous water with Brownian dynamics, yet keeping atomistic effects of the biomolecular-water-solid state interface interactions. Adsorption of the BLIP (beta-lactamase inhibitor protein) protein fused with different homotripeptides to the gold surface is explored. Simulation results are compared with the experimentally observed binding characteristics.

Simulations on the Adhesion Energetics of Peptides and Titanium Dioxide Surfaces
Susan ***Köppen***, Universität Bremen, Walter Langel, Universität Greifswald
We present a method for deducing rupture forces and adhesion energies of peptides on rutile (100) surfaces from force field simulations. Adhesion is mainly mediated by charged side chains forming single contacts to oppositely charged surface groups. A clear distinction can be made between charged and polar side chains having adhesion energies around 100 and 70 kJ/mol, respectively. The adsorption configurations and energy data are in good agreement with results from quantum mechanics for monomers.

Protein adsorption on the solid surface: lysozyme-on-mica studied by MD approach
Karina ***Kubiak*** University of Strathclyde and Nicolaus Copernicus University
Paul Mulheran, University of Strathclyde
We present results of fully atomistic MD simulations of hen egg white lysozyme adsorption on a negatively charged SiO_2 surface that mimics flat and shaped mica surfaces. Comparison of adsorption features on flat and not-flat surfaces with experiment explains well some contradictions in the literature. In all cases, the extended hydrogen bond network between the crucial residues and the water layers at the surface constrains the adsorbed protein diffusion rate supporting our previous experimental results.

Collagen on titanium implant surfaces: a refined model for the interaction of triple helix and telopeptide with titanium dioxide layers
Wenke Friedrichs, Bastian Ohler, Walter ***Langel***, University of Greifswald
Susan Köppen, University of Bremen, Susanna Monti, IPCF-CNR, Pisa
Recently, enhanced bone tissue formation was observed on collagen coated titanium based implants. The networking of collagen peptides with other molecules is largely determined by terminal telopeptides with variable structures. Our calculations show that the telopeptides relax to a very flexible structure consisting of partial α- and collagen folds. We present calculations on longer fragments for observing the curvature of the strands and the structure of surfaces with roughness of about 10–20 Å.

Molecular dynamics studies of peptides binding to quartz surfaces
Rebecca ***Notman*** and Tiffany Walsh, University of Warwick
We have studied strong and weak quartz-binding peptides in solution using replica exchange MD. In solution, weak binders form intramolecular hydrogen bonds that stabilise the peptide whereas strong binders tend not to. The proline residues interact directly with the surface and strongly influence the conformations of the peptides by reducing the flexibility of the backbone. It seems that that peptides that have a high binding affinity have many local minima on the binding energy landscape.

Knowledge-based design of GEPI (Genetically Engineered Proteins for Inorganics)
E. Emre ***Oren***, R. Samudrala, M. Gungormus, J. Horst, T. Kacar, M. Hnilova, H. Fong, J. S. Evans, C. Tamerler and M. Sarikaya, University of Washington
We combine experimental knowledge with bioinformatics, generating novel material specific scoring

matrices that optimize the similarities within the strong-binding peptide sequences and the differences between the strong- and weak-binding peptides. Hence, we designed novel peptides with specific affinities and multiple functionalities (e.g. peptides capable of binding to only quartz or gold, both or neither).

Experimental and Computational Studies of Peptide/Protein Mineral Interactions

C. C. ***Perry***, O. Deschaume and S. V. Patwardhan, Nottingham Trent University

A wide range of experimental techniques (microscopic, spectroscopic, particle sizing, thermal methods and solution methods) are used to study interactions between (bio)molecules and molecular and colloidal species that are coupled with computational simulation studies to gain as much information as possible on the molecular scale interactions. Our goal is to identify 'rules' or 'guiding principles' that could be used to explain and hence predict behaviour for a wide range of (bio)molecule-mineral systems.

Molecular recogition of solid-binding peptides

Mehmet ***Sarikaya***, University of Washington

We are combining genetic tools with synthetic nanoscale constructs and create a hybrid methodology, molecular biomimetics. We will review the latest developments, focusing on i. Fundamental issues in genetic design, molecular recognition, and assembly of peptides; ii. Bioenabled nano-photonics, -magnetics, and -electronics; and iii. Practical implementation in inorganic biosynthesis and fabrication towards molecular and nano-imaging, sensing (diagnostics), and tissue regeneration.

Nanomechanics of monolayers of biomolecules on metal surfaces

Maria ***Sushko***, University College London

The sensitivity of curvature measurements in cantilever sensors is now high enough to follow chemical reactions and subtle physical transformations in the active layer, such as deprotonation reactions, swelling of polymer brushes, DNA hybridization. I will present a systematic study of these three systems, based on classical DFT and atomistic simulations, and the first quantitative model underpinning the mechanism for transduction of the molecular signal into the macroscopic response of the device.

Inorganic binding peptides as fundamental molecular systems

Candan ***Tamerler*** and Mehmet Sarikaya

Istanbul Technical University and University of Washington

The Genetically engineered peptides for inorganics (GEPIs) are experimentally selected using biocombinatorial techniques (phage and cell surface display), bioinformatically refined and knowledge-based-designed for specific synthesis, binding and assembly functions. We provide proof-of-principle examples of their utilization as molecular linkers, couplers and growth modifiers for future bio-based materials.

Protein-like folding and thermodynamics for a homopolymer chain

Mark P. ***Taylor***, Jutta Luettmer-Strathmann, Wolfgang Paul, Kurt Binder

Hiram College and University of Mainz

We have recently shown that a flexible homopolymer chain with sufficiently short range interactions undergoes an "all-or-none" first-order transition from an expanded coil to a compact crystallite: a distinctive feature of one-step protein folding. Wang-Landau (WL) sampling shows that the transition proceeds via the formation of a folding nucleus (a small crystallite attached to one or more unfolded chain segments) consistent with the nucleation-condensation picture of protein folding.

Large scale periodic B3LYP modeling of oxides relevant as biomaterials

P. ***Ugliengo***, R. Dovesi, M. Corno, A. Pedone and A. Rimola, University of Torino

Realistic models of amorphous silica surfaces and MCM-41 mesoporous material will be illustrated as the result of large scale B3LYP simulation. Comparison with structural and vibrational experimental data confirms the validity of these models. B3LYP simulations of the interaction between a miniprotein (13 aminoacids) with the most stable (001) surface of HA will be reported. The same approach was also adopted for simulating the full vibrational spectrum of an amorphous model of the Hench's glass.

Understanding adsorption of peptides on metals from all-atom MD simulations

Ana ***Vila Verde***, Janna K. Maranas, AMOLF, Amsterdam

Here we report all-atom molecular dynamics simulations of adsorption of gold-binding and non gold-

binding peptides on gold surfaces. Our results indicate that stronger adsorption occurs when the peptide is structurally unstable and flexible enough to maximize the number of contacts with the surface, e.g. mostly random coils or containing flexible hinges. These effects are as important for adsorption as the content in amino acids with high affinity for the surface.

Molecular dynamics simulations of charged peptides on calcite surface

Mingjun ***Yang***, S. L. S. Stipp, University of Copenhagen

Mark Rodger, University of Warwick, John Harding, University of Sheffield

A series of MD simulations have been carried out to investigate the interactions between charged peptides and a calcite (104) surface in water solution. The results show that acidic amino acids can have strong electrostatic interactions with calcite surface, while the basic and neutral amino acids tend to stay around the second water layer. It has also been found that specific configurations of the peptides have great influences on surface binding.

Modelling Binding Affinity at Peptide-Surface Interfaces: the role of mutations

Tiffany R. ***Walsh***, University of Warwick

Using molecular simulation, we have identified the crucial role of intra-peptide interactions in peptide-inorganic binding for titania. We have also made a detailed investigation of the importance of tryptophan in nanotube-binding peptides via point mutations, and advance a hypothesis based on interfacial shape, possibly explaining why aromatic residues might not dominate in graphite-binding peptides.

Poster Presentations

Computer modelling of the interface of alcohol and water with calcite surfaces

David ***Cooke***, Richard Grey and James Elliott, Universities of Huddersfield and Cambridge

Free energy adsorption at mineral surfaces

Colin L ***Freeman*** and John H Harding, University of Sheffield

Is clay the key to chiral selection?

Dawn ***Geatches***, Chris Greenwell, Stewart Clark, University of Durham

Water chains on metal steps

Luca M. ***Ghiringhelli***, FHI, Berlin, Luigi Delle Site, MPI for Polymer Research, Mainz

Models for the nucleation and growth of calcium carbonate

John ***Harding***, University of Sheffield, and EPSRC Materials Modelling Consortium

Theoretical studies of hydrogen-bonded supramolecular structures on surfaces

N. ***Martsinovich*** and A. Troisi, University of Warwick

Mechanisms and dynamics of protein clustering on a solid surface

Paul Mulheran, Karina Kubiak and Hakim ***Meskine***, University of Strathclyde

Conformational mechanics of polymer adsorption transitions at attractive substrates

Monika ***Möddel***, Michael Bachmann and Wolfhard Janke, University of Leipzig

Horseradish peroxidase enzyme: a computational study

A. ***Palma***, CNR-ISMN, Rome, et al.

Influence of chain stiffness and sequence on knottedness in polymer globules

Daniel ***Reith***, University of Mainz

Monte Carlo simulation of lattice peptides near surfaces

Adam ***Swetnam***, University of Warwick

Modelling the interaction between peptides and graphitic surfaces using a polarisable force-field: the role of mutations

Susana ***Tomasio*** and Tiffany Walsh, University of Warwick

Discussion, Results and Impact

Several important issues came out of the discussions between participants.

Frequently the solid surface is modelled as a rigid entity, and sometimes the details of solvent structure are neglected, or the solvent is omitted altogether. Both these approximations may have serious consequences. Some of the atomistic simulations indicate that the structure of the water layers near the surface may be more important than the precise nature of the solid underneath. For some systems, experiments suggest that water is expelled when the peptide layer forms. Also, water rearrangement around the biomolecule is likely to play a significant role in the thermodynamics. In all cases, relaxation and equilibration of the interface may be important. Although all these features may be subtle, system specific, and point to the need for realistic simulations, the expense of those simulations may put these phenomena out of reach. The development of suitable coarse-grained models, to explain specificity of adsorption, remains a challenge.

Several talks raised issues of disorder in peptides and proteins in solution, the contribution of flexibility and multiple absorbed configurations on the thermodynamics, the role of cooperativity and aggregation in the process of adsorption, and in general the relative contributions of energetic and entropic effects. The most coarse-grained models, notably lattice models, but (as mentioned in some of the talks) also now off-lattice models, can be analyzed in great detail, giving general insight into the phase transitions and families of conformations of folded and unfolded polymers and proteins both away from, and near to, simple surfaces. However, there is a considerable gap to be bridged between these models and chemically accurate ones. How much of the chemistry and physics is really necessary? Are the established coarse-graining techniques sufficient?

Experimentalists and simulators discussed surface characterization, and the variety of surfaces that are of interest. The effects of adsorption strength on the rate of growth of different crystal facets is one example; but the situation becomes more intersting and complicated when one considers adsorption in mesoporous materials, on amorphous material surfaces, and on nanoparticles which may vary in size, composition and possible surface contaminants. The presence or absence of oxide layers, surface charges and hydrogen ions are relatively simple examples, but they are not the only ones. For systems that are close to the *in vivo* situation, such as biomineralization, adsorption of peptides and proteins may be preceded by the development of concentration gradients of other biomolecules near the surface. It was emphasized that, to make contact between experiment and modelling, one needs to be sure of the context in which, and the conditions under which, the data is obtained.

It is expected that the meeting will further stimulate a lively area of computer modelling, which is attempting to address highly complex issues at the (multidimensional) borderline between chemistry, physics, biology, and materials engineering.

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Final Programme

	Wednesday March 18th	
09:00 - 09:05	**Welcome**	
09:05 - 09:50	M. Sarikaya	*Molecular recognition of solid-binding peptides*
09:50 - 10:20	W. Janke	*Aggregation and crystallization of semiflexible polymers*
10:20 - 10:50	H.-P. Hsu	*Adsorption of multi-block and random copolymer on a solid surface*
10:50 - 11:10	**Coffee and Posters**	
11:10 - 11:40	C. Tamerler	*Inorganic binding peptides as fundamental molecular systems*
11:40 - 12:10	M. Taylor	*Protein-like folding and thermodynamics for a homopolymer chain*
12:10 - 12:40	M. Bachmann	*Modeling and simulation of peptide adsorption at silicon substrates*
12:40	**Lunch**	
14:30 - 15:00	L. Delle Site	*Large molecules near metal surfaces: a DFT-based bridging-scale approach*
15:00 - 15:30	M. Sushko	*Nanomechanics of monolayers of biomolecules on metal surfaces*
15:30 - 15:45	**Tea and Posters**	
15:45 - 16:15	D. Kokh	*Brownian dynamic simulation of protein adsorption on metal surfaces*
16:15 - 16:45	K. Goede	*Mid-IR spectroscopy of thin amino-acid and peptide layers on semiconductors*
16:45 - 17:15	E. Oren	*Knowledge-based design of Genetically Engineered Proteins for Inorganics*
17:15	**Discussions and wrap up**	
	Thursday, March 19th	
09:00 - 09:30	J. Evans	*Intrinsically disordered protein sequences: preferred tools for bio-inspired inorganic materials*
09:30 - 10:00	T. Walsh	*Modelling binding affinity at peptide-surface interfaces: the role of mutations*
10:00 - 10:30	M. Yang	*Molecular dynamics simulations of charged peptides on calcite surface*
10:30 - 11:00	S. Corni	*Simulating the interaction of peptides and gold surfaces in water*
11:00 - 11:25	**Coffee and Posters**	
11:25 - 11:55	C. Perry	*Experimental and computational studies of peptide/protein mineral interactions*
11:55 - 12:25	R. Notman	*Molecular dynamics studies of peptides binding to quartz surfaces*
12:25 - 12:55	A. Vila Verde	*Understanding adsorption of peptides on metals from all-atom molecular dynamics simulations*
12:55	**Lunch and Free Afternoon**	
Evening	**Posters, Discussion, Bowling Competition**	
	Friday, March 20th	
09:00 - 09:30	P. Ugliengo	*Large scale periodic B3LYP modeling of oxides relevant as biomaterials*
09:30 - 10:00	K. Kubiak	*Protein adsorption on the solid surface: lysozyme-on-mica studied by molecular dynamics approach*
10:00 - 10:30	W. Langel	*Collagen on titanium implant surfaces: a refined model for the interaction of triple helix and telopeptide with TiO_2 layers*
10:30 - 10:45	**Coffee and Posters**	
10:45 - 11:15	M. Corno	*Hydroxyapatite surfaces in interaction with biomolecules from H_2O to amino acids*
11:15 - 11:45	S. Köppen	*Simulations on the adhesion energetics of peptides and TiO_2 surfaces*
11:45 - 12:05	**Discussion, Wrap Up and Farewell**	