Molecular Dynamics Simulations of Protein-Surface Interactions

Daniel Cole, Mike Payne
Theory of Condensed Matter Group, Cavendish Laboratory, Cambridge, U.K.

Lucio Colombi Ciacchi
Institute for Reliability of Systems and Devices, Karlsruhe, Germany
Fraunhofer Institute for Mechanics of Materials, Freiburg, Germany

TCM

IWM
Institut
Werkstoffmechanik

Introduction

That looks like Biology.

Why protein-surface interactions are important in selecting candidate materials for biomedical applications.

Where are the electrons?

Ab-initio study of Si surface structure, native oxide growth and its interactions with water.

What's that got to do with proteins?

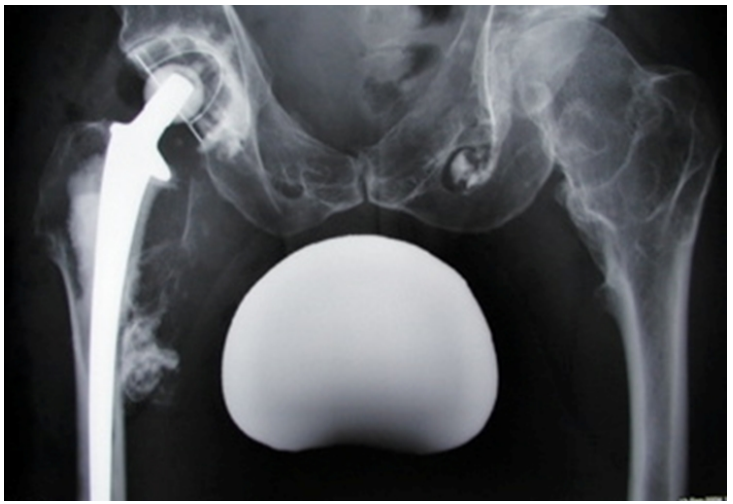
Investigate adhesion at the solid/liquid interface, taking into account the molecular nature of the solvent and considering a realistic model for the Si surface.

Materials design

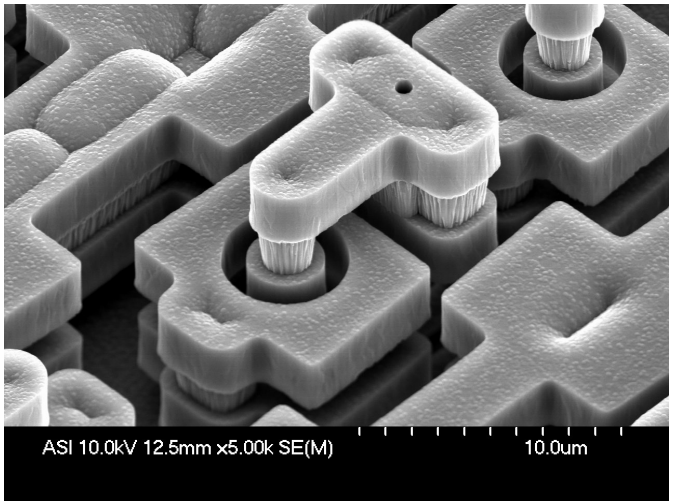
Behaviour of surfaces in physiological environment important for design of materials for biomedical applications.

Ti-based orthopaedic implants

Biosensors for measurement of pH, pressure, analyte conc.



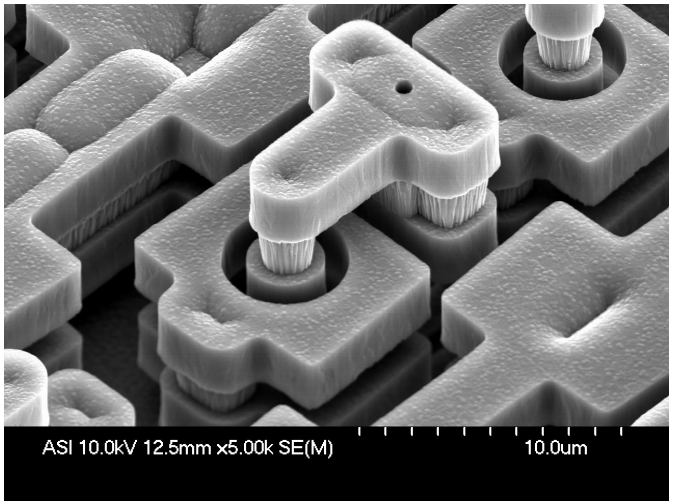
MEMS



Si-based microelectromechanical systems (MEMS)

- transduce physical/chemical stimuli into electrical signals
- well-established manufacturing techniques
- small size

MEMS

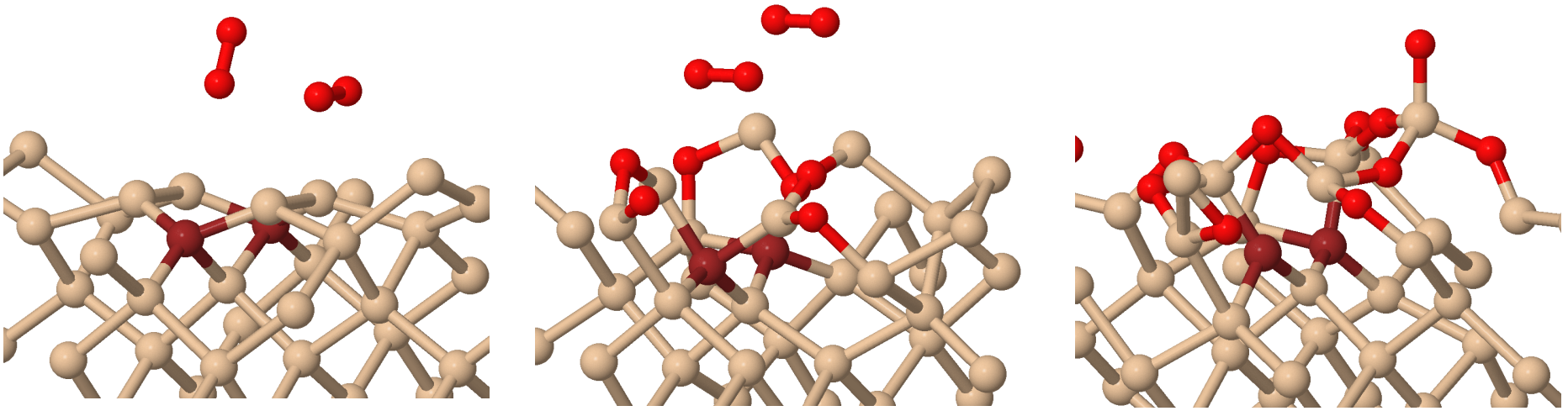


Device surface mediates response to external environment

Such interactions may be influenced by P/B dopants in the bulk if they segregate to the surface

Under physiological conditions, Si is terminated by a thin native oxide layer

Dopant segregation

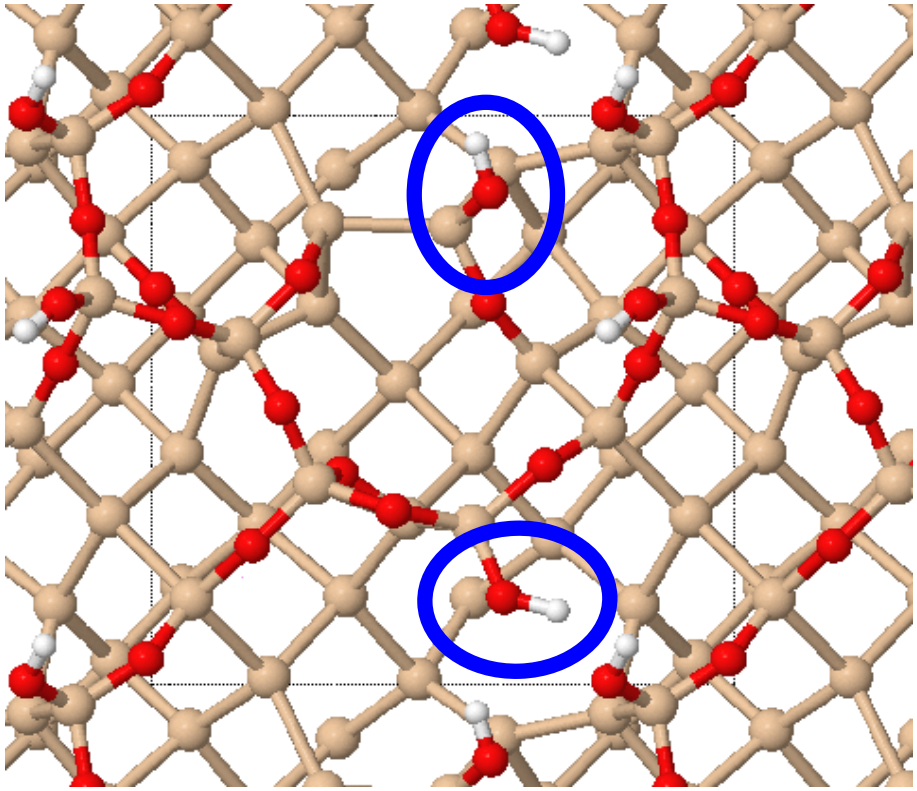


Oxide is built up on surface while dopants remain trapped at Si/SiO_x interface

Dopants do not affect interactions with external environment

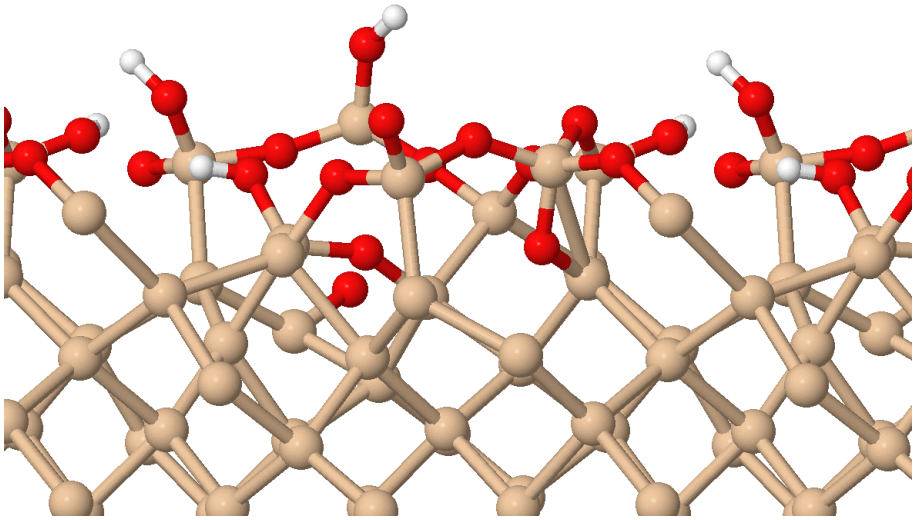
D. J. Cole, M. C. Payne, L. Colombi Ciacchi *Surf. Sci.* **601**, 4888 (2007)

Water adsorption



top view

In humid environment, water attacks strained Si-O bonds



side view

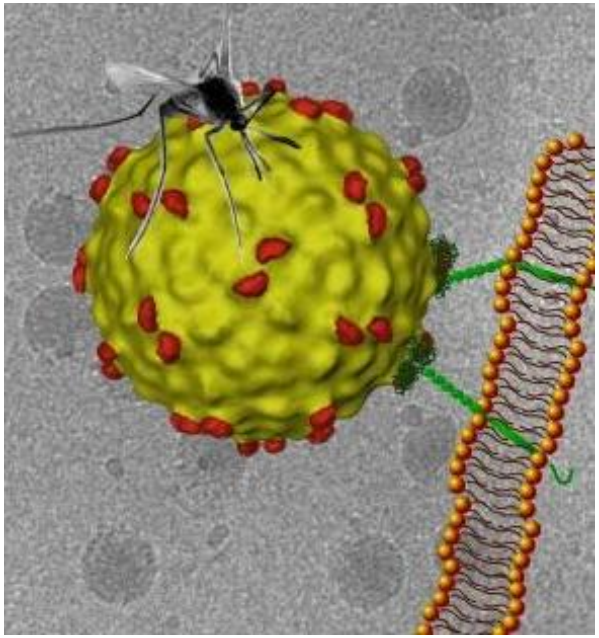
L. Colombi Ciacchi, D. J. Cole, M. C. Payne, P. Gumbsch, submitted for publication

Extra-cellular matrix

Implanted device should guide cell assembly to promote biocompatibility with surrounding tissue

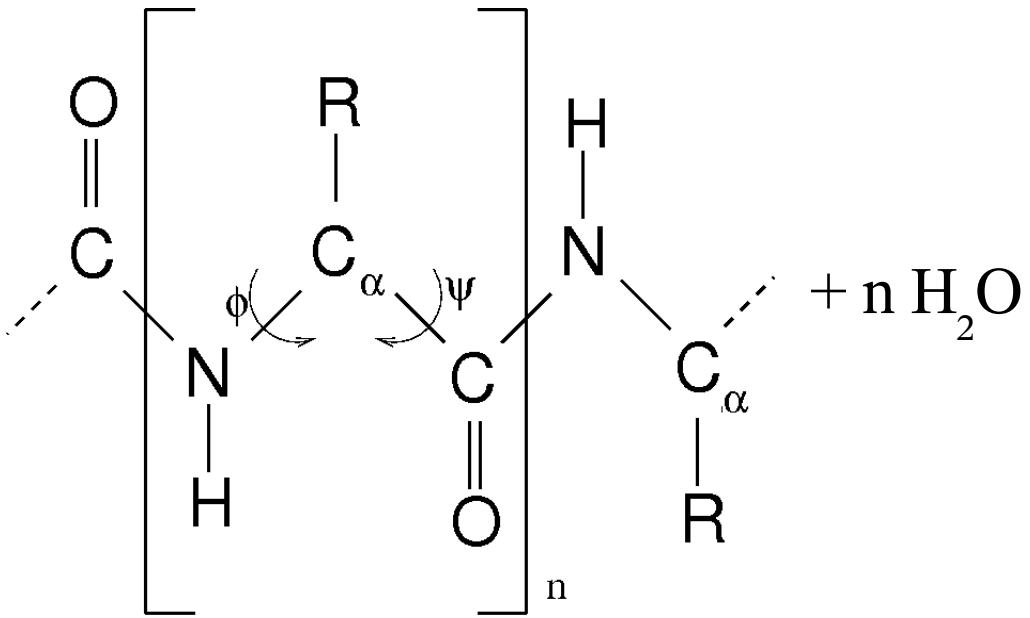
Helps to anchor device, discourages immune response, minimises bacterial contamination

Cells do not adhere directly to implanted surfaces, but instead bind to proteins in the extra-cellular matrix (ECM) via integrin receptors



Aside - proteins

Proteins are long-chain polymers formed by the condensation of amino acid residues

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ASP ALA HIS LYS SER GLU VAL ALA HIS ARG PHE LYS ASP
LEU GLY GLU GLU ASN PHE LYS ALA LEU VAL LEU ILE ALA
PHE ALA GLN TYR LEU GLN GLN CYS PRO PHE GLU ASP HIS
VAL LYS LEU VAL ASN GLU VAL THR GLU PHE ALA LYS THR
CYX VAL ALA ASP GLU SER ALA GLU ASN CYX ASP LYS SER
LEU HIS THR LEU PHE GLY ASP LYS LEU CYX THR VAL ALA
THR LEU ARG GLU THR TYR GLY GLU MET ALA ASP CYX CYX
ALA LYS GLN GLU PRO GLU ARG ASN GLU CYX PHE LEU GLN
HIS LYS ASP ASP ASN PRO ASN LEU PRO ARG LEU VAL ARG
PRO GLU VAL ASP VAL MET CYX THR ALA PHE HIS ASP ASN
GLU GLU THR PHE LEU LYS LYS TYR LEU TYR GLU ILE ALA
ARG ARG HIS PRO TYR PHE TYR ALA PRO GLU LEU LEU PHE
PHE ALA LYS ARG TYR LYS ALA ALA PHE THR GLU CYX CYX
GLN ALA ALA ASP LYS ALA ALA CYX LEU LEU PRO LYS LEU
ASP GLU LEU ARG ASP GLU GLY LYS ALA SER SER ALA LYS
GLN ARG LEU LYS CYX ALA SER LEU GLN LYS PHE GLY GLU
ARG ALA PHE LYS ALA TRP ALA VAL ALA ARG LEU SER GLN
ARG PHE PRO LYS ALA GLU PHE ALA GLU VAL SER LYS LEU
VAL THR ASP LEU THR LYS VAL HIS THR GLU CYX CYX HIS
GLY ASP LEU LEU GLU CYX ALA ASP ASP ARG ALA ASP LEU
ALA LYS TYR ILE CYX GLU ASN GLN ASP SER ILE SER SER
LYS LEU LYS GLU CYX CYX GLU LYS PRO LEU LEU GLU LYS
SER HIS CYX ILE ALA GLU VAL GLU ASN ASP GLU MET PRO
ALA ASP LEU PRO SER LEU ALA ALA ASP PHE VAL GLU SER
LYS ASP VAL CYX LYS ASN TYR ALA GLU ALA LYS ASP VAL
PHE LEU GLY MET PHE LEU TYR GLU TYR ALA ARG ARG HIS
PRO ASP TYR SER VAL VAL LEU LEU LEU ARG LEU ALA LYS
THR TYR GLU THR THR LEU GLU LYS CYX CYX ALA ALA ALA
ASP PRO HIS GLU CYX TYR ALA LYS VAL PHE ASP GLU PHE
LYS PRO LEU VAL GLU GLU PRO GLN ASN LEU ILE LYS GLN
ASN CYX GLU LEU PHE GLU GLN LEU GLY GLU TYR LYS PHE
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GLN VAL SER THR PRO THR LEU VAL GLU VAL SER ARG ASN
LEU GLY LYS VAL GLY SER LYS CYX CYX LYS HIS PRO GLU
ALA LYS ARG MET PRO CYX ALA GLU ASP TYR LEU SER VAL
VAL LEU ASN GLN LEU CYX VAL LEU HIS GLU LYS THR PRO
VAL SER ASP ARG VAL THR LYS CYX CYX THR GLU SER LEU
VAL ASN ARG ARG PRO CYX PHE SER ALA LEU GLU VAL ASP
GLU THR TYR VAL PRO LYS GLU PHE ASN ALA GLU THR PHE
THR PHE HIS ALA ASP ILE CYX THR LEU SER GLU LYS GLU
ARG GLN ILE LYS LYS GLN THR ALA LEU VAL GLU LEU VAL
LYS HIS LYS PRO LYS ALA THR LYS GLU GLN LEU LYS ALA
VAL MET ASP ASP PHE ALA ALA PHE VAL GLU LYS CYX CYX
LYS ALA ASP ASP LYS GLU THR CYX PHE ALA GLU GLU GLY
LYS LYS LEU VAL ALA ALA SER GLN ALA ALA LEU GLY LEU
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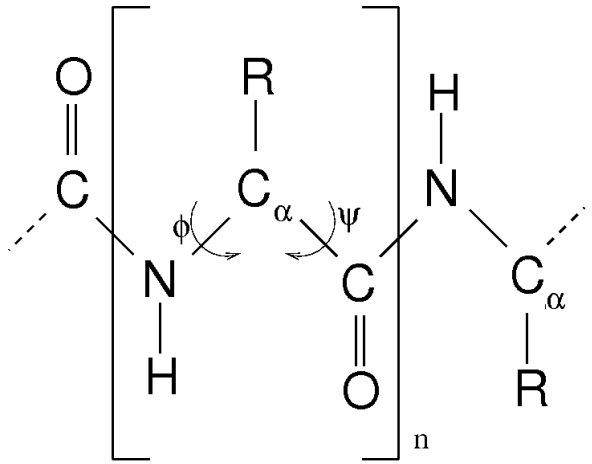
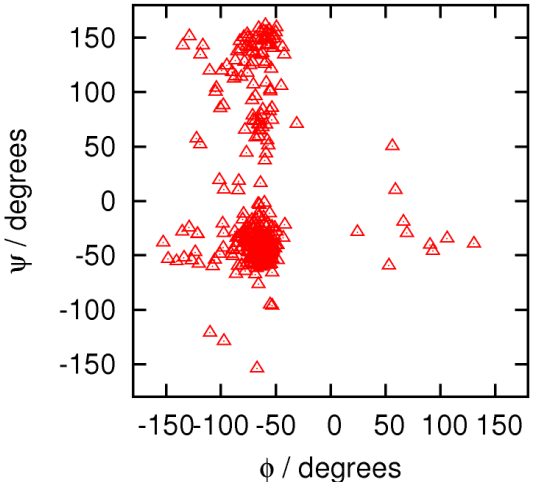
Aside - proteins

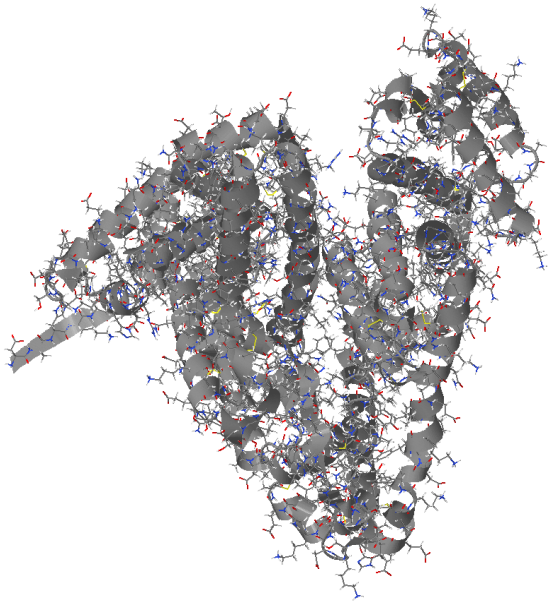
Protein backbone consists of repeating -N-C_α-C- motif

Pattern of backbone atoms gives secondary structure

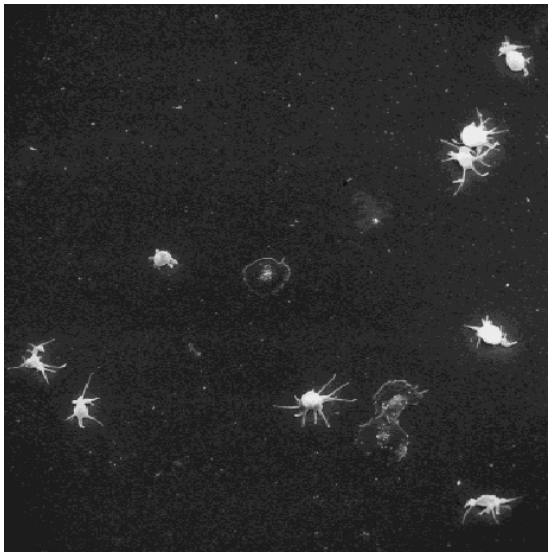
Strong relationship between protein structure and function

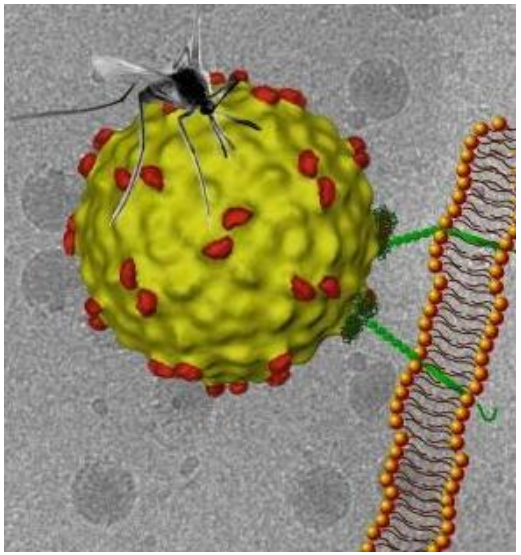


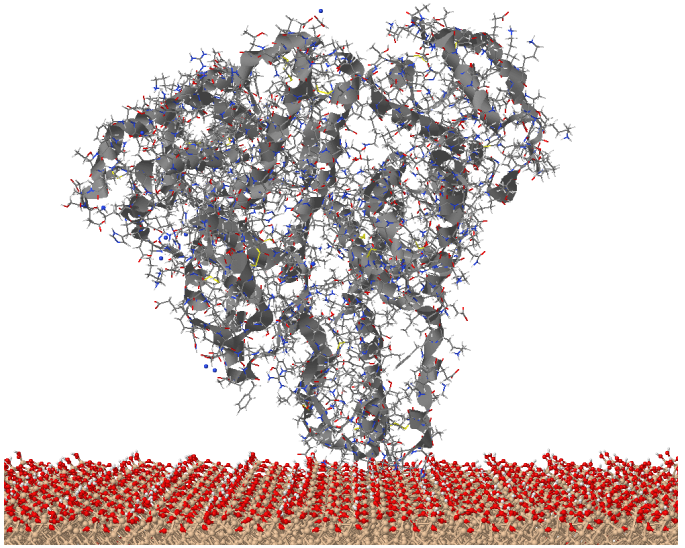




Rational design of MEMS



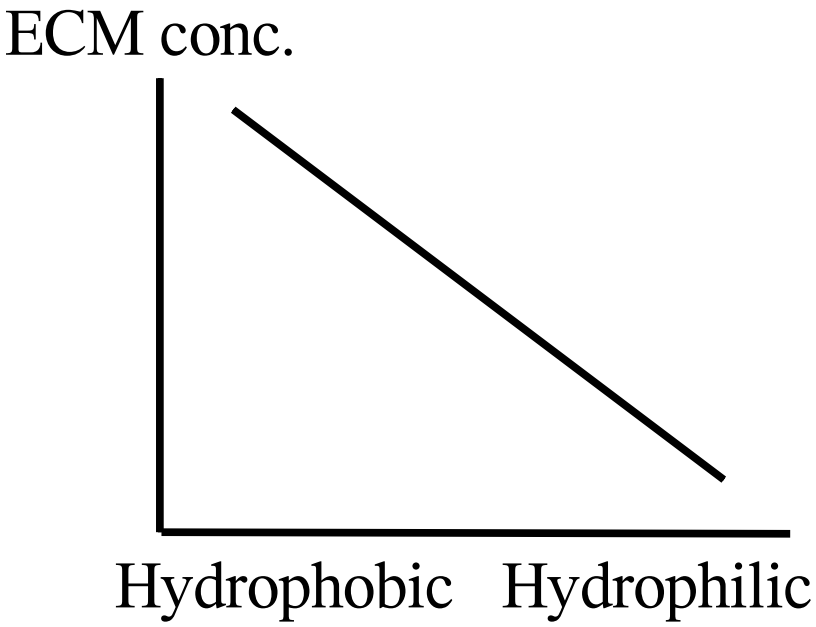


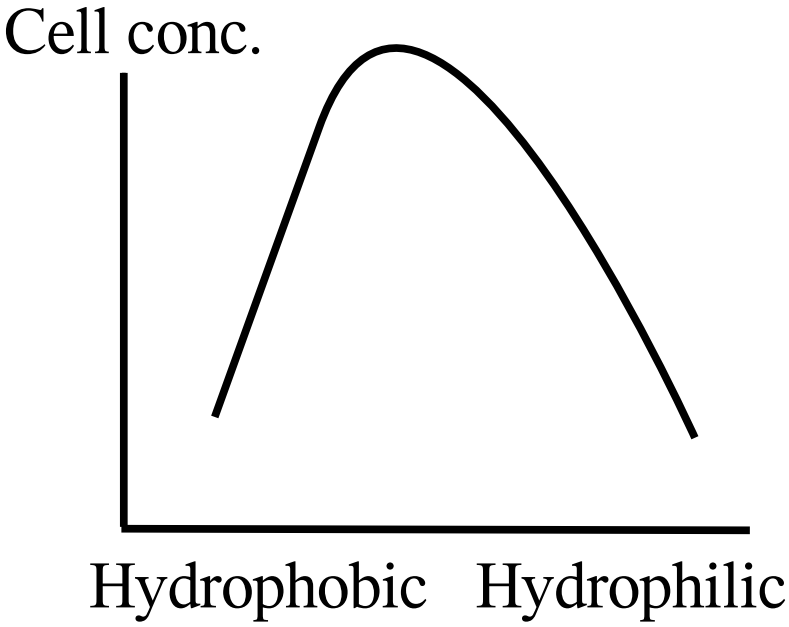


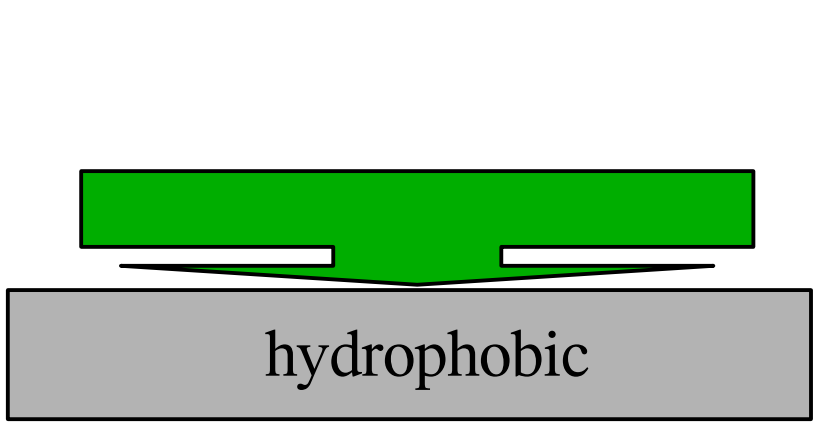
Integrins recognise specific amino acid sequences on extra-cellular matrix proteins and so surfaces must be designed to adsorb proteins in the correct orientation for integrin binding

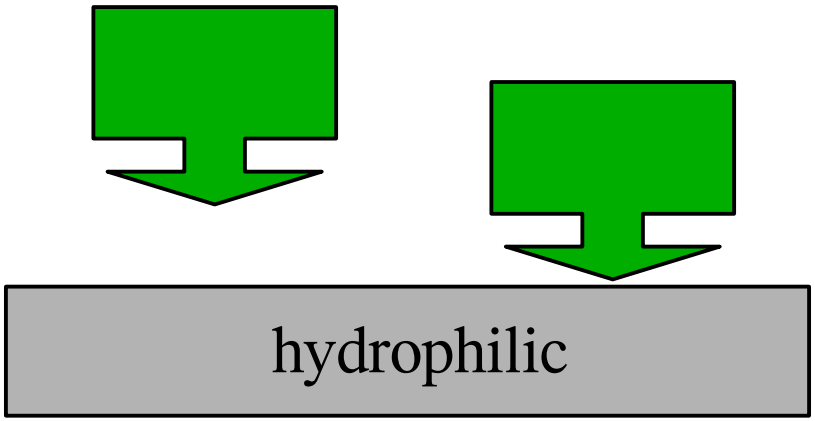
Control over adhesion achieved by manipulation of surface properties – isoelectric point, functional group termination, topography, **hydrophobicity**

Effect of surface hydrophobicity









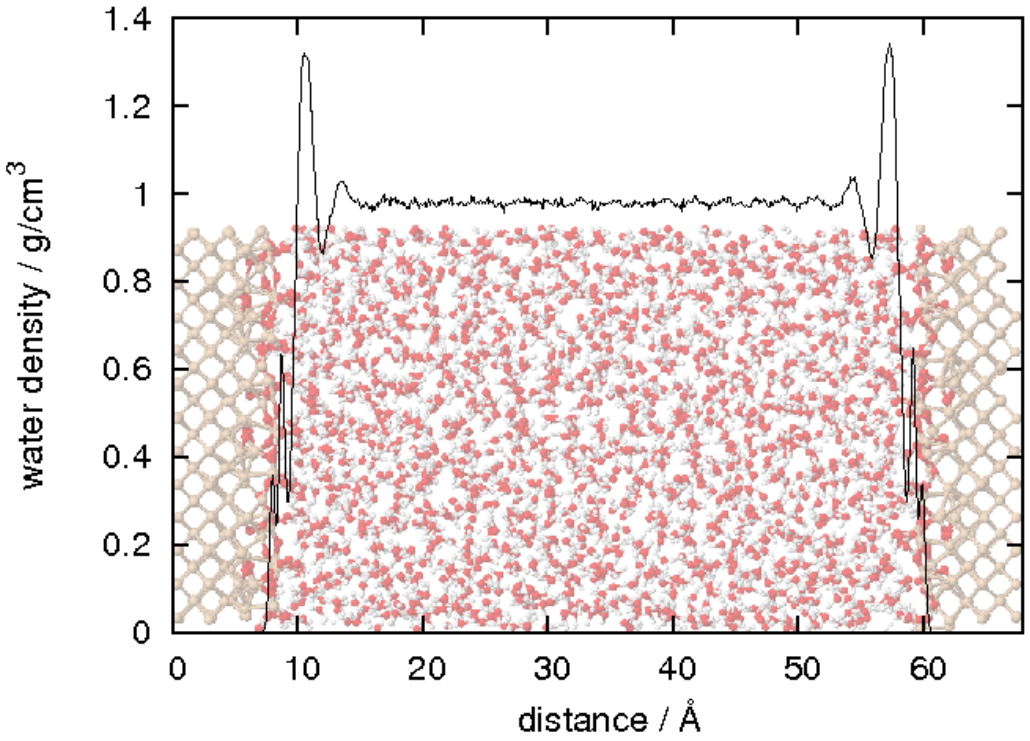
Effect of surface hydrophobicity

Atomistic details of the interactions at the surface/protein interface are unclear.

Continuum theories, such as DLVO, treat the surface and protein as macroscopic objects interacting via short-range vdW interactions and longer-range electrostatic double layer forces between charged surfaces.

DLVO works well at large separations, but neglects:
- hydrophobic interaction
- chemical nature of adsorbate
- solvent structure close to surface

Water at a hydrophilic surface

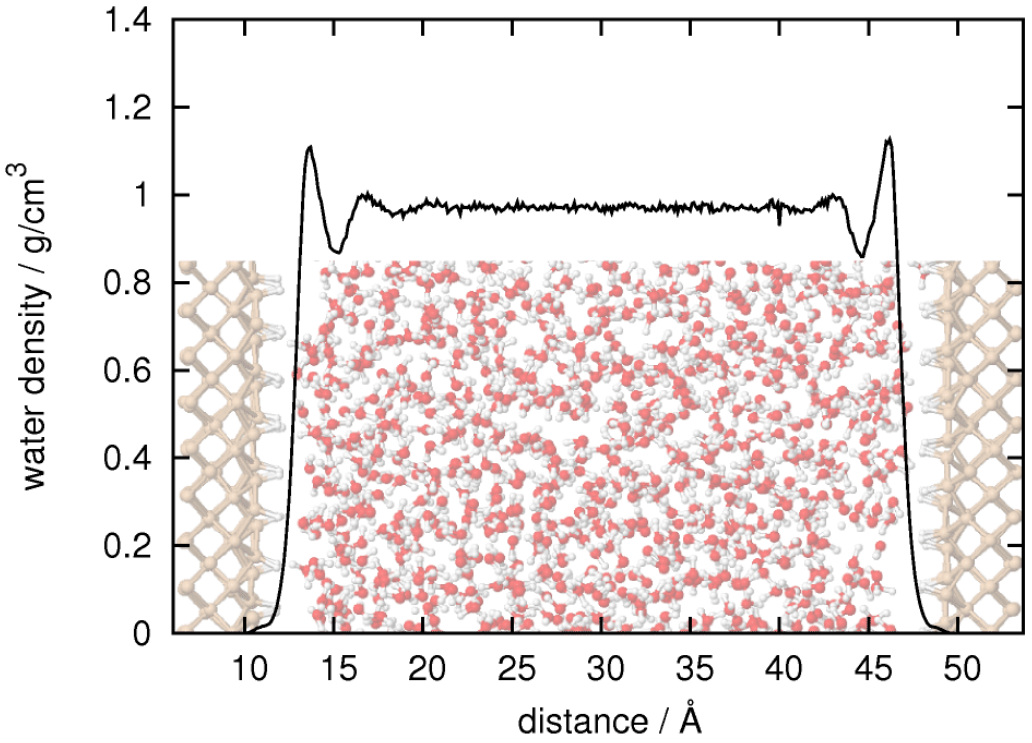


At the native oxide, strong surface-water interactions overcome the decrease in water entropy at the surface.

Water density oscillations explain strength of mutual bonding between pairs of Si wafers.

D. J. Cole, G. Csányi, S. M. Spearing, M. C. Payne, L. Colombi Ciacchi
J. Chem. Phys. **127**, 204704 (2007)

Water at a hydrophobic surface



Water is repelled from the hydrophobic H-terminated Si surface and formation of the interface is energetically unfavourable.

Summary so far...

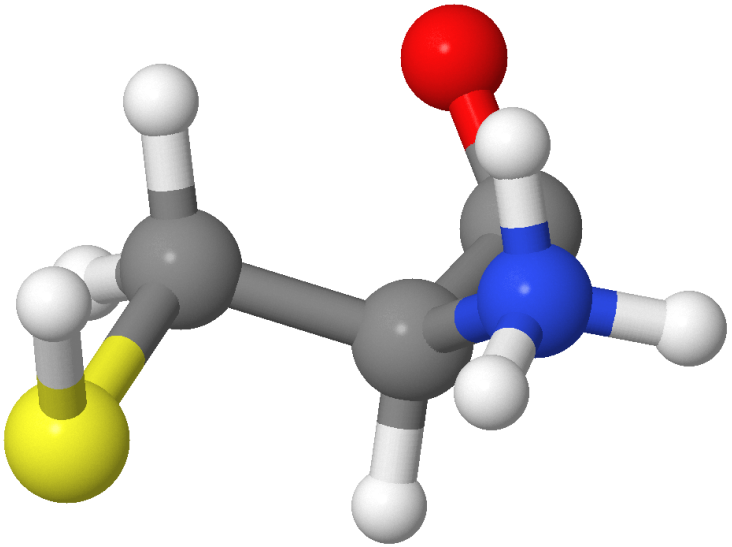
For the rational design of materials for biomedical applications, ECM protein adhesion must be guided.

We're interested in studying the atomistic details of the interactions that determine protein binding modes on surfaces of different hydrophobicity.

Given the importance of interfacial water structure in the mutual adhesion between Si surfaces, is it also important in determining the adhesion between the surface and proteins?

...let's use classical molecular dynamics to find out.

Classical MD



System of nuclei and electrons replaced by atom-centred point charges.

Surface-water interactions described by Coulomb and L-J. Parameters tuned to reproduce correct heat of immersion of silica.

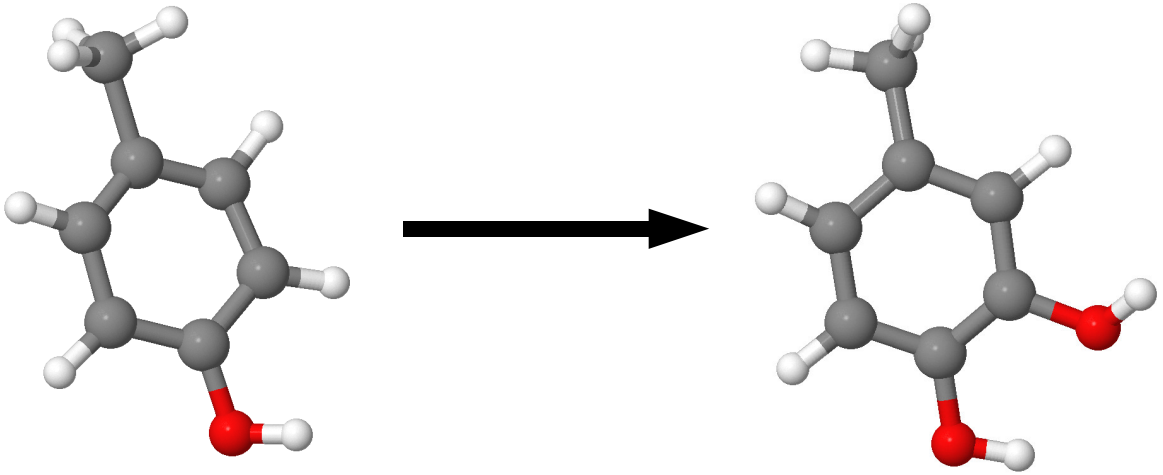
Potential adapted to include standard AMBER biomolecular force field.

Mussel strength

Mussels achieve long-lasting adhesion to many inorganic and organic surfaces in a wet environment – even teflon.

Mussel strength

Mytulis edulis foot proteins contain a high concentration of dopamine.

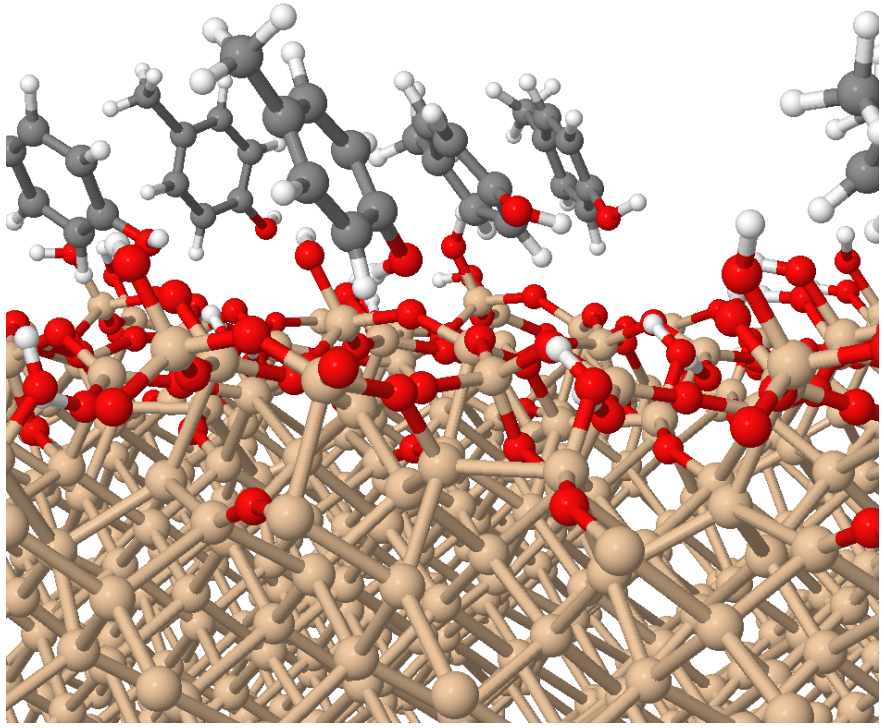


TYR 0.1 nN

DOPA 0.8 nN

on Ti surface

Mussel strength



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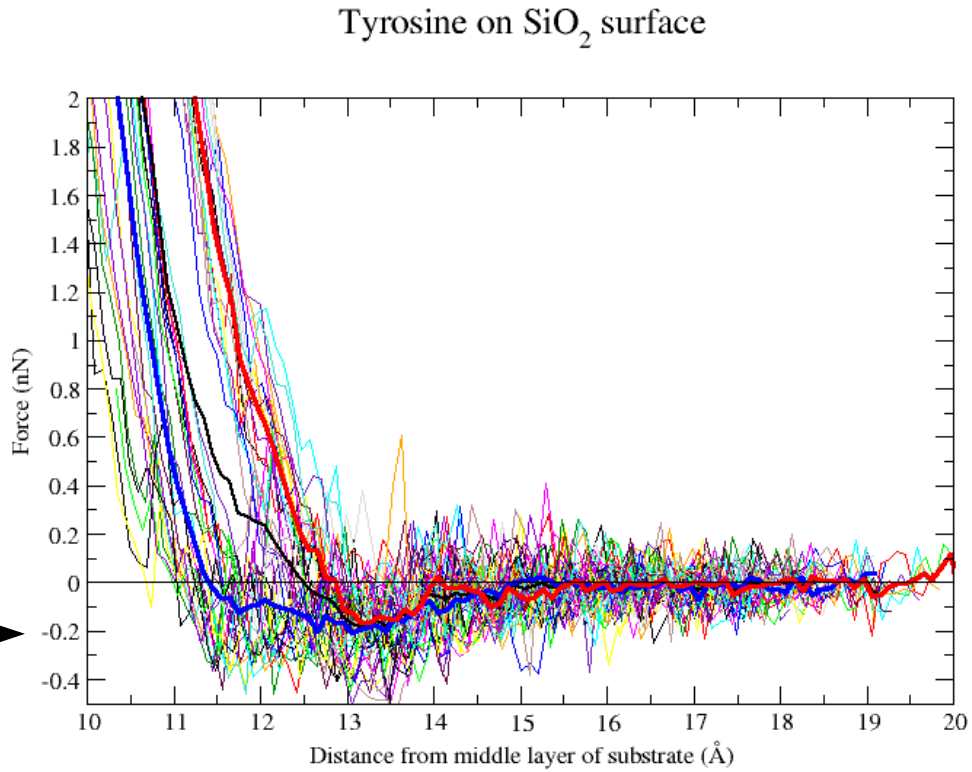
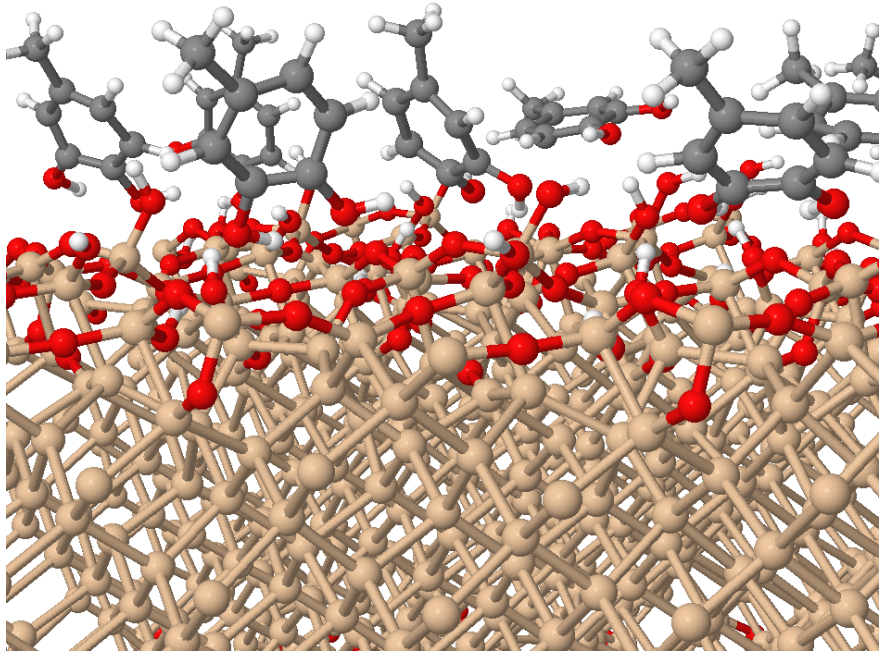
Maximum force = 0.21 nN

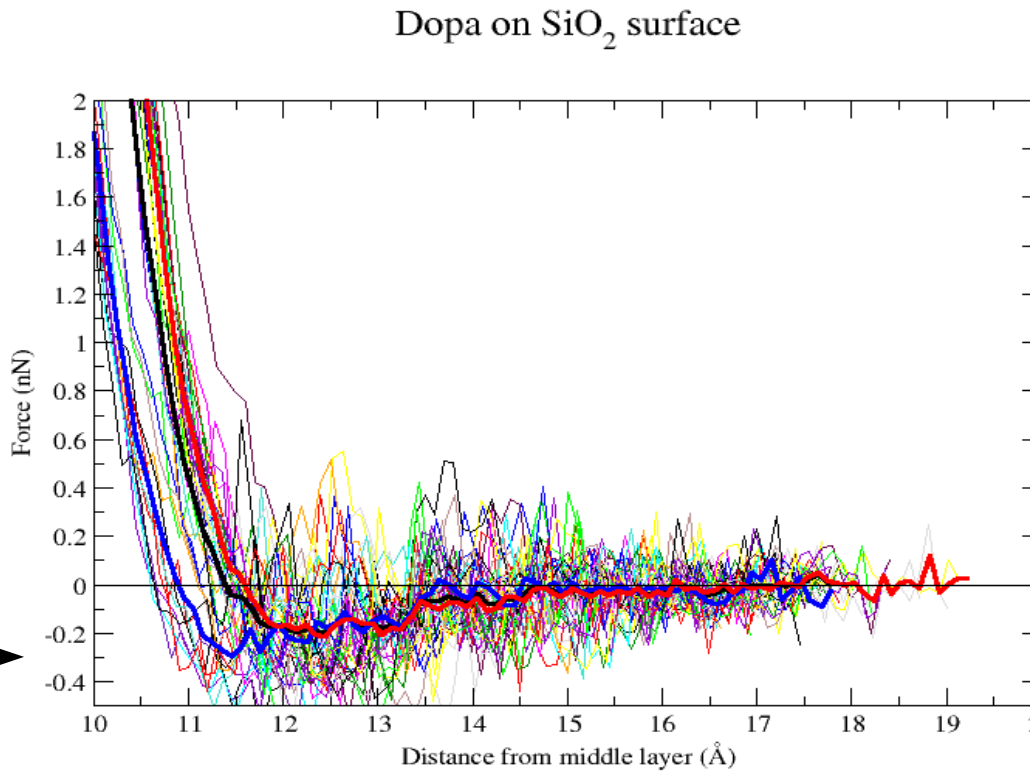


Mussel strength

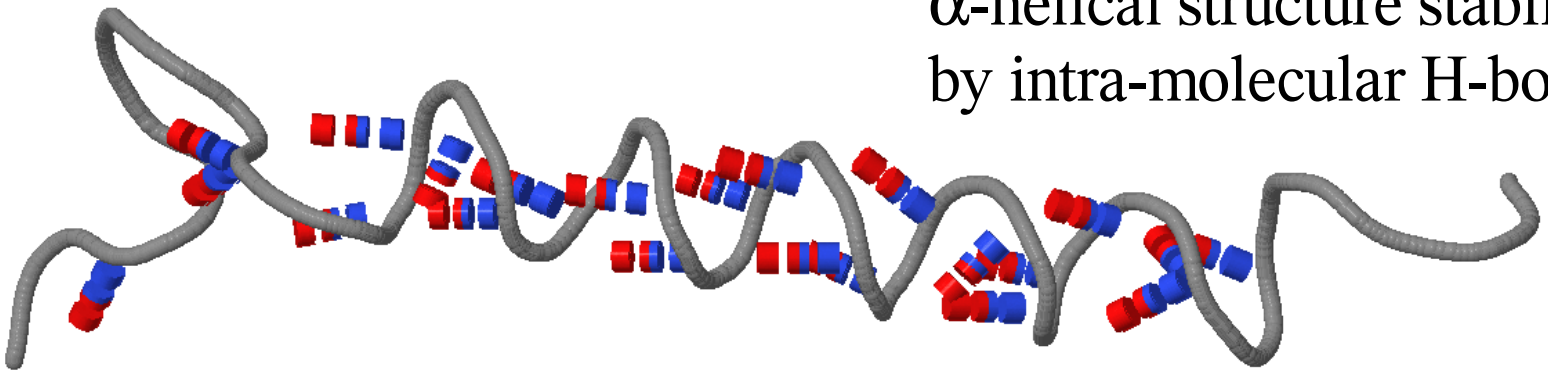


Mohammad Koleini,
Lucio Colombi Ciacchi

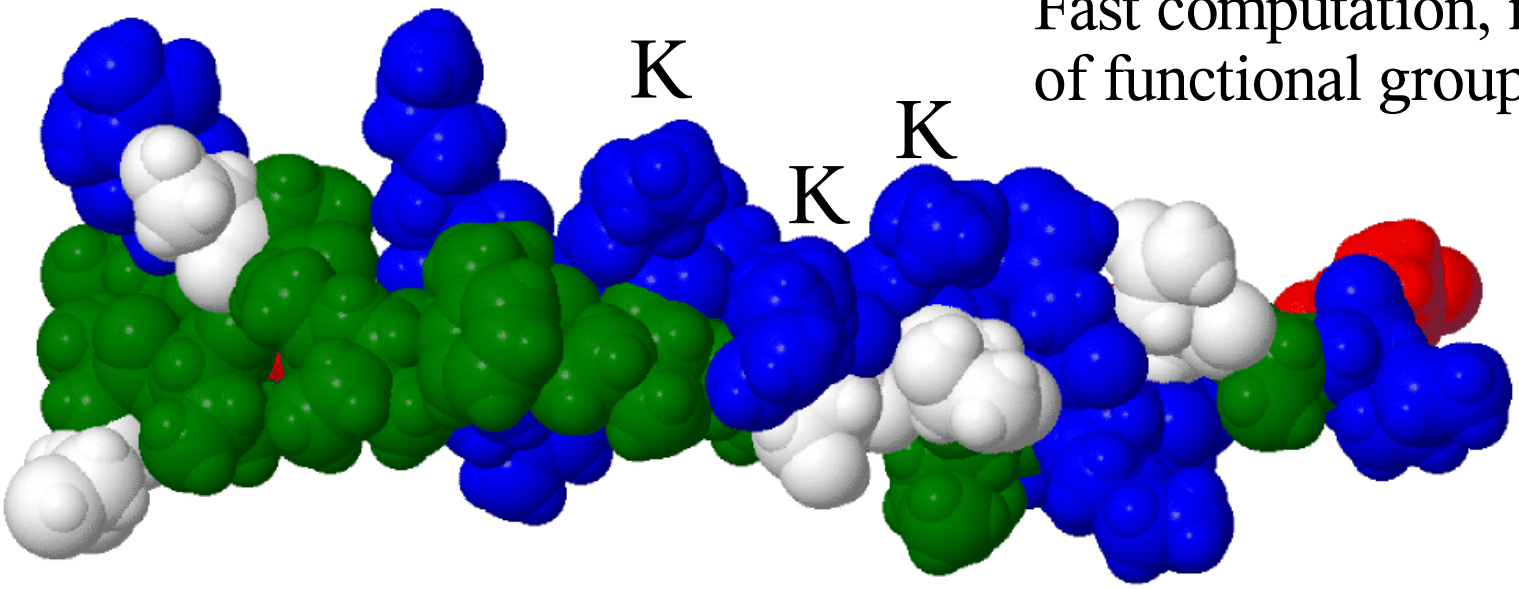
Maximum force = 0.30 nN



NC1 Domain of Collagen XIV



α-helical structure stabilised by intra-molecular H-bonds

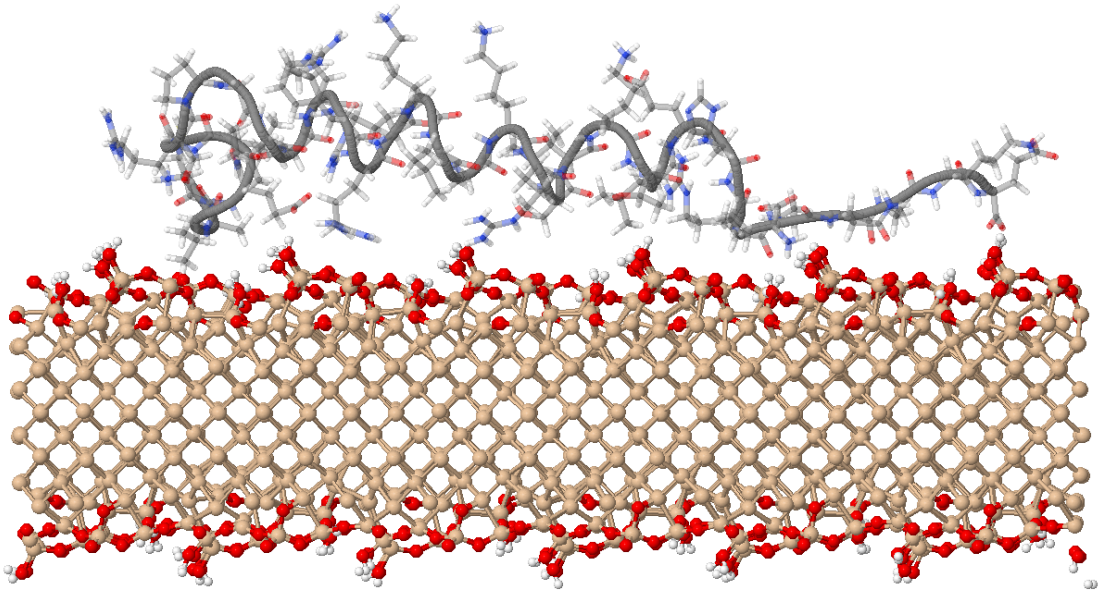


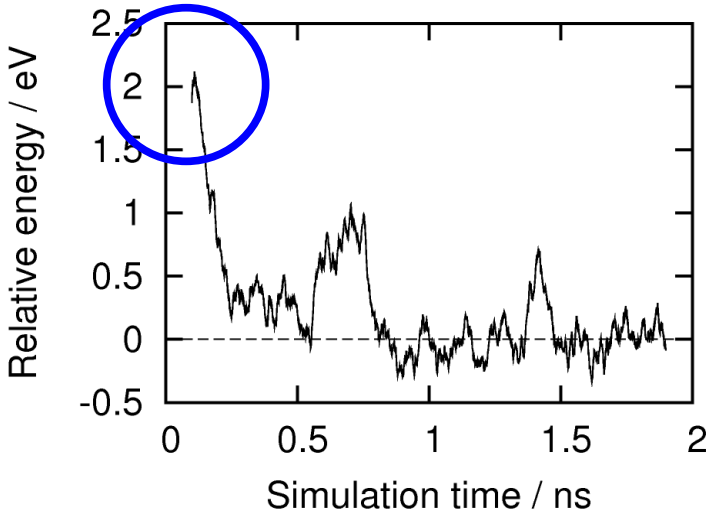
Fast computation, range of functional groups

Collagen on a hydrophilic surface

0.00 ns

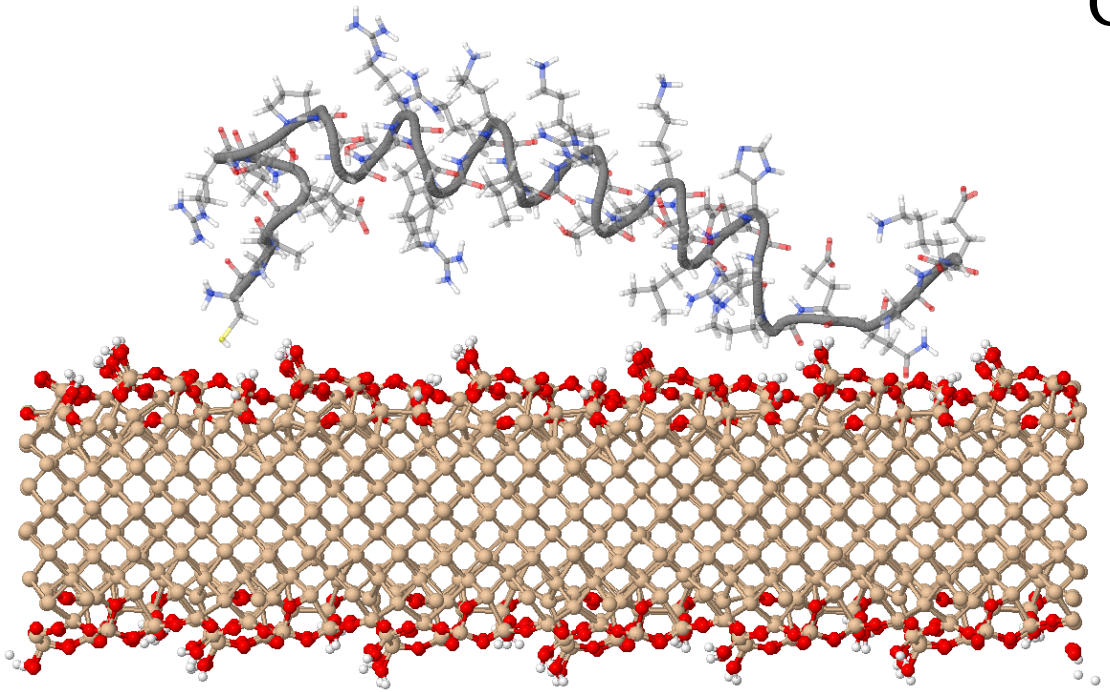
NVE relaxation in vacuum
Fill with water at 1g/cm^3
Run at 300K for 2ns
Compare to unbound system



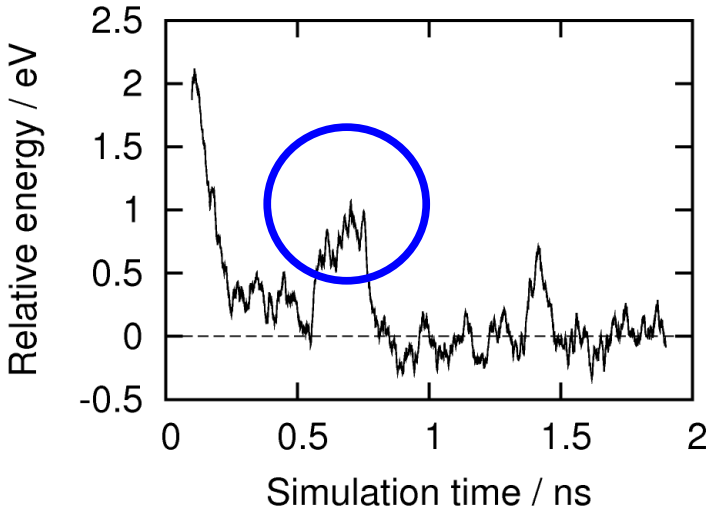


Collagen on a hydrophilic surface

0.65 ns

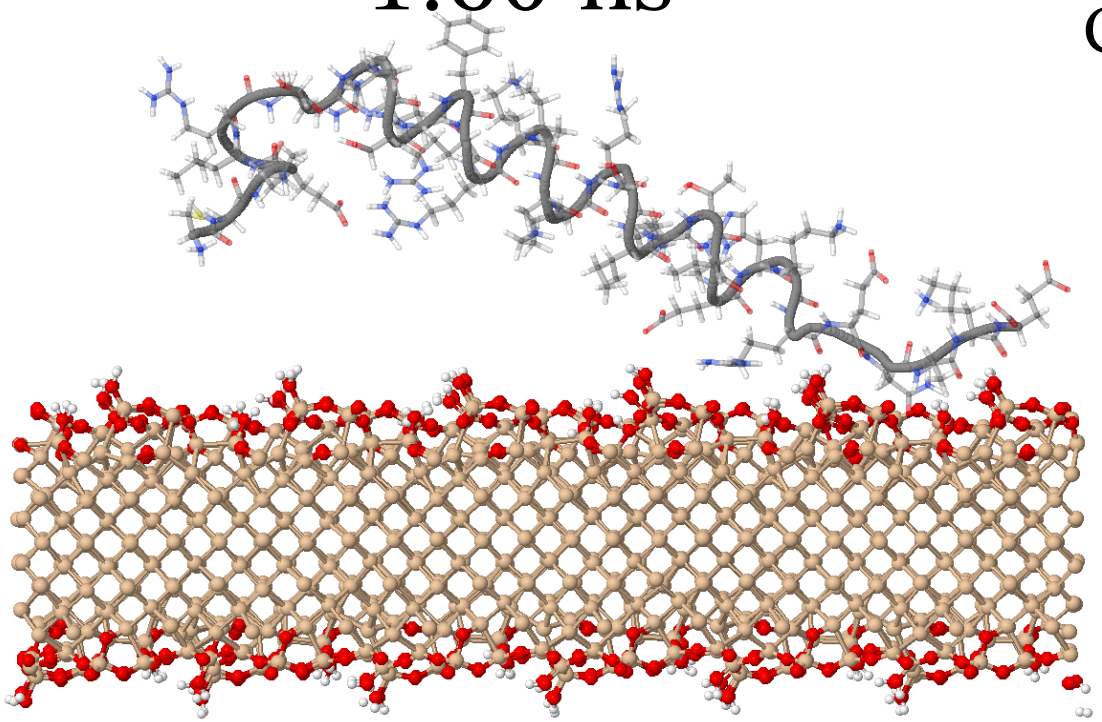


NVE relaxation in vacuum
Fill with water at 1g/cm^3
Run at 300K for 2ns
Compare to unbound system

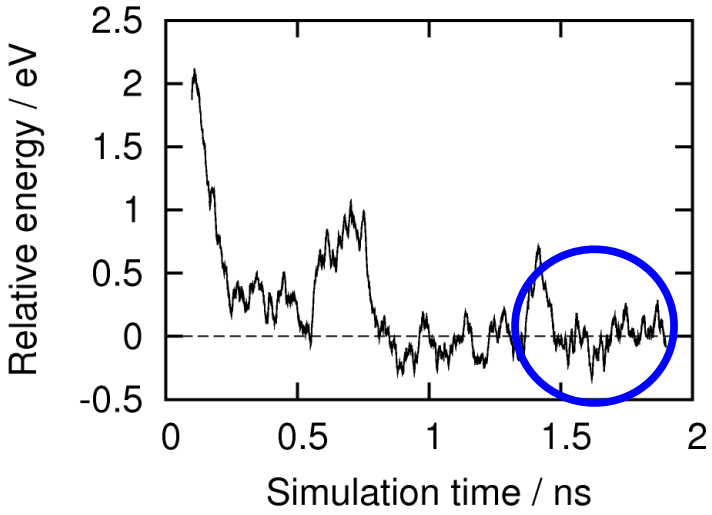


Collagen on a hydrophilic surface

1.60 ns

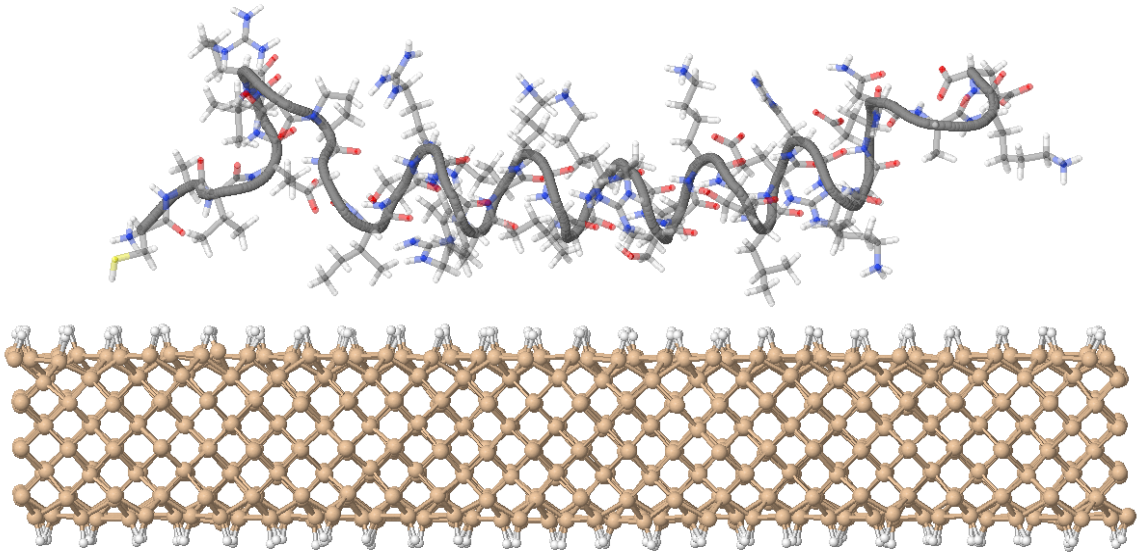


NVE relaxation in vacuum
Fill with water at 1g/cm^3
Run at 300K for 2ns
Compare to unbound system

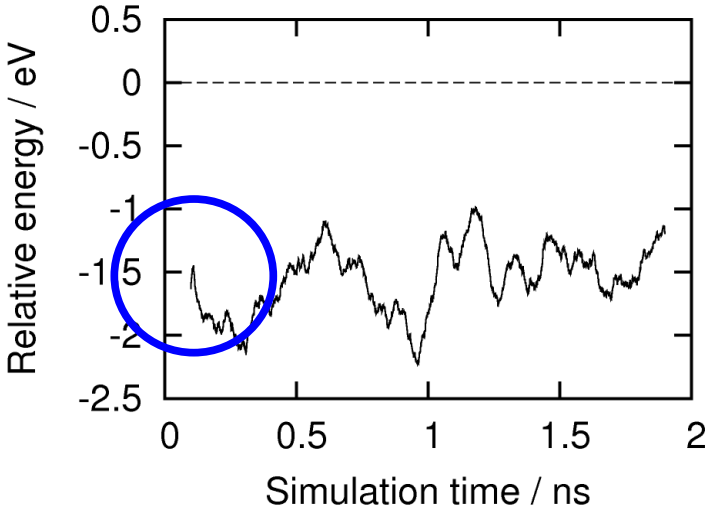


Collagen on a hydrophobic surface

0.00 ns

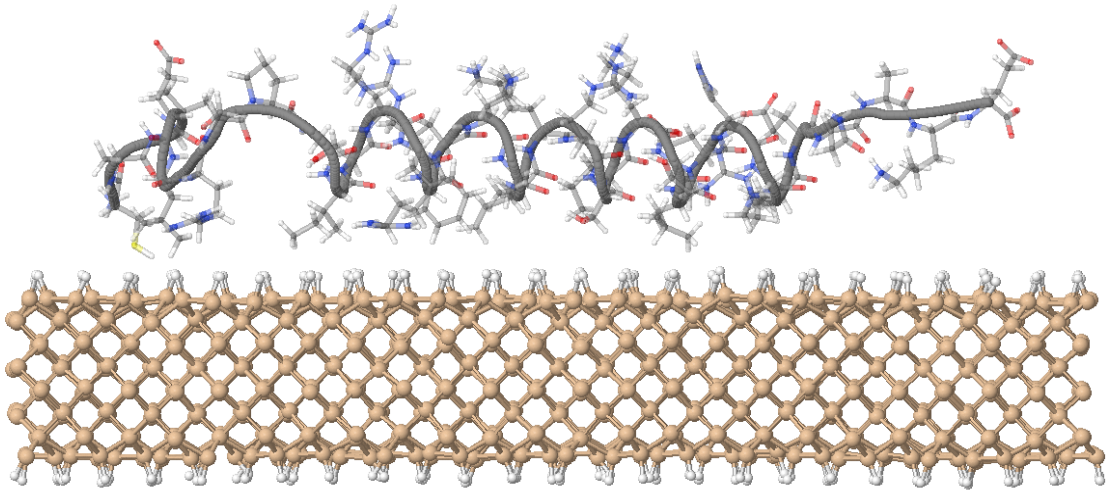


Average binding energy
= 1.6eV

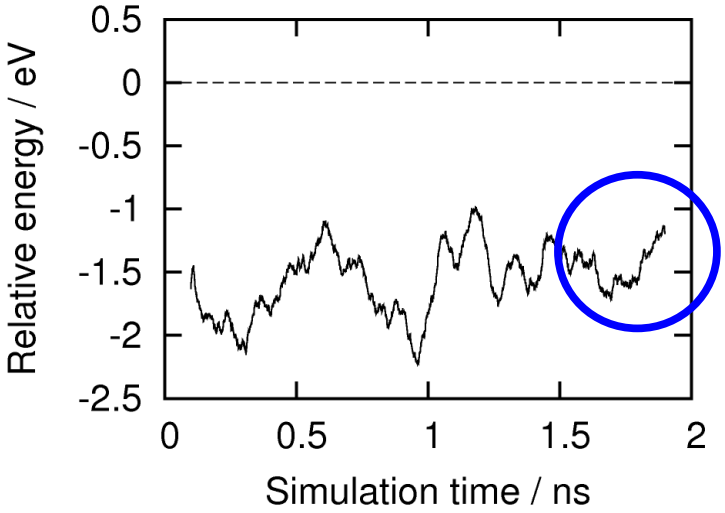


Collagen on a hydrophobic surface

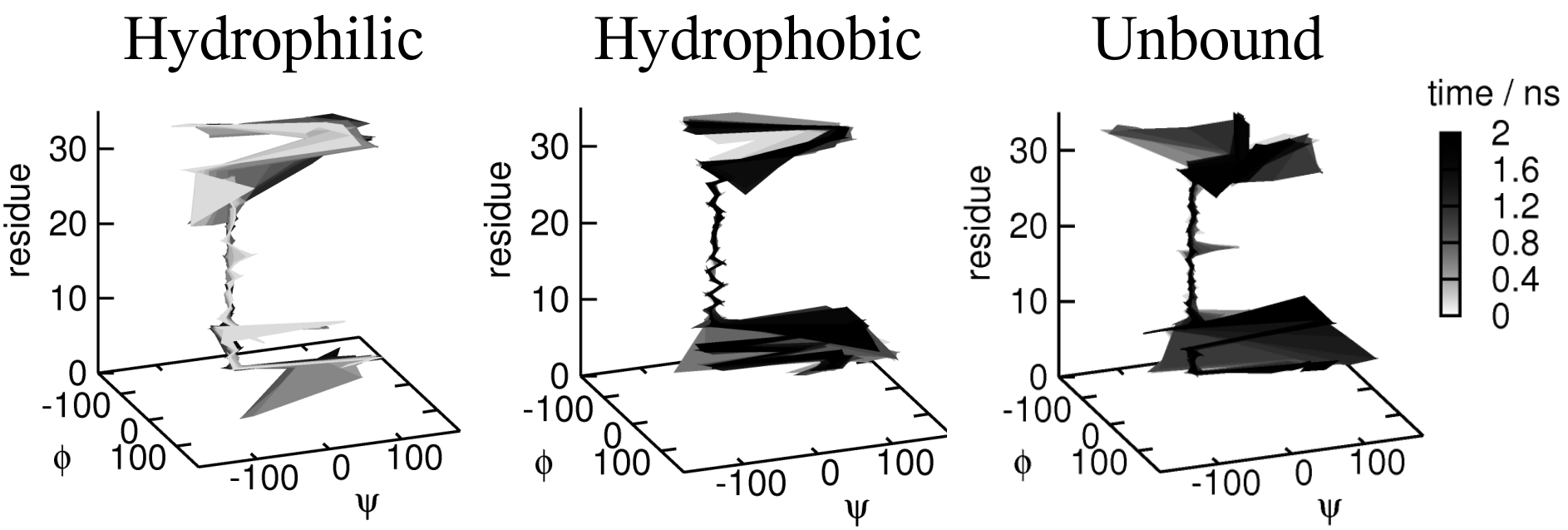
2.00 ns



Average binding energy
= 1.6eV



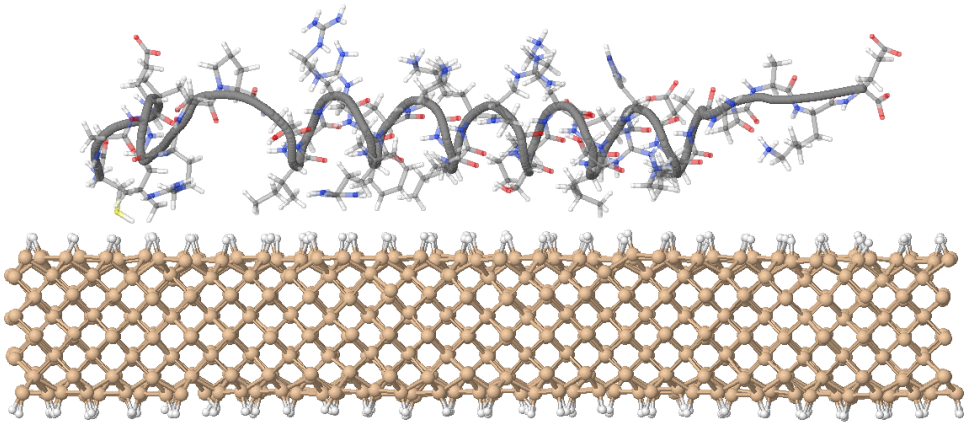
Ramachandran plots



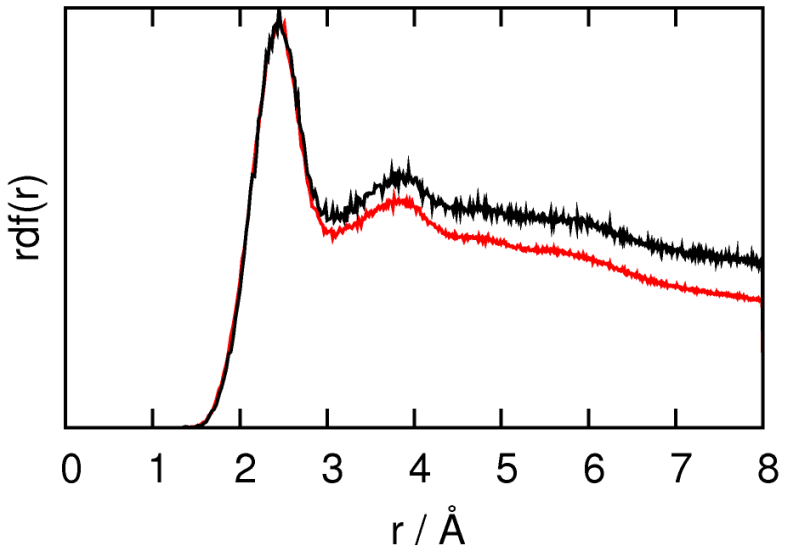
Binding energies and Ramachandran plots are consistent with experimental observations – collagen α-helix is stabilised by adsorption onto hydrophobic surfaces.

Water structure at the interface

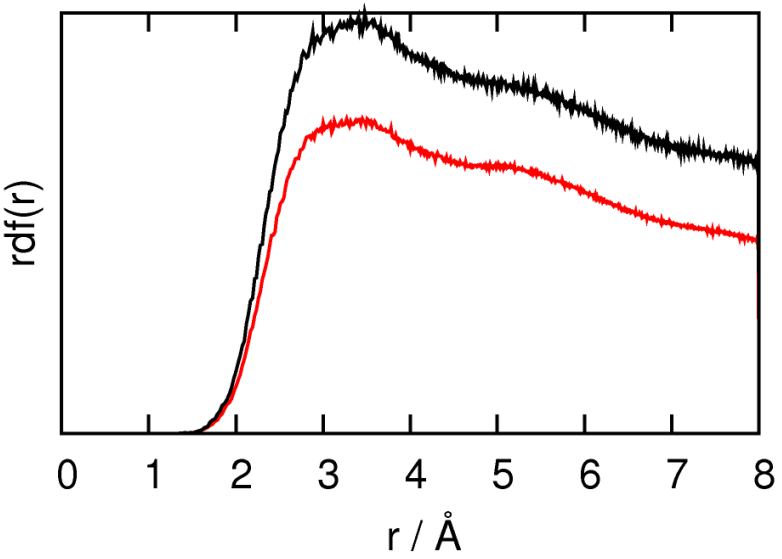
Water structure around protein at hydrophobic surface (red) unchanged from structure around unbound protein (black).



Hydrophilic

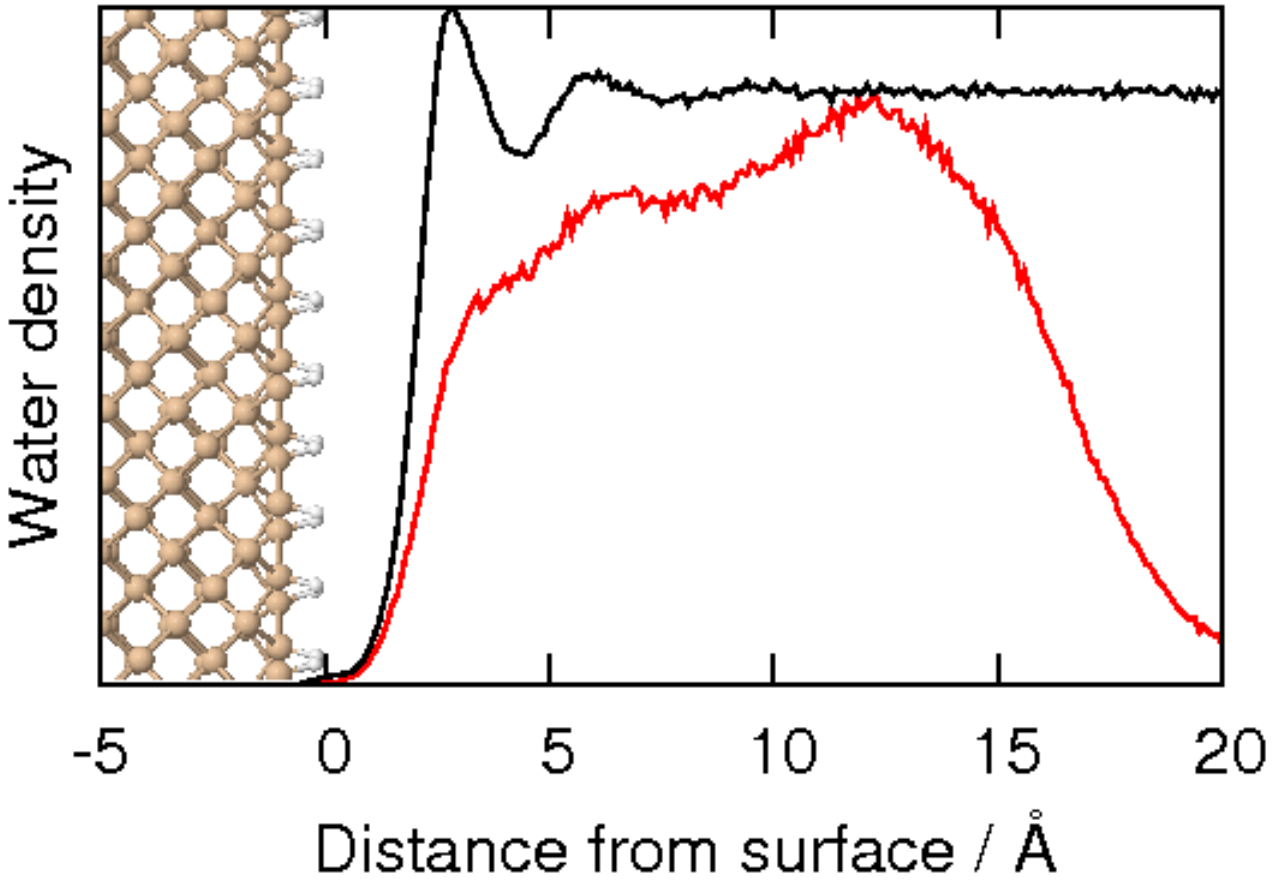


Hydrophobic



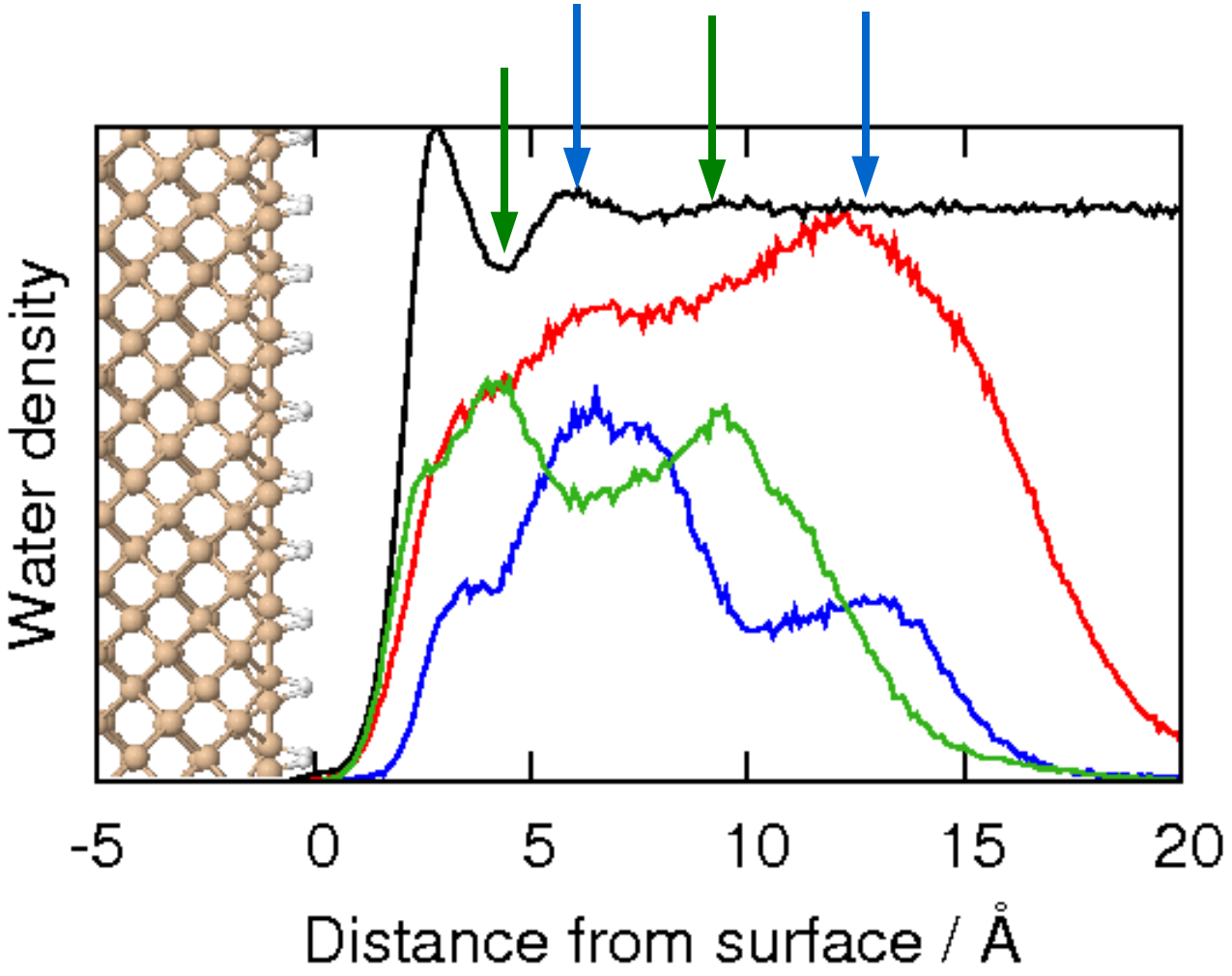
Water structure at the interface

Water bound to the protein shows similar density oscillations perpendicular to the surface.



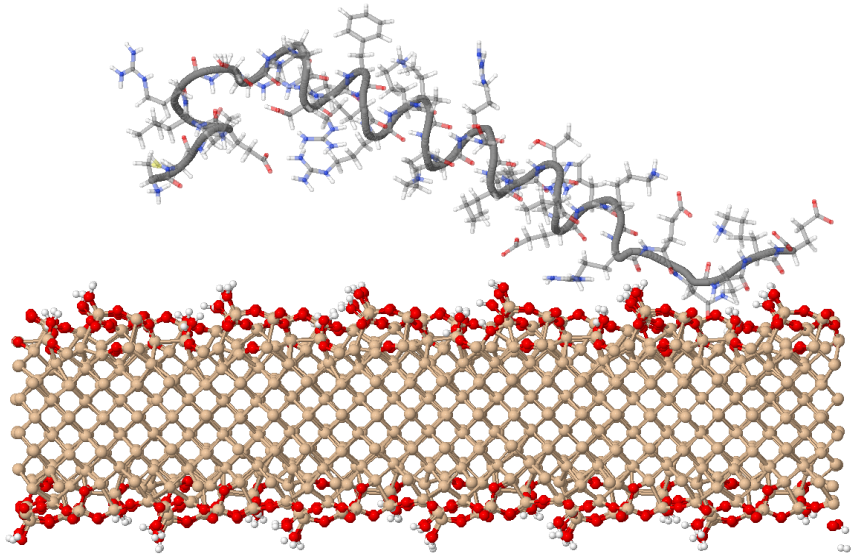
Water structure at the interface

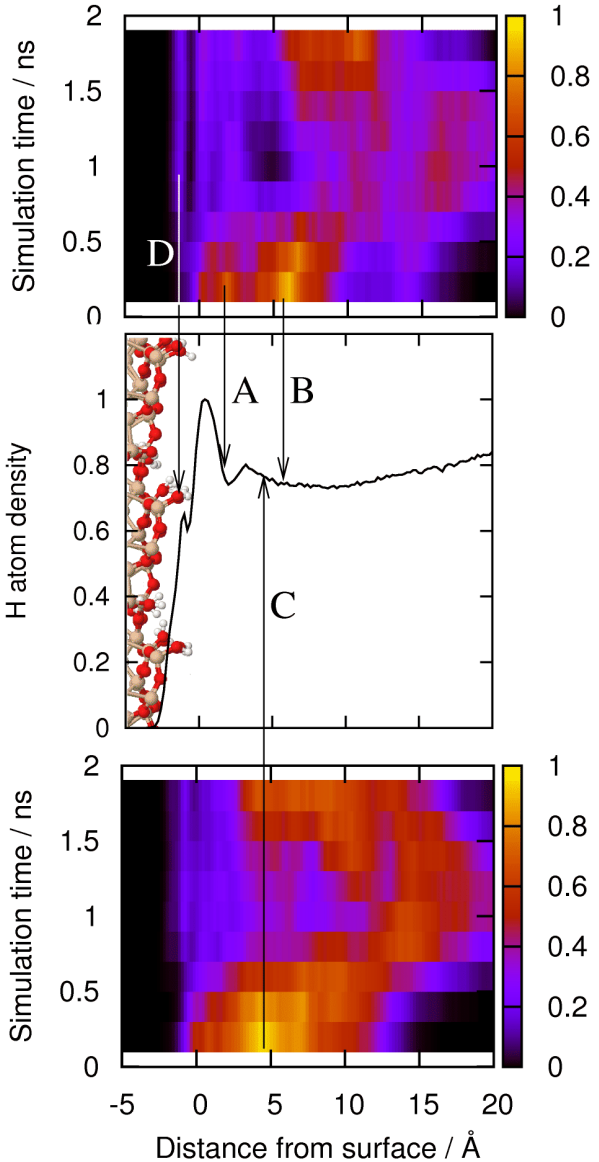
Observe protein structuring to maintain water interactions.



Water structure at the interface

On hydrophilic surface, initially observe no stabilising protein-water interactions and protein is screened from surface by high density water peak.





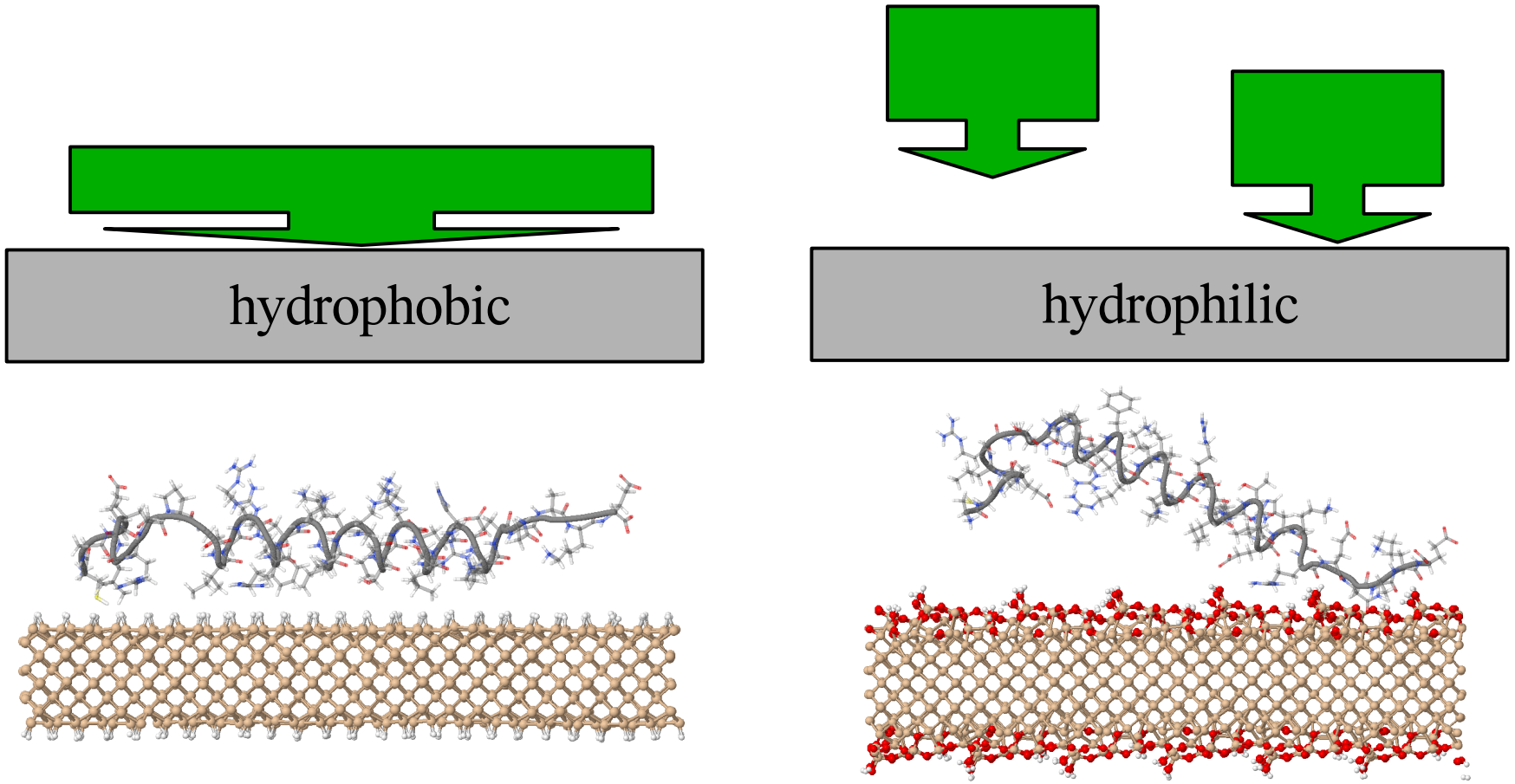
Problem with dielectric models

Simple dielectric model for water, which does not account for its molecular nature, predicts strong adhesion on both the hydrophilic and the hydrophobic surface.

This is qualitatively correct for the hydrophobic model, but misses possible protein re-structuring at the interface due to interactions with the solvent.

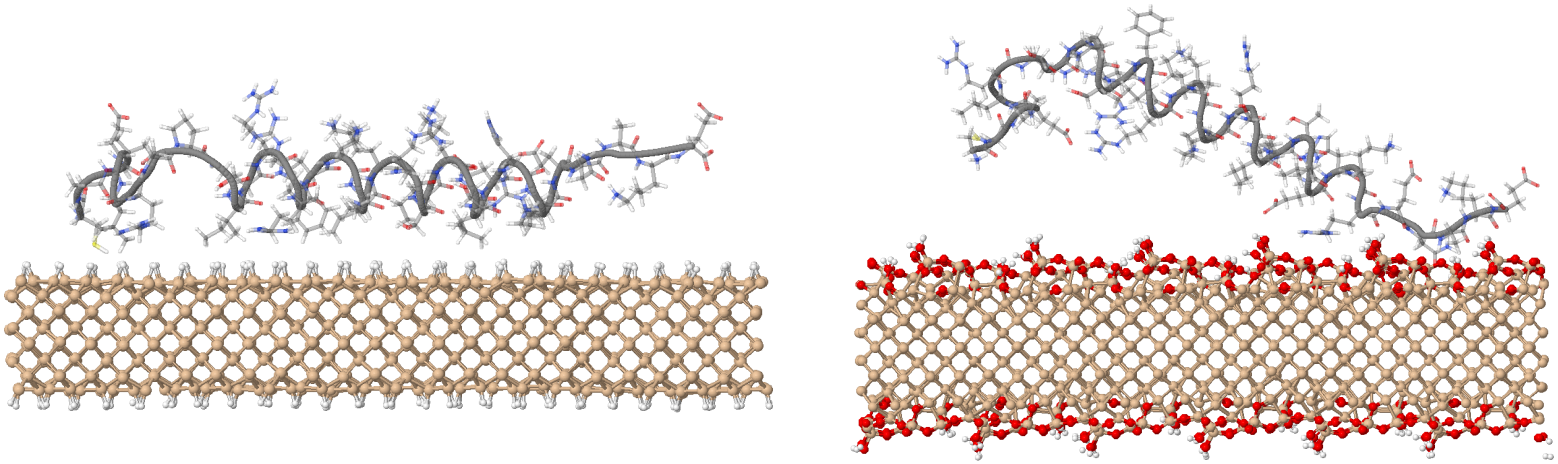
This is wrong for the hydrophilic surface, where the protein is screened from the surface by a high density water layer and desorbs.

Conclusions I



Collagen XIV adsorbs with large adhesion energy on hydrophobic surfaces, but leaves the surface-bound hydration layer on hydrophilic surfaces intact.

Conclusions II



Adsorption vs. desorption behaviour is determined by interplay between p-s, s-w and p-w interactions.

Solvent interactions at the hydrophobic surface restructure the protein and may contribute to the adhesion energy.

Unfavourable p-w interactions and screening of the p-s interactions lead to desorption from the hydrophilic surface.

Further acknowledgements

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Bye!