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PROJECT FINAL REPORT

Grant Agreement number: 229205

Project acronym: ADGLASS

Project title: Adhesion and Cohesion at Interfaces in High Performance Glassy Systems

Funding Scheme:

Period covered: from 01/09/2009 to 28/02/2013

Name of the scientific representative of the project's co-ordinator[1], Title and Organisation:

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4.1 Final publishable summary report

4.1.1 Executive summary

The ADGLASS European Consortium brought together leading experts in the fields of computational materials modelling, experimental materials research and industrial development of high-performance glass materials. The scientific and technological activities of the consortium were devoted to improving the efficiency, functionality and reliability of glass products, to develop custom solutions for applications in protein-based drug storage and solar energy collection.

The increasing demand for protein-based drugs such as recombinant proteins and antibodies poses significant challenges to the development of glass surfaces with specific anti-adherent properties. ADGLASS studied the driving forces at the basis of protein adhesion and worked on innovative coating solutions to avoid the loss of precious active agents and the risk of uncontrolled side-effects upon drug storage.

The efficient collection of solar energy relies on the availability of functional layers on extended glass surfaces with both tailored optical properties and optimal mechanical cohesion. ADGLASS gathered an atomistic understanding of interface cohesion mechanisms and develops new coating materials and processes specifically suitable to being implemented in new-generation solar collectors.

Spanning between academic research and industrial production, ADGLASS covered all aspects of modern materials simulation, design and implementation in innovative products, all the way from the acquisition of atomic-scale knowledge to the testing of prototypes. The scope of our work was to gain a detailed, atomic-scale knowledge of chemical and physical processes taking place at glassy interface systems. The Consortium has further developed a recently proposed atomistic modelling method which spans across multiple time and size simulation scales bridging the quantum-mechanical with the classical level of precision. The method has been applied to two scientific problems which require quantum precision and very large model system sizes. Namely, we have investigated (i) the adhesion between a glassy SiO_2 phase and a protein-containing water solution, relevant to pharmaceutical applications and (ii) the propagation of fracture in brittle materials, which is relevant to a wide range of glass applications, in particular limiting the lifetime of systems with heterogeneous interfaces such as coated glass slides for solar panel protection. The theoretical work was carried out in close coordination with experimental activity both in the field of brittle fracture propagation and in that of protein-surface interactions. As an important part of the research, we have investigated the performance of pharmaceutical packages and of glass covers for photovoltaic panels in end-user applications such as lyophilisation and light transmission, respectively. On the basis of the acquired knowledge, novel materials have been designed and implemented into product prototypes within the R&D infrastructure of a leading European glass-producing company. Our results have been disseminated through scientific papers, workshops and training activities especially conceived for members of the industrial sector as well as for the scientific academic community.

4.1.2 Summary description of project context and objectives

Project context

ADGLASS is a European Consortium bringing together leading experts in the fields of computational materials modelling, experimental materials research and industrial development of high-performance glass materials. The scientific and technological activities of the consortium are devoted to improving the efficiency, functionality and reliability of glass products, to develop custom solutions for applications in protein-based drug storage and solar energy collection.

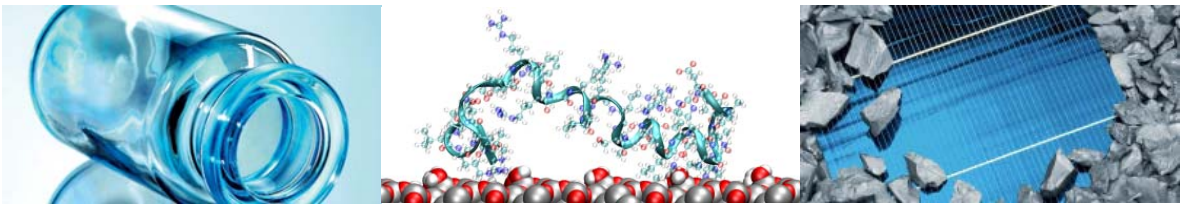
The successful commercialization of novel high-performance glass products depends on their increased functionality with respect to previously available products, on their efficient processability, high reliability, long-term durability, and low cost, especially if they are targeted for large-scale market sectors. On flat glass, functionality is often introduced in the form of inclusions or by multi-layer coatings. In this case, reliability and durability crucially depend on the properties of the interfaces between the different glassy phases. In some case the outmost interface between the glass material and the surrounding environment determines the behaviour of the final product. This is for instance the case for self-cleaning glasses (typically coated with a TiO_2-based layer responsible for the photocatalytic lysis of deposits on the glass surface), and for glass containers (packages) for pharmaceutical applications. In pharmaceutical packages containing protein-based drugs, adhesion of the dissolved active principles on the container's wall is not desirable, because of the loss of efficiency and the dangerous side-effects which this may cause.

Given the increasing number of requirements posed on glassy products and the ever higher performance level needed to achieve a market success, an intense research effort and in particular the investigation of the elementary mechanisms at the basis of the glass functionality has become mandatory. In recent years, elucidation of such mechanisms has been aided by physical modelling, from the macroscopic level (e.g. with Finite Element Methods describing the stress and strain distributions during processing under realistic load conditions) down to the atomic scale. A detailed knowledge of the delicate interplay between the atomic arrangement of the glass matrix and external stimuli of mechanical or chemical nature is becoming unavoidable for the design of novel glass materials for high-performance applications (knowledge-based design). In the case of interfaces between two radically different phases, knowledge of such interplay becomes crucial for predicting the efficiency and the reliability of the final product devices. Understanding the molecular mechanisms underlying these properties is a necessary step toward a knowledge-based improvement of the life-time and performance of a range of glass-based products containing interfaces. These are widespread in modern high-tech applications, from household appliances to fibre optics and solar cells. Atomic-level investigations of glassy interfaces have thus nowadays a high potential impact on society as a significant added value to their success measured in purely scientific terms.

The atomistic modelling of glassy interfaces involves dealing with mutually interacting phenomena spanning multiple time and length scales and requiring different levels of precision. Long-range interactions of electrostatic or mechanical nature can be modelled by classical molecular mechanics (MM). However, these interactions have a strong influence and in turn depend on chemical processes occurring in localised system regions which require a quantum-mechanical treatment. In such cases, a concurrent hybrid quantum/classical simulation approach (also known as QM/MM) must be taken. Typical examples of phenomena where QM/MM approaches are unavoidable and have been successfully applied comprise chemical reactions occurring within a

protein systems (e.g. at active centres in enzymes) or propagation of cracks in solid materials.

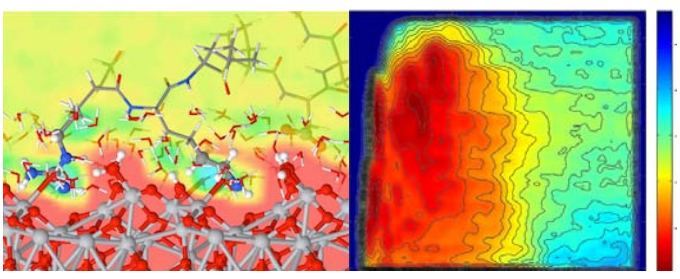
Due to the dynamical nature of the phenomena cited above, it is often necessary to include in the simulation scheme a mobile and adaptive QM region that can automatically follow the chemical processes (e.g. moving with the tip of a propagating crack or with the chemically active species diffusing along an extended chemical path). Numerous schemes have been developed to study chemical reactions occurring in biopolymers, but very few studies allowed for a dynamical rearrangement of the quantum zone. In the case of crystalline or amorphous solid materials, QM/MM methods are more difficult to implement due to the extensive area of the interface between the QM and the MM regions (dictated by the number of chemical bonds which run across such an interface). At present, the only technique fulfilling these requirements and suitable for investigations of covalent materials is the “Learn-On-The-Fly” method, recently developed and applied by some of the project participants. However, significant extensions of the method are required to investigate glassy interfaces, as has been envisaged in the work of our Consortium.



Project objectives

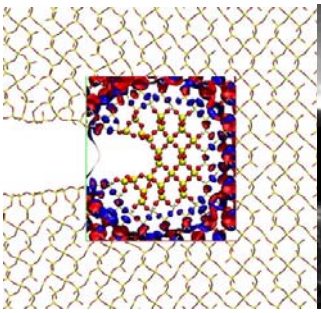
The increasing demand for protein-based drugs such as recombinant proteins and antibodies poses significant challenges to the development of glass surfaces with specific anti-adherent properties. ADGLASS studies the driving forces at the basis of protein adhesion and works on innovative coating solutions to avoid the loss of precious active agents and the risk of uncontrolled side-effects upon drug storage.

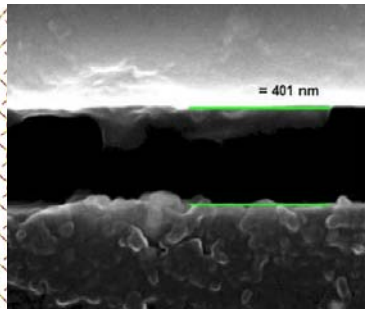
To reach this goal, we planned to elucidate the mechanisms of protein adhesion at the interface between a SiO_2-coated glass and a protein-containing liquid phase. The acquired knowledge can be then exploited to develop a novel coating material for pharmaceutical packaging units (such as vials, ampoules, syringes, etc.). Namely, the properties of such a material can be optimized through a knowledge-based protocol including theoretical modelling and experimental work on SiO_2/protein$_{(aq)}$ interfaces, reaching atomic-scale details of the adhesive interactions between the glass and the protein solution. Experimental work is necessary to determine the chemical nature and strength of the adhesion as well as the amount and structure of the adsorbed peptides. QM/MM simulations of peptide adhesion at a model SiO_2/water system would be desirable to reveal the atomistic features of the interactions involved. Prerequisite for a successful work is the further development of a multi-scale method allowing the concurrent inclusion of localised chemical effects and long-range electrostatic interactions between the proteins, the glass substrate, and the polar water solvent containing dissolved ions.



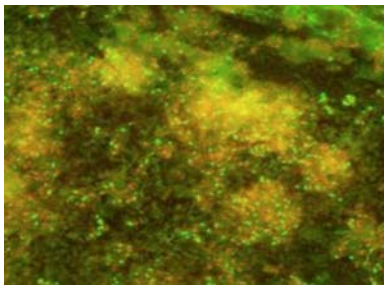
The efficient collection of solar energy relies on the availability of functional layers on extended glass surfaces with both tailored optical properties and optimal mechanical cohesion. ADGLASS gathers

an atomistic understanding of interface cohesion mechanisms and develops new coating materials and processes specifically suitable to being implemented in new-generation solar collectors.





In our Consortium we address the problem from several perspectives. A first objective is to gather fundamental knowledge about mechanisms of brittle fracture propagation in both crystalline and glassy materials. This includes state-of-the art atomistic simulations of crack advancement as a consequence of chemical bod rupture at the crack tip, as well as experimental monitoring of the same phenomena under controlled crack conditions. The systems in which such effects can be investigated with a sufficiently deep level of precision are silicon and silicon oxide. Important is the inclusion of corrosive agents (in the simplest case, water molecules) which can accelerate the crack or induce it even at very at low level of stress (sub-critical crack propagation). As a second objective, we have planned to optimize the composition of coating layers for solar glass panels in order to tune its refractive index and enhance the light transmission without compromising the mechanical cohesion within the layer and at its interface with the glass substrate. Third, we monitor the evolution of the transmission coefficient of glass panels coated with various materials for long time (three years) under realistic operation conditions that is exposed to urban and rural atmospheres. Fourth, we rationalize the performance of the coating in terms of its capability of actively prevent the formation of an organic biofilm on its exposed surface. This will include the development of methods for accelerated biofilm growth in laboratory along with comprehensive microbiological analysis of the samples.



The Consortium

Spanning between academic research and industrial production, ADGLASS covers all aspects of modern materials simulation, design and implementation in innovative products, all the way from the acquisition of atomic-scale knowledge to the testing of prototypes. The scope of our work is to gain a detailed, atomic-scale knowledge of chemical and physical processes taking place at glassy interface systems. The Consortium is further developing a recently proposed atomistic modelling method which spans across multiple time and size simulation scales bridging the quantum-mechanical with the classical level of precision. The theoretical work is carried out in close coordination with experimental activity both in the field of brittle fracture propagation and in that of protein-surface interactions. As an important part of the research, we are investigating the performance of pharmaceutical packages and of glass covers for photovoltaic panels in end-user applications such as lyophilisation and light transmission, respectively. On the basis of the acquired knowledge, novel materials are designed and implemented into product prototypes within the R&D infrastructure of a leading European glass-producing company. Our results are disseminated through scientific papers, workshops and training activities especially designed for members of the industrial sector as well as for the scientific academic community.

Coordinated in Germany by the Fraunhofer Society, the Consortium is carefully shaped to match the complex and broad range of our objectives, so that high-level scientific research is concretely applied to –and inspired, guided and tested by– technologically strategic product development. A list of the participant institutions is included in the scheme here below:

Fraunhofer IFAM — Fraunhofer Institute for Manufacturing Technology and Advanced Materials, Bremen, Germany

Fraunhofer Institute for Mechanics of Materials, Freiburg, Germany — Fraunhofer IWM

SCHOTT glass made of ideas — Schott AG, Mainz, Germany

King's College London, London, UK — King's College London

University of Cambridge, Cambridge, UK

The Abdus Salam International Centre for Theoretical Physics, Trieste, Italy

Technion - Israel Institute of Technology, Haifa, Israel

Aérial, Strasbourg, France

4.1.3 Description of main S&T results/ foregrounds

WP1 Technical development and validation of the LOTF technique and generation of high quality classical potentials

1. Development of the LOTF technique

Starting in 2001, some ADGLASS participants (Alessandro De Vita, Mike Payne, Peter Gumbsch and Gabor Csanyi) developed a multiscale hybrid code for solid systems using the "Learn-on-the-fly" (LOTF) approach to solve the boundary problems, which brought with it the ability to move the QM zone. The first few versions of the code were restricted to using simple interatomic potentials of Silicon, and a few quantum packages, notably Castep, Siesta and DFTB. Later the software development effort continued in the groups of Gabor Csanyi and Alessandro De Vita, with other developers such as Noam Bernstein joining the effort. As a part of this development, "libatoms" was written as a general purpose library to handle atomic configurations, I/O, dynamics etc. Then on top of this, the package QUIP was developed, implementing many different interatomic potentials and a generalised framework for calling external packages (QM, MM and also QM/MM). Different ways of combining any two potentials is also part of QUIP, in addition to the original LOTF scheme, other force-mixing and energy-mixing schemes were implemented.

The foundation of the software is the libatoms library, which is about 52,000 lines of code. It implements the basic data structures required for an atomistic simulation: properties of atoms (collected in an Atoms object), their neighbourhood properties (neighbour lists and connection tables), routines for integrating the dynamical equations of motion, constraints, parallelisation support, I/O support etc. The libatoms library can be compiled independently of QUIP and can be used as a platform for the development of any code that needs a framework of particle dynamics.

The QUIP_Core modules contain the implementation of physical models in the form of energy functionals and their derivatives. Several abstraction layers are present so that different models such as various interatomic potentials, tight binding models and even external packages that implement e.g. density functional theory look analogous and can be used as black boxes by routines higher up via an object of type "Potential". Different models can be used simultaneously, by e.g. simply summing the potential energies, or by mixing them in a hybrid scheme e.g. in the LOTF scheme or some other force- or energy-mixing scheme. Several routines deal with partitioning the atoms into subsystems according to various rules specified by the user which are then passed on to the different models (see Deliverable 1.3 for a detailed description of the code structure and capability).

Two models are of particular relevance to ADGLASS work packages, namely the Density Functional Theory implementations of the Castep and CP2K codes. In both models, the computation of energies and forces for a single configuration of 50+ atoms takes several minutes or more. Therefore it was deemed unnecessary to create a subroutine-based interface with QUIP, noting the significant amount work that would have been involved. Instead a scripted interface was created, which from the QUIP side is called FilePot and is the same for both packages. QUIP writes out the atomic configuration into a file, and calls an external script/program that creates the appropriate input files for CP2K or Castep, based on templates. The QUIP/libatoms package provides such templates. Further, for Castep, a Python script driver is provided that uses these templates to create input files, while for CP2K, a driver program in Fortran is provided that takes the XYZ positions of the atomic configuration, performs a template-based identification of atomic groups to generate a PDB file and an associated PSF file (describing the bonding topology and relevant

force-field parameters) that are suitable input files for CP2K. Both driver programs then run the appropriate DFT package, and analyse the output, returning forces, energies and, if appropriate, stresses to QUIP.

2. Development of classical potentials

During the course of the project, we have developed and tested a number of classical potentials to study both fracture propagation in oxides and oxide/water interfaces, following various conceptual schemes:

1) Potentials for SiO_2/water/protein [1] and TiO_2/water/protein [2,3] interfaces have been constructed under the constraint that they can be seamlessly combined with available biological force-fields such as AMBER or CHARMM. In both cases, we use a fixed-charge approach and a combination of Coulomb and Lennard-Jones potential terms for the interactions across the solid/liquid interfaces. The details have been presented in Deliverables 1.1, 1.2 and described extensively in the previous Reports.

2) Polarisable force fields according to the Tagney-Scandolo (TS) scheme, to be used for fracture propagation modelling, have been constructed for SiO_2 [4] and TiO_2 [5]. The parameters of the potentials have been optimised using forces, stresses, and energies extracted from ab initio molecular-dynamics simulations of rutile at high temperature. The potential gives the correct energy ordering for all common oxide phases, and predicts their bulk moduli with an accuracy comparable to density-functional theory calculations. It also provides an excellent description of the vibrational properties and of the temperature dependence of the lattice constants.

3) Water dissociation is a crucial aspect in the surface chemistry of oxides at wet conditions. We have generated a new all-atom classical potential for water that describes the molecular as well as the dissociated state of water with high accuracy [6]. The parameters of the potential have been determined by best fit to a set of density functional calculations for the liquid at ambient conditions. In order to describe the molecular state, the standard Tangney-Scandolo form has been modified to include an extra term in the short-range interaction. The potential describes reasonably well both the structural (Fig. 1 left panel) and the vibrational (Fig. 1, right panel) properties of water at ambient conditions.

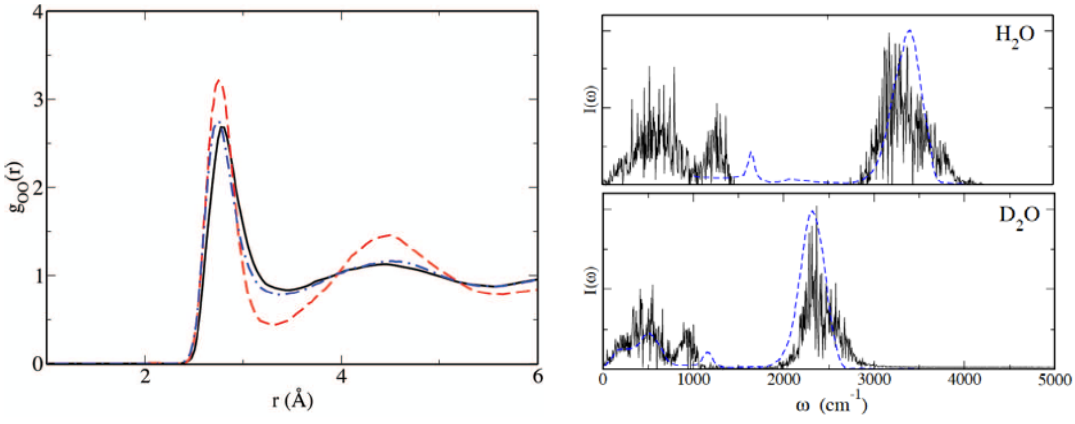


Fig. 1: Left: O–O radial distribution functions for water at T = 298 K obtained with the new force field (black line); BLYP calculations (red dashed) and experiments (blue dotted line). Right: Infrared spectra for H2O (top) and D2O (bottom) at *T* = 298 K calculated with the new force field (black line); the blue dashed lines show the spectra from experiments (top) and BLYP calculations (bottom).

The water potential describes reasonably well also the dissociated species, including the Eigen and Zundel configurations for the solvated proton [6], as well as the dissociation process and the dissociation constant (see Fig. 2).

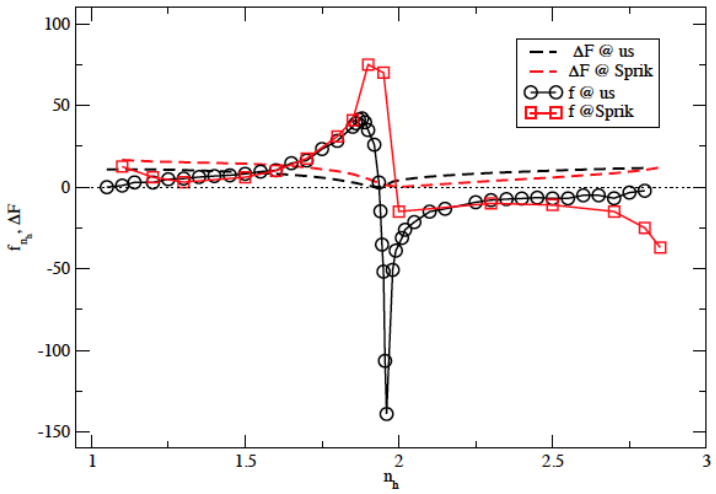


Fig. 2: Comparison between the free energy (ΔF) and the force of constrain (f) obtained with our classical molecular dynamics along a trajectory in which the number of protons surrounding a selected oxygen atom is varied adiabatically from 2 to 1 and from 2 to 3, leading to the formation of a OH- and of a H_3O+ complex, respectively. For comparison we have included the results obtained by Sprik et al. using ab-

4) We developed and tested models for the interface between crystalline SiO_2 and crystalline TiO_2 (anatase), as well as for the interface between glassy SiO_2 and crystalline TiO_2 (rutile). Regarding the crystal-crystal interface the model consists of 168 atoms. The electronic structure of the interface has been analyzed by density functional theory, showing how specific interface states contribute to the edge of valence and conduction bands (see Fig. 3). To further analyze these effects, a model of a silica monolayer on an anatase surface has been developed and analyzed as well [7].

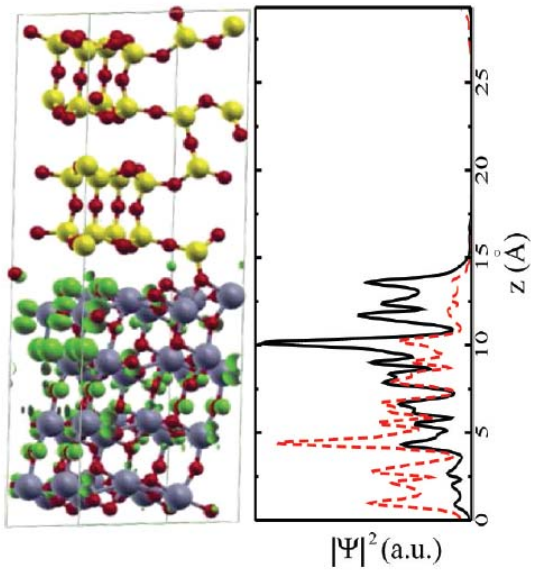


Fig. 3: The two uppermost states of the valence band for the bulk titania/silica interface. (a) Isosurface of the electron density of the uppermost state (green); gray balls: titanium; yellow balls: silicon; red balls: oxygen. (b) Planar average of the electron density of the uppermost state (solid black line) and of the second-highest state (red dashed line), in planes parallel to the titania/silica interface.

5) We have worked on the development and testing of potentials for SiO_2 and TiO_2 materials based on a novel approach developed in the group of G. Csanyi at the Cambridge University, known as “Gaussian Approximation Potentials”, or briefly GAP [8]. The early results, described in the previous Report, are very promising as far as bulk oxide phases are concerned. Tests are now being conducted to explore their performance in the study of complex systems such as propagating cracks.

References WP1

[1] A. Butenuth, G. Moras, J. Schneider, M. Koleini, S. Köppen, R. Meißner, L. B. Wright, T. R. Walsh, L. Colombi Ciacchi, “Ab-initio derived force-field parameters for molecular dynamics simulations of deprotonated amorphous-SiO2/water interfaces”, *Physica Status Solidi (b)* **249**, 292-305 (2012) (Back Journal Cover).

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[3] J. Schneider, L. Colombi Ciacchi, “ First principles and classical modeling of the oxidized titanium (0001) surface”, *Surface Science* **604**, 1105-1115 (2010).

[4] J. R. Kermode, S. Cereda, P. Tangney, A. De Vita, A first principles based polarizable O(N) interatomic force field for bulk silica, Journal of Chemical Physics 133, 094102 (2010)

[5] H. J. Han et al., “Polarisable interatomic force field for TiO_2 parametrised using density functional theory”, *Physical Review B* **81**, 134108 (2010).

[6] C. Pinilla et al., "Ab initio parameterization of an all-atom polarizable and dissociable force field for water", *J. Chem. Phys.* **136**, 114511 (2012).

[7] N. Seriani, C. Pinilla, S. Cereda, A. De Vita, S. Scandolo, "Titania-Silica interfaces" *Journal of Physical Chemistry C* **116**, 11062-11067 (2012)

[8] A. P. Bartók, M. C. Payne, R. Kondor and G. Csányi “Gaussian Approximation Potentials: The Accuracy of Quantum Mechanics, without the Electrons”, *Physical Review Letters*, **104**, 136403 (2010).

WP2 Hybrid simulations of glassy biological interfaces

In this work package we have performed atomistic simulations of protein adsorption at the interfaces between (amorphous) oxides such as SiO_2 and TiO_2 and water at the quantum, quantum/classical (QM/MM) and purely classical levels. The purely classical simulations are largely based on the potentials developed in WP1. The hybrid QM/MM simulations take advantage of the development of the QUIP package (also developed in WP1).

1. Quantum mechanical simulations

Full quantum simulations (at the level of Density Functional Theory, DFT) were performed on systems comprising model SiO_2 surfaces and single amino acids. Crystalline surface served us both as a model system for reactive sites at the amorphous silica surface and to study the effect of possible defect sites typically found in silica systems. Here, we found that the binding affinity to the hydroxylated crystalline surface is governed by the structure of hydrogen-bonded hydroxyls on the surface. As for amorphous surfaces, we tried different strategies to model the binding in a way suitable for ab initio methods (i.e. considering systems of the size of ~ 150 atoms). Representative results are reported in Fig. 2-1. For a detailed description of the gained knowledge, we refer to the Report after the first reporting period.

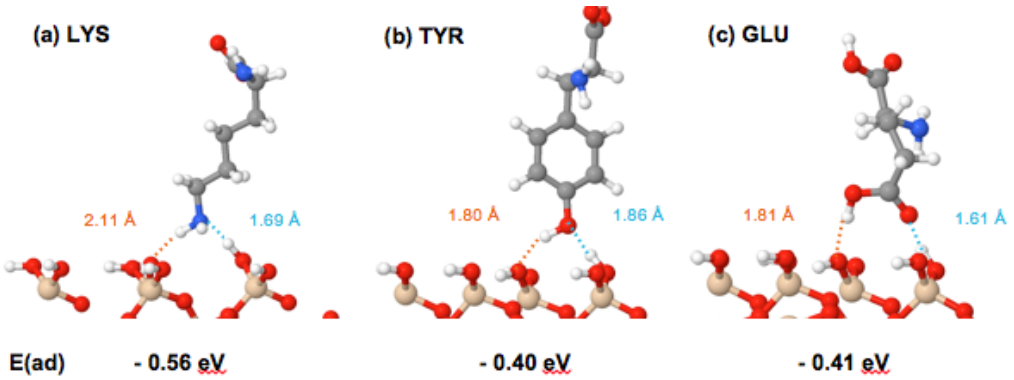

Fig. 2-1: DFT optimised geometries, adsorption energies and h-bond length of LYS (a), TYR (b) and GLU (c) on the fully hydroxylated (0001) α-quartz surface.

2. QM/MM simulations

The simulation of solid/liquid interfaces at the QM/MM level presents great challenges, which were only partly solved within the present project. Since the LOTF method is based on a force-matching scheme between the classical and the quantum regions of the systems, it was important to establish to which extent forces could be computed in the mixed QM/MM scheme with negligible errors with respect to fully quantum systems. In an extensive series of tests including crystalline and amorphous oxide bulk and surfaces, we could conclude that very large sizes of the QM region need to be taken into account to minimize the error on the central atoms (see Fig. 2-2). Interestingly, the convergence depends only slightly of the chosen embedding strategy. An “electrostatic” embedding is only slightly better than a simple cluster approach, in terms of obtaining accurate QM forces. Although the mechanical embedding does only perform worse in bulk silica, we consider both the electrostatic embedding with O* terminated clusters and the simple clusters favourable over the mechanical embedding, because unlike the latter they preserve the systems charge neutrality. While electrostatic embedding can help to correctly reproduce the charges at the border of the quantum region, it is not able to reduce the force-error on the QM atom to the amount achieved in QM clusters of other, non-polar QM solid state systems (silicon). We suspect that the long-range electrostatic interaction between quantum and classical zone is corrected only partly for in the embedding into a set of classical point charges. Nevertheless, it performs better than a simple cluster approach in the presence of water above the surface.

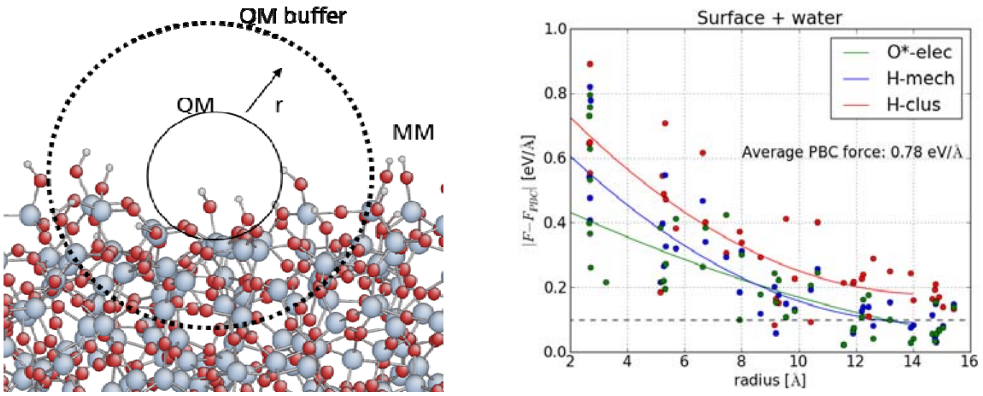

Fig. 2-2: Left: model of the embedding system to perform QM/MM simulations of amorphous SiO_2-water interfaces, comprising a quantum zone (QM), a classical zone (MM) and a buffer zone in between. The water molecules are not displayed, for clarity. Right: average error on the forces on the central atom of the QM zone as a function of the radius of the QM zone.

3. Classical simulations

The work within ADGLASS concerning the classical simulations of protein adsorbing at solid/liquid interfaces led to great advances with respect to the state of the art especially as far as a quantification of the adsorption free energy and of the secondary structure of small peptides is concerned. This is remarkable, because it allows a direct comparison between computed and experimental observables. In MD simulations, this is only possible if the peptide samples all possible configurations while it moves along a representative reaction coordinate, for instance the height of its centre of mass over the surface layer.

The problem of sufficiently accurate sampling of the so-called “phase space” necessitates of advanced MD techniques, which we have implemented in the MD code LAMMPS, namely Replica Exchange with Solute Tempering (REST) [Liu, P.; Kim, B.; Friesner, R. A.; Berne, B. J. Proc. Natl. Acad. Sci. U.S.A. 2005, 102, 13749−13754] and Metadynamics [Laio, A.; Gervasio, F. L. Rep. Prog. Phys. 2008, 71, 126601−126622]. We refer to the original literature for details of the techniques. By means of these tools, we have been able, for the first time, to compute accurately converged values of the free energy of adsorption of the RKLPDA peptide on titanium. Namely, our computed value of the adsorption free energy amounts to ΔG_{ads} = -0.40 ± 0.04 eV, which is in excellent agreement with the experimental estimate of -0.394 eV [Sano, K.-I.; Sasaki, H.; Shiba, K. Langmuir 2005, 21, 3090−3095]. Furthermore, by means of Steered Molecular Dynamics (SMD) we have computed adhesion forces on Ti about 1.5 times larger than on Si, again in excellent agreement with values measured by means of AFM force spectroscopy [Hayashi, T.; Sano, K.-I.; Shiba, K.; Iwahori, K.; Yamashita, I.; Hara, M. Langmuir 2009, 25, 10901−10906] (Fig. 2-2). Our simulations reveal that only R and K contribute significantly to the maximum adhesion forces on both materials. This finding contradicts the experimental hypothesis that different adhesion forces result from an electrostatically driven selectivity of the surfaces toward specific residues. Instead, we have found a striking correlation between the adhesion forces and the nanoscale features of the water structuring at the solid/liquid interfaces. A novel, crucial finding of our study is that the local solvent density variations near a heterogeneous, rough surface are sensed by the side chains of a peptide in a way that bears many features characteristic of the specific recognition in biomolecular aggregates (Fig. WP2-3). Our simulations highlight the importance not only of direct surface-molecule interactions at the anchoring points but also of an alternation between hydrophilic and hydrophobic residues to optimize the matching with the solvent density oscillations. In this picture, electrostatic interactions still play an important role in driving the approach of charged residues toward surfaces with opposite charge density, but they are, at least in this case, of secondary importance as far as adhesion forces are concerned.

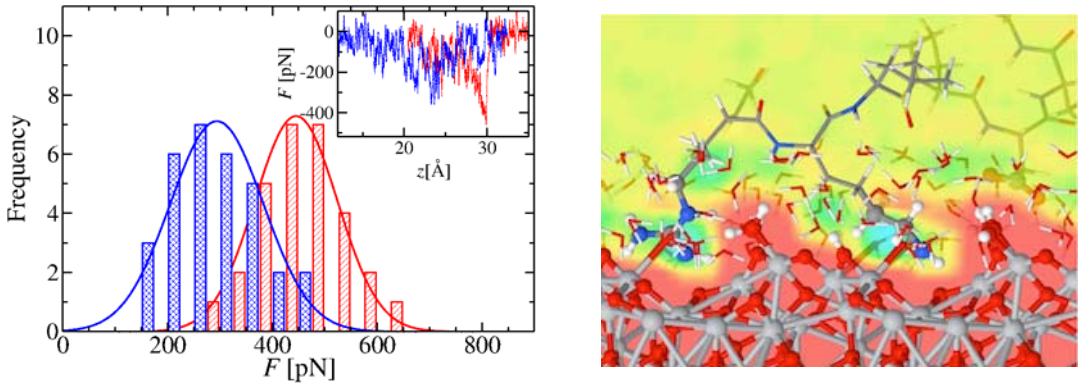

Fig. 2-3: Left: histograms of the SMD force peaks and typical force-displacement curves (displayed in the

inset) of the RKLPDA peptide on titanium (*red*) and on silicon (*blue*). Right: Adsorbed peptide on oxidised Ti, with a map of the unperturbed water density (displayed within a vertical plane, which includes the R and K end groups).

In further simulations, we evaluated the helicity loss of an alpha-helical shaped peptide on adsorption to a negatively charged silica surface as done previously with CD and ^{1}H-NMR spectra by Burkett et al. [Langmuir, 17:5059-5065 (2001)] and Read et al. [J Colloid Interf Sci, 261:255-263, (2003)]. From simulation results obtained with the RESTmetaD approach, we find strong adsorption to anionic silica surfaces induced by the positively charged arginine residues which interact with the deprotonated Si-O$^-$ groups of the deprotonated silica surface. Most importantly, exploiting the converged free energy profiles of the adsorption process as a function both of the height over the surface and of the internal helicity of the peptide, we have been able to predict the full CD spectra of the adsorbed vs. desorbed states by means of the DichroCalc software. In these simulations, weighting of the spectra of all possible peptide conformation according to their respective free energy is essential to achieve a quantitative agreement with the experimental results. Namely, we predict for the adsorbed and desorbed states a helicity fraction of 0.18 and 0.59, respectively, which agrees well with the experimental results (0.20 and 0.55, respectively). Moreover, the CD peak intensities associated with the alpha helix secondary structure element are predicted to be -0.49 and -1.49 10^4 deg cm^2 dmol^{-1}, versus the experimental values of -0.60 and -1.62 10^4 deg cm^2 dmol^{-1} in the two states, respectively. To the best of our knowledge, this is the first time that results of MD simulations reproduce with quantitative accuracy the complete features of CD experiments for materials-binding peptides.

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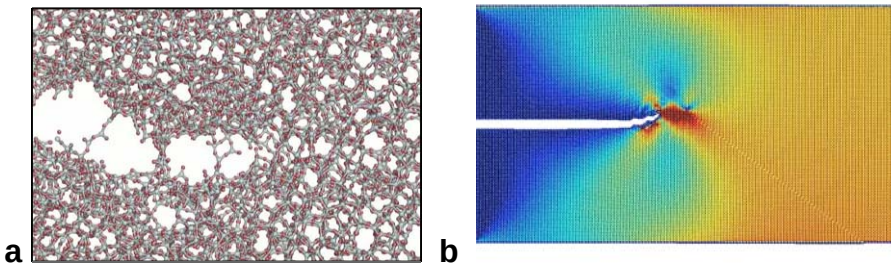
WP3 Hybrid simulations of the mechanical and chemo-mechanical properties of glassy thin-layer interfaces

As originally planned, in WP3 we have primarily performed computational simulations of crack propagation in various systems, using the Learn on the Fly (LOTF) scheme to reach the QM level of accuracy required where bonds break at crack tips. This main production part of the activity was extremely successful throughout the project.

Namely, In the dynamic fracture regime, where crack speeds are relatively high (of the order of 1000 m/s) we have studied (i) dynamical fracture instabilities in silicon [1], and (ii) catastrophic brittle fracture of crystalline and amorphous silica (Fig 3-1a). We have also identified crack-defect interactions mechanisms, where cracks interact with (iii) partial dislocations [2] (Fig 3-1b) or (iv) isolated substitutional impurities (Fig 3-1c), where we find a single atomic defect can influence the microstructural features of the fracture surface, in excellent agreement with the observations of consortium partners at Technion.

At the opposite end of the crack speed spectrum, we have (v) carried out the first QM accurate simulations of fracture via stress corrosion cracking in Si, initiated by both H [3] and (vi) O_2 (see Fig 3-1e). Finally, at intermediate crack speeds, we have investigated (vii) the transition from thermally activated to catastrophic brittle fracture, as well as modelling three dimensional aspects of fracture at the QM level for the first time (Fig. 3-1d), finding that kink nucleation and growth may well explain the dynamics of crack propagation at 100s of m/s.

Moving beyond fracture applications, we have carried out an intense method development activity, throughout the project. This generated accurate QM-based polarisable force fields for SiO_2 [4] and TiO_2, and novel QM/MM electrostatic embedding techniques for SiO_2. Very notably, technical difficulties had to be overcome in the part of the project connected with the generation of classical interatomic potentials to model advanced oxide interfaces. The issue was intensely investigated in a close collaboration between the KCL and ICTP groups and led to a novel approach where rather than the polarizable TS potential envisaged for TiO_2 at the outset, a novel potential was produced using the Gaussian Approximation Potential (GAP) framework. Whilst we have now successfully built good potentials for both SiO_2 and TiO_2, this slowed somewhat the progress of this WP, so that accurate classical potentials for the TiO_2/SiO_2 interface and quantum accurate classical simulations of interfacial cracks are still technically out of reach (to the partners of this consortium as well as to any other research group worldwide). However, the collaboration led to a number of original *ab initio* level results, including ZrO_2–CeO_2 [5] and titania-silica interfaces ([6], Fig 3-1f).



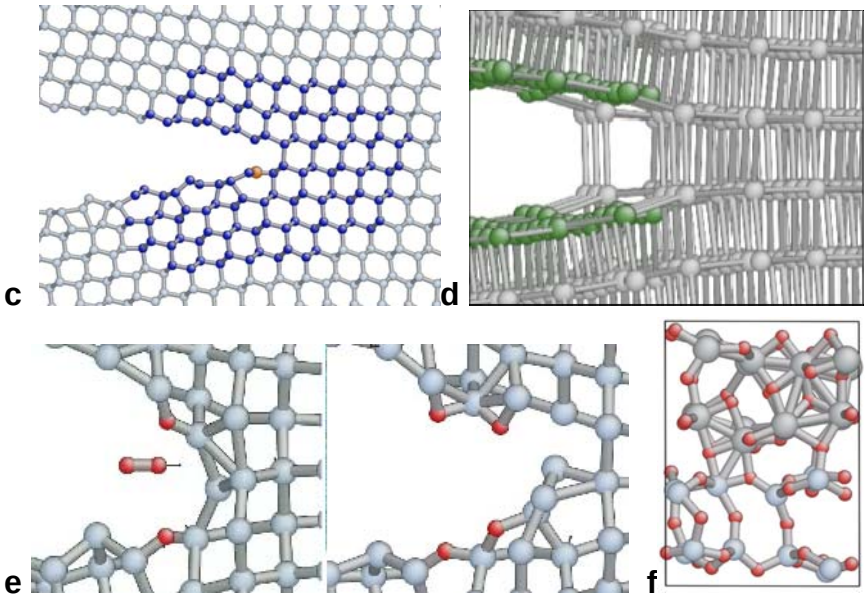


Fig 3-1: Simulations accomplished within WP3, including: **a** catastrophic fracture of amorphous SiO_2, proceeding by void nucleation, growth and coalescence; **b** fracture scattering by partial dislocations and **c** boron impurities; **d** three dimensional crack front advance via kink nucleation and growth; **e** subcritical crack growth in silicon initiated by O_2 stress corrosion. **f** SiO_2 – TiO_2 interface (anatase above, silica below).

One very positive unexpected deviation from the work plan resulted from the excellent experimental input from and synergy with the Technion group (greatly helped by Dov Sherman's regular travelling to Europe to meet the ADGLASS partners), which allowed several original results e.g. crack-defect interactions and stress corrosion cracking. Despite many significant technical improvements made to the electrostatic embedding methodology, the computational cost of QM/MM force evaluation for SiO_2 systems is still very significant (~10,000 core hours per picosecond). This has slightly reduced the scope of our SiO_2 fracture calculations, but this has been more than compensated for by the increased investigation of other fracture systems and mechanisms as outlined above.

References WP3

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WP4 Experiments of peptide adhesion at glass/liquid interfaces

The Main objective of the WP4 was to perform experiments of adhesion at glass/water interfaces using small oligopeptides and proteins synthesised ad hoc or from original sources in order to accompany the simulation work in WP3 with experimental information, and guide the design of anti-adherent materials in WP7. The main outcome of the research of WP4 can be summarised in the following three topics described below. Further information about detailed results can be found in the relevant deliverables and annual reports.

1. Methods to identify adhesive protein sequences and their synthesis with the solid-phase-peptide-synthesis (SPPS) followed by the adhesion analysis

Within the work of WP4 it was possible to establish a new technique for the characterisation of adhesive protein sequences in means of the identification of strong and weak surface binding peptides. This work was accompanied by the chemical analyses of model glass surfaces guided by ToF-SIMS, AFM, XPS and chemical methods. The identified peptide sequences have been successfully synthesised by the solid-phase-peptide-synthesis and subsequently used for adhesion-related experiments. Different methods like MALDI-ToF MS, QCM-D or AFM experiments have been applied to prove the gained results (Figure 4-1). By this it was possible to accompany the simulation work in WP3 with experimental information in terms of small peptide sequences. The several methods established in WP4 have deepened the long lasting competencies of the Consortium partners, in particular the Fraunhofer IFAM, within the science of protein adhesion.

Fig. 4-1: Process of peptide identification and adhesive peptide testing.

In particular, a new technique for the identification of surface binding peptides (overview shown in Figure 4-2) has been developed and a German patent application submitted by the Fraunhofer IFAM.

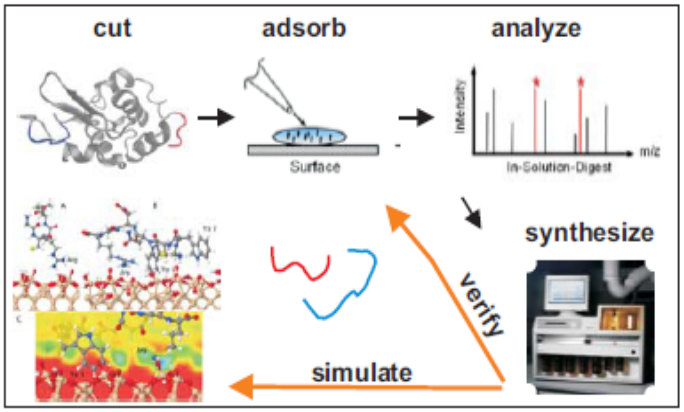


Fig. 4-2: MALDI-ToF MS depletion technique for identification of adhesive peptide sequences. [patent pending].

2. Adhesion parameters and involved processes of the adhesion of proteins

The characterisation of the peptide adhesion features at liquid/solid interfaces showed that several parameters have a strong impact to the adhesion process. Within the WP4 the influence of the protein concentration, buffer, pH, incubation time, formulation of excipients, surface composition and peptide sequences were investigated with physicochemical methods leading to a better understanding of the protein and peptide adhesion to glass surfaces. Long terms experiments in combination with different glass surfaces have also been used to study the protein adhesion parameters and possible changes in the secondary structure of the used pharmaceutical relevant proteins like antibodies. In doing this, we have combined QCM-D with FTIR spectroscopy techniques in order to collect information about the correlation of kinetics, concentration and secondary structure changes of adsorbed proteins (Figure 4-3). This enabled us to perform analysis of peptides and proteins adhered on dry versus wet surfaces. The established technique will be transferred to other systems such as enzymes, antifreeze proteins, and others.

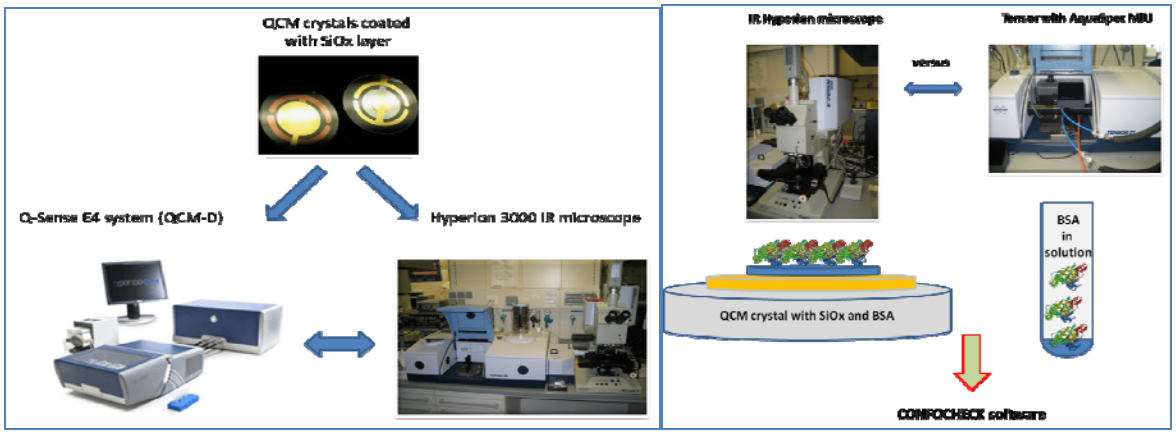
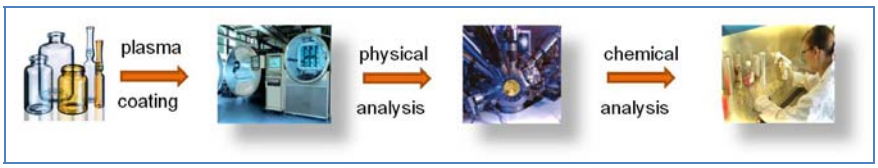


Fig. 4-3: Combination of QCM-D with FTIR (ATR) to collect information about the amount, kinetics and secondary structure of adsorbed proteins.

3. Development of PEG-like anti-adhesive plasma coatings and their testing

The work in WP4 was also linked to the investigations in WP7 dealing with the development of anti-adherent materials, in a close collaboration between the Fraunhofer IFAM and Schott AG. A type of PEG-like coating alternative to the one developed at Schott AG (see WP7 for further detail of PEG-like coatings) was tested at the IFAM. Figure 4-4 shows a brief overview about the obtained results of the analysis of the IFAM PEG-like coating.



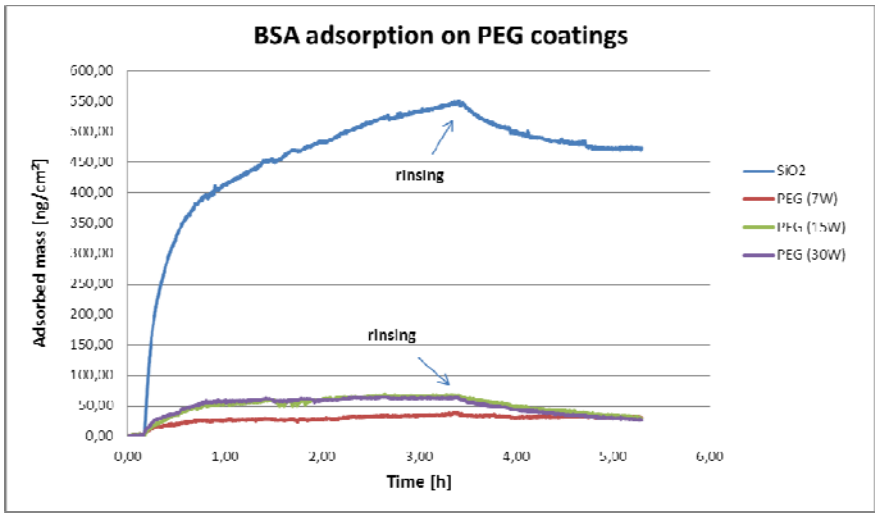


Fig. 4-4: Design and production of a PEG-like coating at the IFAM. The lower part of the figure shows QCM-D results of the testing of a PEG-like coating with the model protein BSA.

The used PEG-like coating shows a dramatic decrease in the protein adsorption of BSA in the range of 25 ng per cm^2 compared to 500 ng per cm^2 for the uncoated control. In other words, this coating is able to reduce the protein adsorption approximately by 95 %. Future work, on the basis of the gained results within the ADGLASS project, will deal with development of a broader range of new anti-adhesive coatings based on plasma processes (e.g. for medical devices/ antifouling surfaces).

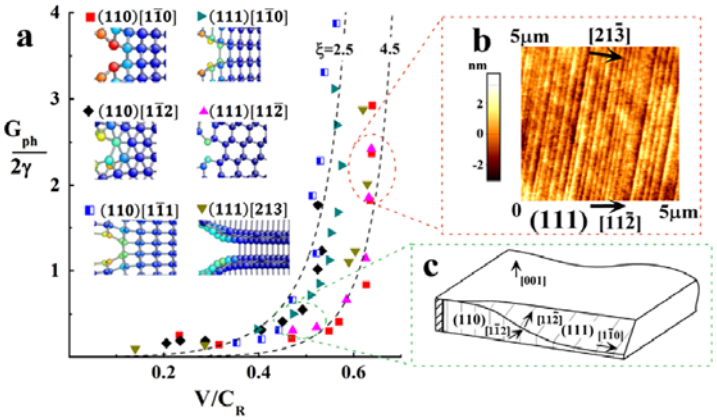
WP5 Experiments of crack propagation at glassy thin-layer interfaces

In WP5 we have carried out a large number of investigations on the fundamental mechanisms of brittle fracture propagation, lead by the group of Dov Sherman at the Technion. The main results are summarized in the following sections.

1. Phonon emission energy release rate in fracture of anisotropic material

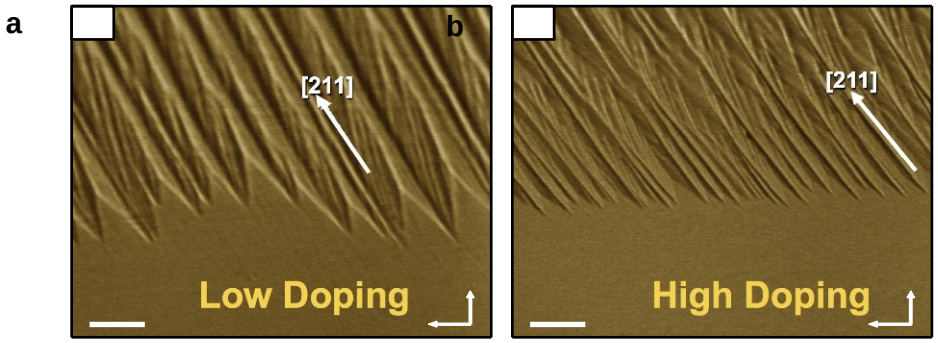
We used molecular dynamics simulations to calculate the phonon energy emitted during rapid crack propagation in brittle crystals. We showed that this energy is different for different crack planes and propagation directions and that it is responsible for various phenomena at several length scales: energetically preferred crack systems and crack deflection at the atomic scale, reduced maximum crack speed with volume at the micrometre scale, and the inability of a crack to attain the theoretical limiting speed at the macro-scale. We proposed to include the contribution of this energy in the Freund equation of motion of a dynamically propagating crack.

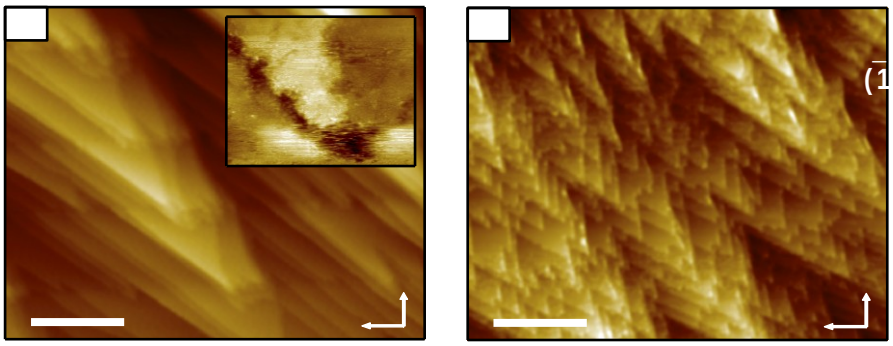
We showed that on the atomic scale, G_{ph} dictates the preferred direction of crack propagation and crack deflection. These results are in excellent agreement with experimental results. On the sub-micrometre scale, G_{ph} dictates the maximum crack speed, such that the maximum crack speed only reaches about 0.6 C_R, which is practical in fracture of nanotubes or grapheme sheets. On the other hand, at the macro-scale, this energy prevents the crack speed from attaining C_R, the theoretical limit speed, though this effect is relatively small in large volumes. It was shown that G_{ph} strongly depends on crack speed, volume, and on the atomistic arrangement at the crack tip. An additional term was suggested to the Freund equation of motion of a dynamically propagating crack. Consequently, the modified Freund equation of motion now can be utilized in a continuum-based model, such as finite element analysis.



2. Crack Defects Interaction in silicon crystal

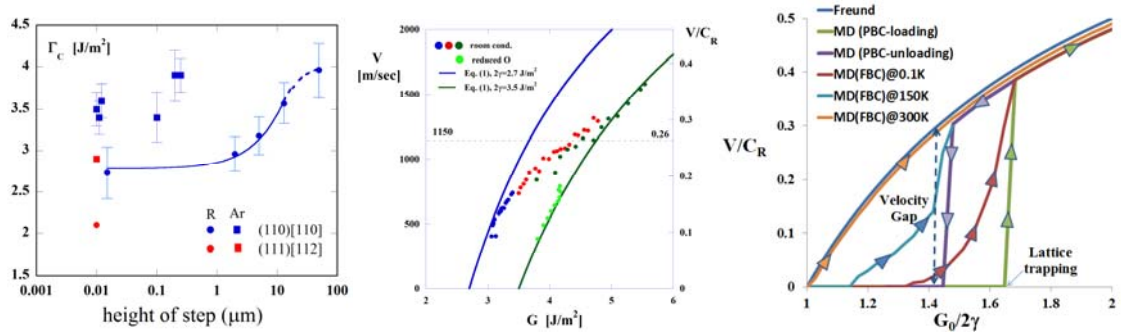
Brittle crystals such as coloured gems or doped silicon wafers have long been known to cleave with atomically smooth fracture surfaces, despite being impurity laden. This suggests that isolated atomic impurities do not generally cause cracks to deflect. Whether cracks can ever deviate when hitting an isolated atomic defect, and if so how they can go straight in real materials which always contain many such defects, is however still an open question.3, 4 Here, we carry out multiscale molecular dynamics simulations5 and high resolution experiments on boron-doped silicon. Our simulations reveal that cracks can be deflected by individual B atoms. The process, however, requires a characteristic minimum time, which must be less than the overall time spent by the crack front at the B impurity site. We also experimentally observe deflection in B-doped Si crystals, for crack speeds which are low, but still high enough that deflection cannot be induced by intrinsic propagation instabilities. This involves independent initiation of micron-sized “ridge” surface features, which intensify if we increase the B-dopage level. A simple model shows that if the ridges initiate at B atoms, their spatial distribution along the crack propagation direction must take a universal Rayleigh form. This fits well our experimental observations at $1.10{\cdot}10^{19}$ cm^{-3} B-dopant concentration, and then correctly predicts the much coarser distribution observed in experiments at 1.05^{15} cm^{-3} dopant concentration. Taken together, our results show that single substitutional defects can cause crack deflection in a brittle crystal, contrary to the common assumption. This could be generally true and still consistent with the perfectly smooth fracture surfaces commonly obtained by fast cracking. Indeed, these two facts can be reconciled by the velocity-dependent nature of the crack deflection process, which is possible at low speeds, while fast moving cracks are dynamically steered away from being deflected, yielding smooth cleavage.





3. Energy-speed relationship in brittle crystals

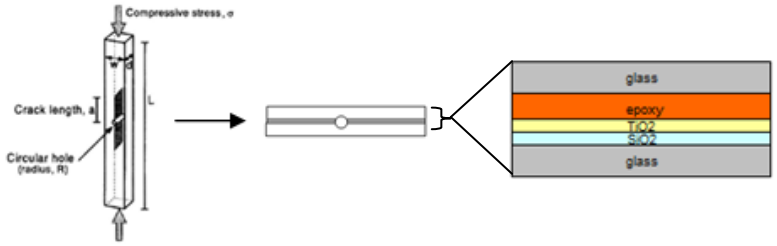
The thermal expansion coefficient mismatch method was examined by using silicon crystal as a model material and evaluating the cleavage energy at initiation of the {110}<110> and {111}<112> low energy cleavage systems under pure Mode I, at room and under reduced oxygen environments, which revealed significant differences, presumably due to the effect of oxygen molecules at the crack front (stress corrosion cracking). Griffith criterion for the initiation of cracks in brittle crystals and the lattice trapping effect are discussed.

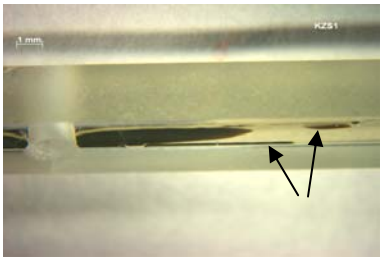


Over the last two decades, theoretical studies and atomistic computer calculations, 2D in nature, have been in accord with the common intuition, suggesting that the energy barrier for bond breaking on the crack front is sometimes 60 % higher than the accepted Griffith 2γ threshold and crack speed can't be lower than 2,000 m/sec. However, our high-resolution fracture experiments and quantum mechanics atomistic calculations suggest completely different behaviour. Here we show that cracks in brittle crystals are manifestly 3D in nature, the crack front is curved and constructed from enormous planar atomistic-scale steps, which sets a new length scale in fracture and responsible for very small energy barrier for crack initiation; hence, the physics of crack initiation and propagation is completely different than the accepted wisdom-cracks can initiate at Griffith energy of 2γ, propagate at low speed, and obey, unexpectedly, the continuum based Freund equation of motion. Based on those, we performed 3D atomistic computer calculations of crack dynamics at the quantum mechanical level of accuracy, and show that cracks in brittle crystals can propagate at speeds as low as ~1 % of the accepted theoretical limiting speed, even at relatively low temperatures. We further show that the mechanism of crack propagation is due to kink formation and subsequent growth rather than the correlated breaking of enormous bonds simultaneously along the front. The 3D multi-scale nature of crack problems turns the individual atom into a key player in failure. In practice, we found that the load to fracture may be half the predicted one so far. Our new insight is required to prevent catastrophic failure of these materials in service.

4. DCDC Crack propagation tests

Controlled crack propagation experiments along SiO_2/TiO_2 interfaces were conducted at SCHOTT useing the Double Cleavage Drilled Compression (DCDC) method. The crucial challenge for these experiments was the sample preparation as foreseen and described in the project application (see figure below, left). Generally, it was proven that the preparation of the specimen (cutting, grinding, polishing) was a critical step, because a pre-damage in one of the layer, interface or the border of the sample is creating wrong initial cracks. No more than 10-20 % of the samples with initial cracks were usable. Most of the samples were unsymmetrical, or there were additional pre-cracks, or the cracks were starting from the border. Microscopic and Scanning Electron Microscope (SEM) investigations revealed that none of the initiated cracks occurred along the SiO_2/TiO_2 interface (one example shown in figure below, right). All various attempts of different sample preparation failed. Therefore, the experiments were terminated. A positive interpretation of the data is that the interface between SiO_2 and TiO_2 phases is so stable that the failure of the prepared samples will always occur at other positions. Therefore, a further optimization of the setup to develop the coating to photovoltaic glass was not seen as necessary.





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WP6 Development of anti-adherent materials for pharmaceutical packages

The objectives of Work Package 6 were to implement the knowledge gained in WP2 and WP4 into the development of a novel material with anti-adherent properties when interfaced with a protein-containing solution, and to develop prototype pharmaceutical packaging (glass vials) coated with the novel material.

As a first step the fundamental driving forces of the adsorption of model proteins (BSA, IgG, lysozyme) on the glass surfaces and the chemical interaction of the buffer solution with the glass surface were evaluated. For achieving this goal various treatments were applied to modify the surface properties of the sample vials: Filling of vials with solutions having varying pH values (from 3-10) or containing different buffers, gradient of hydrophobicity of surface by coating applied at varying deposition conditions, NH_3 plasma treatment of inner vial surface, autoclaving under different conditions, depyrogenation, SO_2 treatment, application of organic contamination, etc. The resulting surfaces were analyzed by SEM, ToF-SIMS (spectra and depth profiles), AFM and XPS.

Long term storage stability tests were performed and ICP/MS was used to quantify glass elements leaching into the buffer / protein containing solutions. The evaluation of the data by means of statistical methods (PCA, PLS) and the correlation with protein adsorption data revealed that ionic interactions played an important role in protein adsorption on glass surfaces and that potential contaminations of the surfaces (e.g. by silicones) must be avoided.

These results and other considerations were directly transferred into the requirements for a protein deterrent coating: It must be non-ionic, hydrophilic, H-bond accepting and must exhibit a steric hindrance for the biomolecules. PEG-like layer had been identified as an ideal solution providing all necessary requirements. To be suitable for industrial commercialization the process for the application of the layer must be cheap, scalable, 100% controllable and feasible for deposition of a homogeneous coating on a 3-dimensional internal surface of a glass vial. A Plasma Impulse Chemical Vapor Deposition (PICVD, see Fig. 6-1) process based on a microwave plasma ensured the homogeneity of the layer, a good linkage to the glass surface, compatibility with sterilization methods, 100% process control and the possibility to scale-up of the method to industrial mass production (process time and costs).

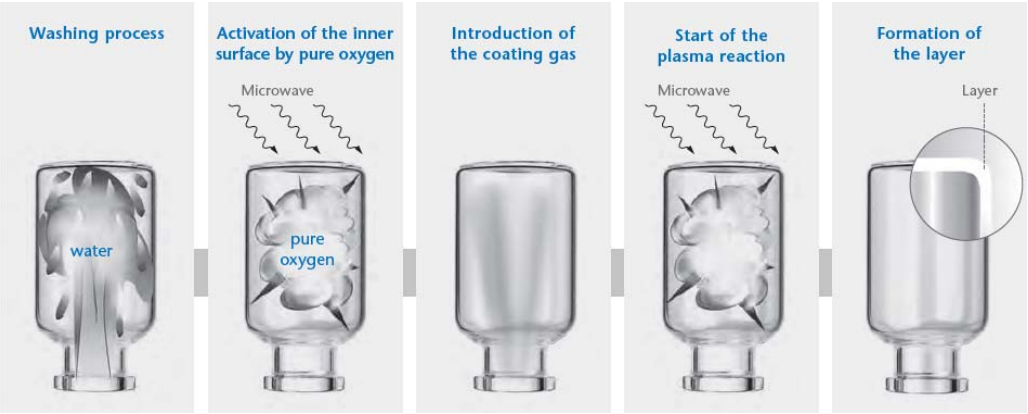

Fig. 6-1: Schematic diagram of the PICVD process.

The newly deposited PEG-like layers applied by the PICVD-method (“organic 1”) were compared to three different uncoated / untreated standard vial surfaces (Fiolax® from SCHOTT AG and one vial each from two competitors), two coated vial surfaces (Type I plus® = SiO_2 and a hydrophobic layer, both SCHOTT AG), chemically treated vials (ammonium sulphate) and polymer vials with regard to their adsorption values after incubation with a 10 µg/mL fibrinogen solution (see Figure 6-2).

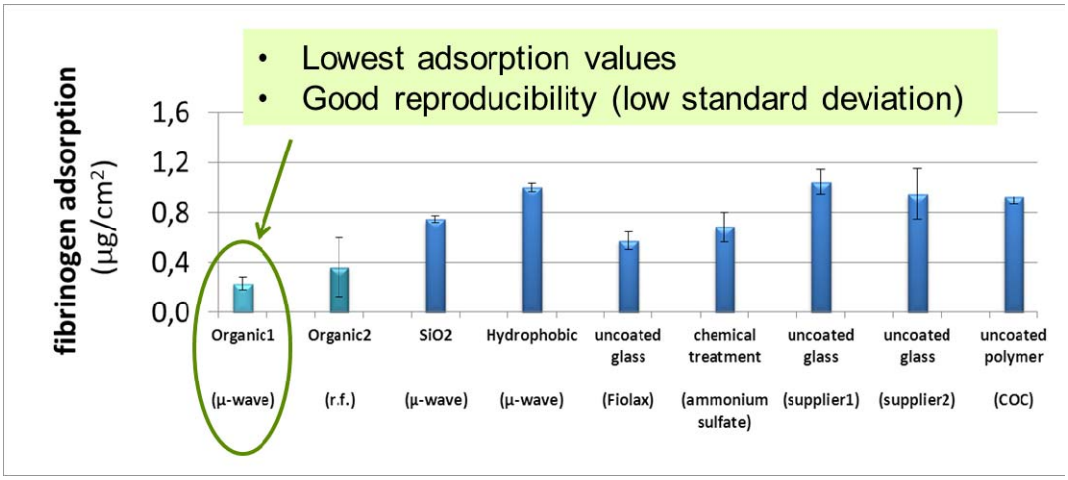

Fig. 6-2: Comparison of the adsorption values of the new PEG-like coating to several reference vials

The PEG-like coating exhibited a significantly lowered adsorption compared to all reference vials. After process optimization a reduction of fibrinogen adsorption of more than a factor of 20 was confirmed in a further experiment. Looking toward the future more test data need to be generated with the new developed PEG-like coating as well as functionality tests under pharmaceutically relevant conditions.

PEG layers are used for quite a long time for coating of polymer tubes and microarrays to achieve protein deterrent properties. For these applications the grafting of the PEG molecules to the substrate is known to be a challenge. For coating of a primary packaging for pharmaceutical applications a new coating process was developed based on a plasma process to deposit a PEG-like coating with a good adhesion of the layer to the glass surface in combination with an improved stability of the layer itself through crosslinking via plasma polymerization. The production process can be reliably controlled 100% (In Process Control, ICP) under well-defined conditions in mass production needed for achieving a competitive price per container. Furthermore it can be used throughout the entire pharmaceutical production chain including different sterilization methods. A comprehensive solution for all of these properties was not available on the market so far.

As a further outlook tailor-made container surfaces might be needed to achieve an optimum for specific protein solutions due to the variety of different interactions.

WP7 Development of adjusted refractive index and self-cleaning thin-layer conditioning materials for glass panels

One of the objectives of Work Package 7 was to implement the knowledge gained in WP3 and WP5 into the development of a novel material with self-cleaning properties and adjusted refractive index. This material should be applied as cover panels of photovoltaic cell modules. The final result would be a prototype glass panel coated with the novel material. This could be achieved by a applying a more or less complex interference layer system of at minimum 2 or more thin films with differing refractive indices, e.g. SiO_2 and TiO_2. But such a solution is too expensive for applications in photovoltaic industries.

An easier and more cost-effective approach addressed within the project was to use a single-layer anti-reflective coating. In this case the theoretically ideal value for the refractive index of the coating is the square-root of the refractive index of the coated glass substrate. An ideal coating for soda

lime glass would possess a refractive index of n = 1.24 and a layer thickness of 100 to 150 nm. But no sufficient dense inorganic, solid, affordable material is available today having such a low refractive index (e.g. SiO_2 (n = 1.46) and MgF_2 (n = 1.38)). Another approach to reduce the refractive index of a single-layer coating was to apply a single layer with a porous material. In this case the refractive index of the layer was the result of mixing the refractive index of the solid material with that of air. Porous layers were be built up by solid particles which had to be nano-sized in order to avoid scattering effects and to ensure a satisfying transparency.

SiO_2 nanoparticles embedded in a TiO_2 phase used as a “binder” material were used as a starting point to achieve anti-reflective and anti-staining properties within one single layer. During the project it turned out that the higher the binder content was, the better was the mechanical stability, but the poorer was the optical performance of the layer. Furthermore, this first multicomponent layer revealed no self-cleaning effect in weathering tests. All alternative approaches as replacement of SiO_2 partially or completely by MgF_2particles failed due to an agglomeration of the MgF_2 particles. The usage of pearl-chain SiO_2 nanoparticles at a ratio of 80:20 wt.-% (SiO_2:TiO_2) resulted in a transmission increase of 6 percentage points for a double-sided coating. But the mechanical stability was still too poor. At the end no suitable solution was found to combine both effects and the work for development of a prototype samples (WP10) was stopped as there was no prospect of success. It was envisaged that super-hydrophobic or super-hydrophilic layers were potential starting points for new developments.

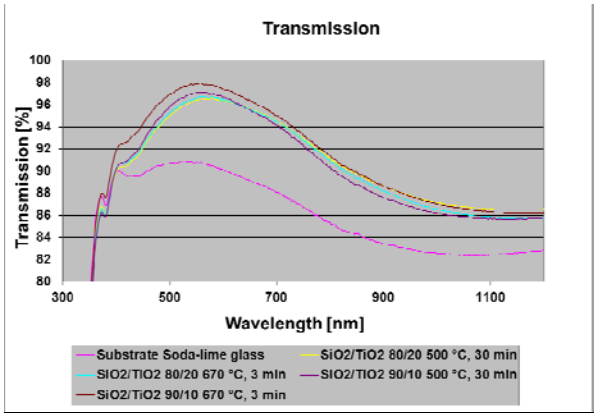

Fig. 7-1: Transmission curves for porous single-layer coatings based on pearl-chain-like SiO_2 nanoparticles on soda-lime glass substrates with different SiO_2 particle: TiO_2 binder ratios

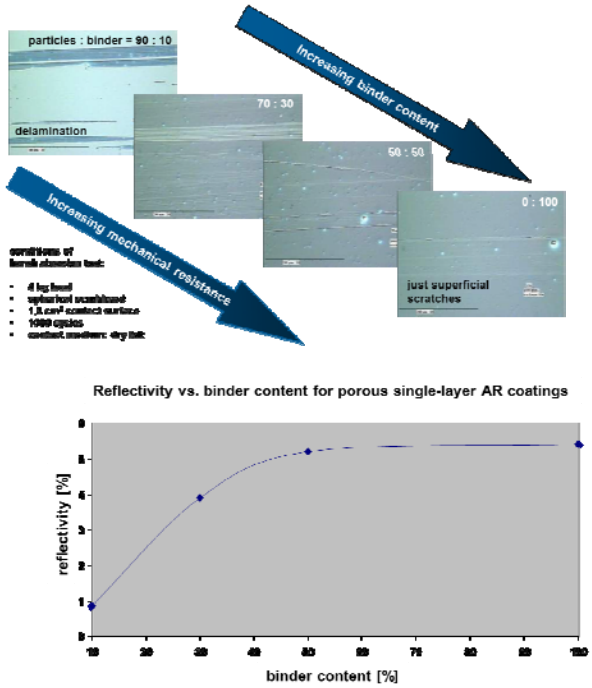

Fig. 7-2: Influence of binder content on mechanical stability (top) and reflectivity (bottom)

WP8: Quantification of adhesion of protein-based drugs on prototype packages

Adsorption is a very common phenomenon but also a very complex one [K. Nakanishi, T. Sakiyama, and K. Imamura, *J Biosci Bioeng* **91**, 233-244 (2001)]. The difficulty to correctly control adsorption

remains particularly in the multifactorial aspect of the phenomenon, since it depends of several parameters such as physico-chemical properties of the protein, of the formulation and of the surface (Figure 8-1).

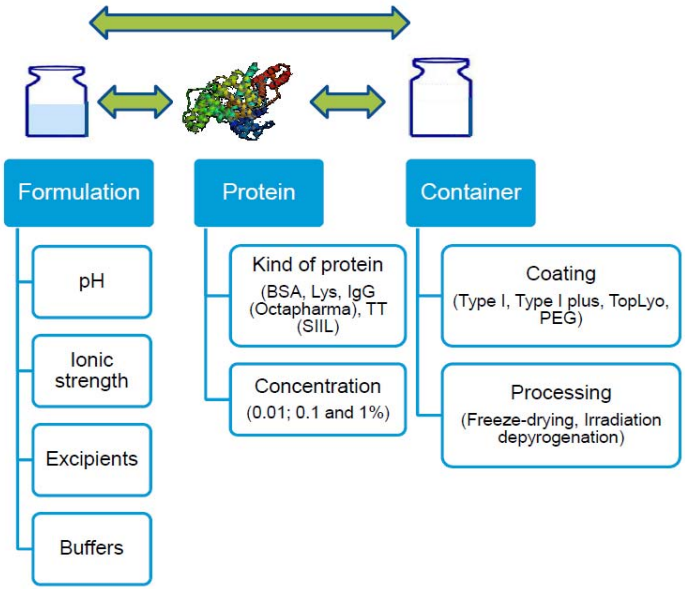

Fig. 8-1: Main parameters influencing protein adhesion in vials. The physico chemical properties that were investigated in the ADGLASS project (pH value, ionic strength, excipients, kind of protein, vial's coating and processing) are presented in the scheme.

Most of the experimental work was performed with BSA (67kDa, pI=4.7, soft protein), IgG (150kDa, pI=5.6, soft protein, supplied by Octapharma) and lysozyme (12kDa, pI=11.3, hard protein), in three kinds of vials (Type I, Type I Plus and TopLyo), supplied by Schott AG. The adhesion of Tetanus Toxoid (TT, supplied by SIIL) was also investigated in some specific conditions. Finally, the new coated vials (PEG-water like coating), developed in the frame of WP6 were tested in real conditions with the four kinds of proteins.

1. Formulation characteristics

The results obtained show that the pH value of the formulation has a big impact on protein adhesion. This is directly related to the electrostatic interactions occurring between the negative charge of the surface and the positive domains of the protein, leading to adhesion. As electrostatic interactions are known to be influenced by an increasing ionic strength, it was interesting to study the effect of ionic strength on protein adhesion. To avoid any interference of formulation components, the investigation of the ionic strength influence was performed in a very simple medium containing Tris buffer pH7, protein and NaCl. The results have shown that the impact of an increase of the ionic strength can be different depending on the protein type and of course the vial surface properties. The results of our investigations let think that adhesion of "soft" protein is decreased when working with a high ionic strength, whereas adhesion of "hard" protein seems to be equivalent or even increased when working with a high ionic strength formulation. Also excipients serve several functions. They provide a stable liquid environment for the active ingredient for some finite time. However, few studies have investigated the effect of sugars on protein adhesion. To our knowledge, only Wendorf et al. studied the impact of 13 sugars on protein adhesion [J.R Wendorf, C.J Radke, and H.W Blanch, *Biotechnol Bioeng* **87**, 565-573 (2004)]. It is clearly established that the addition of sugars has an effect on protein adsorption, however the mechanism involved is not clearly defined. Some hypotheses had been proposed over years, but none of them has been proven yet.

2. Surface/vial coating properties

To evaluate the efficiency of new coated vials (developed in WP6) in term of adhesion, most experiments were performed in 4 kinds of vials (Type I, Type I Plus, TopLyo and the new-coated ones) to be able to compare the results. The drug contact surfaces have different chemical compositions for all four different vial samples as shown in Table1. Different glassy and polymeric layers were tested.

Table 1: Characteristics of vials submitted to study

Vial Type	Drug contact surface	Property	Contact angle for water	Plasma coating
Type I	Type I borosilicate glass ('Fiolax')	glassy	< 20°	-
Type I Plus®	inorganic (SiO_2)	glassy	< 20°	yes
TopLyo®	silicon organic	polymeric	104°	yes
New organic coating	organic (PEG-water like layer)	polymeric	56°	yes

A main observation of this analysis is that the effect of storage time on protein adhesion on the surface of the new developed vials is correlated to the ionic strength of the formulation. At low ionic strength, the new-coated vials limit BSA adhesion. After 30 days of storage at +37°C, in a formulation with a low ionic strength, the new-coated vials are as efficient in term of BSA anti-adhesive properties as Type I Plus. On the contrary, in a formulation with a high ionic strength, the new-coated vials are the less efficient vials with Type I vial concerning BSA anti-adhesive properties.

We can thus conclude that protein adhesion cannot be evaluated only by considering vial coating. The efficiency of the coated vials was investigated using different experimental conditions (formulations) and the parameters considered have a huge influence on the amount of protein adhered to the vial. This is especially true for the pH value and the ionic strength, but the most important point is that these parameters can exert opposite effects, depending on the kind of protein integrated in the formulation. This means that the behaviour of the protein in a kind of vial can be different according to its own size, its isoelectric point or its classification as soft or hard protein.

3. Processing

In a second part of the project, some treatments were applied to the vials and/or to the formulations and their effects on protein adhesion were evaluated. The first process to be integrated in the study was the freeze-drying process. It is clear that protein adhesion is reduced for the freeze-dried samples if compared to the liquid ones. However, this is probably due to the lack of mobility of the protein at the freeze-dried state and not directly linked to the freeze drying process itself. As no significant differences were noticeable between some freeze-dried samples and liquid samples but frozen at -20°C, we conclude that the freeze-drying process does not influence protein adhesion on vials' surfaces.

The second process investigated in this study was irradiation. Irradiation process is widely used for the sterilization of medical devices and pharmaceuticals. The latter represents a significantly growing market. This process is often combined with depyrogenation. The results obtained in the

frame of the ADGLASS project do not put forward any influence of irradiation nor depyrogenation processes on protein adhesion. This leads us to conclude that the vial coatings (Type I Plus and TopLyo) are not sensitive to the investigated processes.

It is clearly established that protein adhesion depends of several factors. The results obtained during the ADGLASS project highlight some of these parameters. As it is very difficult to evaluate which parameter is more influent than others, we do suggest a ranking of the parameters investigated and their effect on protein adhesion (see Figure 8-2). This classification has to be considered carefully since only four proteins were investigated in our study.

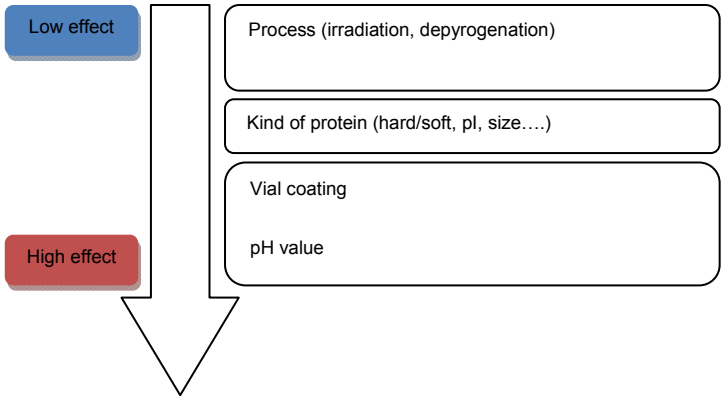

Fig. 8-2: Summary of the investigated parameters and classification of their adhesion effect.

WP9: Quantification of midterm efficiency loss of photovoltaic cells coated with prototype glass panels including monitoring of biofilm formation

Photovoltaic cells convert solar radiation into electric current using semiconductors, such as crystalline silicon, with typical maximum conversion rate between 12 and 16 %. However, their efficiency during long-term operation may decrease due to opacification of the protection glass panels.

The Work Package 9 aims to set up and conduct a mid-term experiment to measure the efficiency loss of photovoltaic cells due to opacization of the protecting glass cover as a consequence of weathering and biofilm[2] formation and to define a test to quantify the reduction of efficiency loss due to coating of the glass with the novel material developed in WP7. To achieve this goal, *in vitro* and *in situ* experiments have been implemented.

In vitro assays were carried out under accelerated ageing conditions. Microbiological methods for monitoring the formation and development of biofilm under ageing conditions have been set up and optimized. The evaluation of glass coatings impact and the establishment of kinetics for biofilm formation were performed using an artificial contamination with *Pseudomonas fluorescens* on three kinds of glass provided by Schott AG in Mainz: Uncoated glass, SiO_2 coated-glass, and SiO_2/TiO_2 coated glass (new coating material). Glass samples are incubated at +30 °C and 95 % relative humidity for 1 day to 2 weeks to promote biofilm development (Figure 9-1). As the photocatalytic property of TiO_2 is initiated with strong light, a full spectrum (white) light is used in order to irradiate (9 hours a day) the 3 kinds of contaminated glass samples during their incubation. This light aims to replace the sun light effect on TiO_2 when exposed *in situ.*

[2] A biofilm is a community of microorganisms (bacteria, fungi, etc.) which form clusters. Biofilm matrix contains: water at 99 % of biofilm weight, extracellular polymeric substances, polyosides, proteins, glycoproteins, nucleic acids and trapped substance.

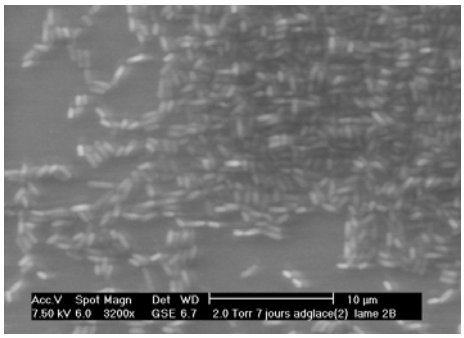

Fig. 9-1: Visualization (x100) of *Pseudomonas fluorescens* biofilm formation using SEM at 48 hours of its development

In situ assays were performed by setting up small glass panels (10x10 cm^2) prepared by SCHOTT AG in Mainz with different surfaces (uncoated, SiO_2 coated surface and SiO_2-TiO_2 coated surface) on the roof of the buildings of Aérial in Illkirch**.** The glass panels have been inserted in aluminium frames (Figure 9-2). The efficiency loss was evaluated by transmittance measurement of these glass panel exposed to the environmental conditions. Transmittance spectra are edited each time and compared over time. In parallel, biofilm growth has been monitored and the contaminant microorganisms have been isolated and identified.

Fig. 9-2: Coated glasses prepared by Schott are placed in the frames on Aérial's roof (Orientation: South - Angle: 30°)

The investigation conducted ***in vitro*** demonstrates a decrease of biofilm (viable bacteria) on contaminated glass submitted to accelerate ageing conditions. This is due to normal lethality (cellular degeneration) and /or photo catalytic effect of TiO_2. The mortality rate due to cellular degeneration and stress culture conditions is evaluated based on the decrease of viable bacteria count on uncoated glass. It reaches almost 1 log over two weeks of incubation under accelerate ageing conditions. The viable bacteria count drops by 0.5 to 1 Log thanks to photocatalic effect of titanium dioxide incorporated at 10% in the glass coating (Figure 9-3). Photocatalytic effect of titanium dioxide is positively correlated to its incorporated rate in the glass coating. A rate of 50% of TiO_2 appears to be the optimum rate to avoid the development of biofilm and allows a reduction of the biofilm by a factor 1000 over a two weeks period of ageing. These results were confirmed using two others environmental bacteria (***Brevibacterium spp and Kytococcus sedentarius)*** isolated from uncoated and coated glasses placed on Aérial's roof.

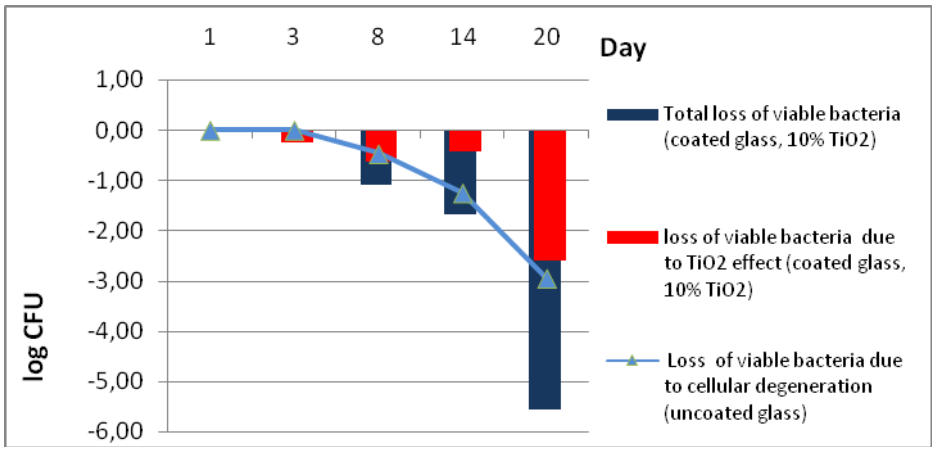

Fig. 9-3: Decay of viable bacteria onto coated glass (10 %TiO_2) according to the exposure duration to accelerated ageing conditions. (Average of 2 measurements)

The investigation carried out ***in situ*** reflected that no significant loss of transmittance of glass panel when exposed to weather conditions (Figure 9-4) could be demonstrated. Indeed, transmittance remains near or little lower than the reference data 100 % transmittance corresponding to the reference glass (i.e uncoated glass before exposure to weather conditions). After 33 months of outdoor exposure, no significant difference can be visible between the three kinds of glass in term of neither transmittance nor bacterial growth. During this period, microorganism populations reached maximum 4 to 5 Log of CFU (Figure 9-5). This rate of microorganisms remains insufficient to allow proper implementation of the biofilm.

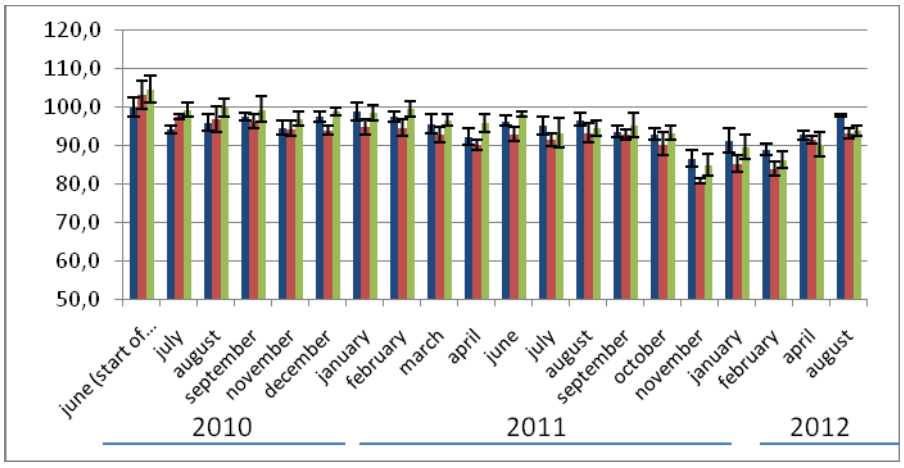

Fig. 9-4: Evolution of transmission efficiency regarding outdoor exposure for reference glass (blue), SiO_2-coated glass (red) and SiO_2/TiO_2coated glass (green). Transmission efficiency is expressed in percent. (Average of 3 measurements)

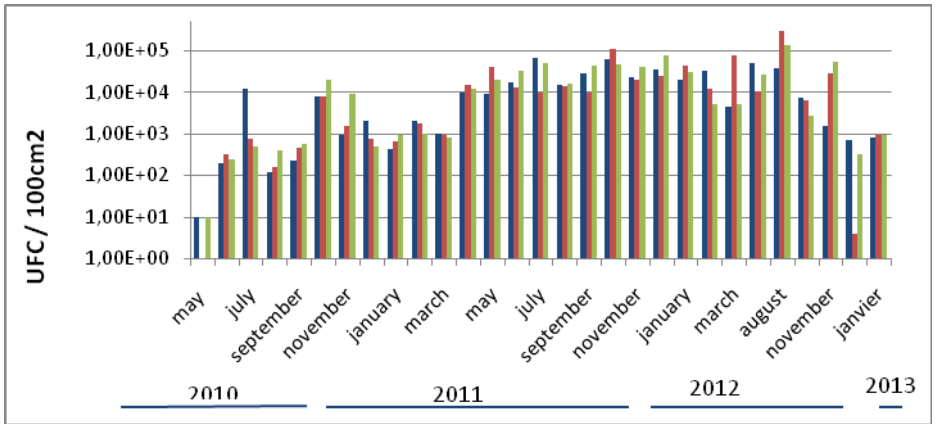

Fig. 9-5: Uncoated glass (blue) SiO_2 coated glass (red) and SiO_2/TiO_2 coated glass (green) contamination by total microbiological flora over time during outdoor exposure on weather conditions.

The low implementation and development of biofilm is not related to the ability of microorganisms to form a biofilm since in the frame of *in vitro* assay, microorganisms isolated from glass panels exposed to weather conditions, showed the ability to form biofilm under ageing accelerated conditions. It seems that the low kinetic growth of microorganisms is especially due to the inappropriate climatic conditions. Indeed, uncoated and coated glasses have been contaminated by *Pseudomonas fluorescens* (characterized by a high capacity to form a biofilm) and placed on Aérial's roof to monitor the biofilm formation. The monitoring of *Pseudomonas fluorescens* growth showed a large decrease of its population in the first week of outdoor exposure on uncoated and coated glass panel making it difficult to form a biofilm.

Conclusion

In vitro assays highlight a loss of viable bacteria under accelerated ageing conditions over 20 days of incubation. In the case of SiO_2/TiO_2 coated glass, this loss is also related to photocatalytic effect of TiO_2. The increase in the rate of incorporation of TiO_2 in the glass coating improves its photocatalytic effect.

The test conducted *in situ* during almost three years in real conditions did not put in evidence the contribution of the new coating of glass panel in terms of efficiencies against opacization. Location and local climate seem to be a factor determining the development of the biofilm. However, based on the results of tests conducted in vitro, it appears that TiO_2 limits the development of the biofilm mainly if its incorporation rates is greater than 50% of the coated glass panel.

WP10 Quantitative performance analysis of prototype packages and panels

The goal of work package 10 was to quantify the performance of the newly produced glass coatings implemented in prototypes, carrying out the tests developed and optimised in WP8 and WP9.

1. Tests of prototype glass vials

Referring to Deliverable 10.1 for details, we can summarize the results of the tests as follows:

- A significant reduction of fibrinogen adsorption on the prototype, PEG coated glass vials has been reproduced and quantified after incubation with a low concentrated protein solution. A reduction of fibrinogen adsorption of more than a factor of 20 with respect to an uncoated reference of same glass composition was confirmed.
- The chemical interaction of a pharmaceutical formulation solution with the PEG-coated glass container surface was investigated in a systematic screening applying a combination of different analytical methods. The results indicate a weak interaction of the selected buffer solution with the glass surface which can be explained by the storage conditions of low temperature and neutral pH value.
- A further key learning is that different sources of contaminations can have an impact on the system performance as for example silicone oil residues identified on the glass container surfaces. To avoid such contaminations will be very important to control biomolecule adsorption on pharmaceutical primary packaging

2. Tests of prototype glass panels

Since the preparation and test of adequate samples failed at an earlier stage of the project, we have not been able to complete a revised work plan up to the stage of a new product prototype. Knowledge of the key requirements for the development of a TiO_2-based material with optimised

cohesion properties to a SiO_2-coated glass substrate has been presented in Deliverable 7.2. Moreover, the performance of coated glass panels with respect to opacization under working conditions for an extended time period has been successfully quantified, as described in WP 9.

4.1.4 Potential impact (including the socio-economic impact and the wider societal implications of the project so far) and the main dissemination activities and exploitation of results (max 10 pages)

1. Broad socio-economic impact

The activity of ADGLASS has led to the development and application of a new atomistic simulation technique designed to tackle multi-scale materials science problems of high industrial relevance with an unprecedented degree of flexibility in terms of model system size and simulation accuracy. The modelling tool which has been developed and the scientific results it has produced, complemented and validated by experiments and end-user product design, is expected to become a new reference for quantum based modelling within the EU (Bio)Materials research. Indeed, the ADGLASS Project has contributed to establishing a culture for the application of this class of modelling techniques in high-tech industrial materials research carried out within the EU area.

This is the result of an effort on the European scale, where some of the major world's experts in the fields of materials modelling and materials design have worked together and in close contact with the R&D department of a market leader producer of glass products for advanced technological applications. By combining large-scale simulations with high-resolution experiments we have set up a simulation framework for the accurate study of heterogeneous glassy interfaces based on realistic models which capture all the essential features of the investigated systems. We have directly implemented the acquired microscopic knowledge of the materials behaviour into the design of novel anti-adherent materials for pharmaceutical packaging and have worked towards the development of novel thin-layer materials with self-cleaning and adjusted optical properties for photovoltaic applications.

The development of novel primary pharmaceutical packaging elements for protein-based drugs will likely help to reduce costs, increase shelf-life and lower potentially severe medical side effects. The enhanced reliability and increased life-time of high-performance thin-layer materials for photovoltaic applications can strengthen the European market in the strategic field of renewable energy production.

2. Impact of the novel developed materials

PEG layers have been used in biotechnological applications (e.g. microarrays) for quite a long time to achieve protein deterrent properties. However, the coating processes used in these applications were not suitable for coating of pharmaceutical containers. Our novel PEG-like material based on plasma-coating technology can be used for pharmaceutical primary packaging applications with very high demands for the coating and the manufacturing process. The production process can be reliably controlled (100 % in terms of In-Process Control, ICP) under well-defined conditions in mass production needed for achieving a competitive price per container. Furthermore it can be used throughout the entire pharmaceutical production chain including different sterilization methods. A comprehensive solution meeting all combinations of these properties was not available on the market so far.

The developed PEG-like layer significantly reduces the adsorbed amount of low concentrated model proteins compared to a standard uncoated borosilicate glass surface. Pharmaceutical companies normally compensate this loss of Active Pharmaceutical Ingredient (API) by overfilling, which means that a higher volume is used than would be needed if no adsorption was taking place (approx. 5 % or even more). This leads to an increase of costs, especially for high-potent drugs which are very

expensive (>1.000 € per vial). Reducing overfilling by only a few percent leads to significant reduction of costs for the patients and the health care systems. There are hints and speculations in the scientific literature that the interaction of the modern biotech drugs with the vials' surfaces (mainly peptides and proteins) could lead to a change in the conformation of the biomolecules. This could result in immunologic responses if these misfolded molecules are applied to sick patients even increasing their health problems. A reduction in the interaction of the drug with the container surface reduces this risk for the patients. When commercially marketed, the (socio) economic impact will be significant. The basis for this impact would be the acceptance by the pharmaceutical industry. Applications of the developed vials would be limited primarily to new drugs which are in early development stages as the costs for re-registering of existing products would be in most cases too high. The help of relevant authorities within the European Community would be of high benefit to increase the acceptance. The results of the performed R&D work are valuable also from a scientific point of view due to a better understanding of the interaction between the drug solution and the container surface, of the mechanism for protein adsorption and requirements for minimization of adsorption.

The aim of the photovoltaic part of the project was to develop a cost-efficient single layer coating for glass sheets used as covers for solar panels which reduces the amount of reflected light. This antireflective coating would lead to a higher efficiency of the panels. In parallel the coating should also exhibit self-cleaning properties reducing the amount of dirt on the surface. This non-staining property would also lead to an improved efficiency over the expected life-time of over 25 years of the solar panel. A further important requirement is to achieve a sufficient mechanical stability of the layer. During the project it turned out that it was not possible to develop a solution meeting all requirements for an improved anti-reflectivity, self-cleaning property and mechanical stability within one single layer. New approaches are necessary to achieve this goal in the future. Although this unexpected outcome was disappointing, it was a clear help for the European photovoltaic industry not to follow traditional ways of thinking and it also gives hints of how the set goal could be reached in the future. The achievement of the goal would be a real benefit to the European photovoltaic industry and could regain market shares in the future recently lost to Asian competitors.

3. Impact of the novel simulation methods and potentials

The development of software which can be used in an industrial environment represents a major step-forward towards the design of new products and technologies on the basis of the knowledge of elementary physical and chemical processes. In the past, a progress of analogous impact has been achieved by the marketing of electronic structure codes based on techniques which were confined to academic environments. We expect that the development of the LOTF methods and the libatom/QUIP packages, with the specific target of industrially-related applications, will result in a success of similar proportions. We note, however, that the development and application, rather than the commercialisation of this package have been the goals of the present project.

At the academic level, the activity of ADGLASS has resulted in the diffusion of a novel modelling method to a vast scientific community. This continues a long European tradition of developing and disseminating revolutionary atomistic modelling techniques. The most striking example was the implementation of basic electronic structure theory in efficient plane-wave pseudopotential DFT codes optimized for production calculations on parallel supercomputers that took place in the eighties and nineties both in the UK (notably within the Physics Department of the University of Cambridge) and in Italy (notably in the Trieste physics community including the ICTP).

A further strong impact of the results achieved by the ADGLASS project is expected to arise from the novel accurate potentials for the study of oxides of relevance for the glass industry. Of particular relevance is the capability of these potentials to describe complex phenomena such as phase transitions, glass structure, and, in the case of water, also dissociation. The availability of a dissociable potential for water will have an important impact also outside the field of research of ADGLASS. For example, it will allow the calculation of the dissociation constant of water at extreme conditions of pressure and temperature, a poorly constrained quantity of fundamental importance in geochemistry. Moreover, the combination of the potentials with existing biomolecular force fields opens up the possibility of quantitatively accurate simulations of protein/surface interactions.

4. Impact on the field of brittle fracture propagation

In the field of brittle crack propagation, following the success of the ADGLASS project, further investigations of stress corrosion cracking in oxides are being carried out at the King's College London (KCL). Moreover, extension of the LOTF scheme to metals (notably $NiAl_3$ superalloys) appears feasible, building on technology developed during the project. To this regards, a number of PhD programmes, in part funded by international industries, have been initiated at KCL. E-learning resources originally developed for ADGLASS schools (namely, fracture simulation tutorials, see the section of Dissemination Activities) and are now routinely used for KCL Physics undergraduates as well as forming part of the training for new members of the KCL Physics Theory and Simulation of Condensed Matter Research Group. Further project proposals which are likely to originate from the success of ADGLASS include:

1 Systematic study of stress corrosion processes, e.g., to investigate fracture in rocks with O_2, H_2O, and additives, a study of embrittlement phenomena and failure modes in other structural materials, namely H embrittlement of steels
2 Study of the dynamical properties (instabilities, velocity-temperature-load interdependencies) of catastrophic brittle fracture
3 Investigations of fracture toughness, stress corrosion mechanisms, plasticity onset in metallic systems, namely high-performance (super)alloys
4 Development of novel machine-learning-based force fields, necessary where classical interatomic potentials fail or are too hard to develop, as learned during ADGLASS.

From an experimental point of view, the acquired knowledge on 'how crystals break' is significant and elucidating the physics of fracture: micron scale surface instabilities initiate at the atomistic level at crack defects interaction, the crack front is constructed from steps and therefore cracks propagate at double kinking mechanisms, which enable crack initiation near Griffith barrier, hence cracks can propagate at low speed at room temperature. We further defined the conditions required for crack deflection under combined tensile and shear stresses: faster cracks require high shear for deflection. These pieces of knowledge are assembled to the greater picture of the physics of crack propagation in crystals. The impact of ADGLASS is evident with continuation of funding by other funding agencies for research in the field of fracture: funding for investigating failure of silicon crystals and ceramic materials was obtained by Technion last year, aiming at assisting industrial companies in Israel in fabricating the new 450 mm silicon wafers free of damage. A research proposal was submitted last year to the Israel Science Foundation to study fast crack propagation, and a new proposal is now under construction to further study the way crystals break.

The ADGLASS project gave the opportunity to investigate fracture in brittle materials not only by experimental fracture mechanics, but also in combination with atomistic simulations, in particular in the collaboration between King's College London and Technion. The combination of experiments

and atomistic calculations has led to significant results; among them stress corrosion cracking in silicon, fracture mechanisms at the crack front, etc. This collaboration is expected to fruitfully continue also after the completion of the ADGLASS project.

5. Impact on the field of protein adhesion

In the field of protein adhesion, the work within ADGLASS has enabled us to gain an unprecedented knowledge of atomic-scale details of the interactions between proteins and solid materials surfaces. The largest impact is expected to arise from the newly developed atomistic simulations. We have shown that for small peptides we are now able to predict, by means of computer simulations, experimental observables such as adhesion free energies, adhesion forces, amount of secondary structure elements and Circular Dichroism (CD) spectral intensities. It is therefore possible to perform hand-in-hand, direct comparisons with results stemming from established experimental methods such as CD spectroscopy and AFM force spectroscopy. The added value coming from the computer simulations is a detailed picture of the structures and interactions governing the behaviour of protein/materials interfaces. In the group of the Coordinator at the University of Bremen an experimental laboratory has been set up precisely to this purpose and will be dedicated to continuing the work started within the ADGLASS project in fields such as:

- Detection of polluting elements, small drug molecules and protein at ultralow concentration by means of fingerprint analysis of traces obtained with force-spectroscopy experiments. In these experiments, an AFM tip functionalized with biomolecules interacts with a solid substrate and the force-distance response is modulated by the presence of additional molecules (the ones to be detected) in the solution environment.
- Biomolecule-induced dissolution of oxide materials, in particular of oxide nanoparticles in contact with living tissues. Here, a precise knowledge of the protein/material interactions, as gained within ADGLASS, is a pre-requisite for understanding dissolution mechanisms which may be responsible for the toxicity of nanomaterials in a biological environment.
- Biomimetic fabrication of materials exploiting the specific biomineralization capabilities of biomolecular templates. The advantage over traditional fabrication methods is that in most cases the synthesis takes place at room temperature conditions and lead to materials that are intrinsically biocompatible. An example would be the construction of magnetic multilayer materials growing on ceramic templates previously functionalized with ferritin protein units.

6. Impact of novel research on glass materials' interfaces

Heterogeneous interfaces were studied within the ADGLASS project both in the context of pharmaceutical primary packaging coatings and of solar panel protection glass coatings. In both these domains, innovative methods and protocols have been developed in order to evaluate the impact of the coatings on protein adhesion and biofilm formation respectively. New competences and know-how have also been acquired in particular by Aérial and the Fraunhofer IFAM, which will contribute to strengthening their roles as research and technical transfer organizations being able to respond efficiently to the customer's needs. In addition, several results extracted from the project are under publication and will help the research organizations to be identified as potential partnerships in future National or European projects. Indeed, the results and benefits of such research projects are Aerial's and IFAM's driving forces for future projects and private development contracts. In this respect, commitment within the ADGLASS project fully matched the set objectives.

7. Main dissemination activities

The results of our projects have been made available to the scientific community in more than 20 peer-reviewed journal articles (many more are under review or in preparation at the moment of writing this report), 3 press releases as well as a large number of conference presentations. Moreover, we have organized two workshops and one school open to the public, as described in the following.

a. A **Scientific Workshop** entitled "Advanced Oxide Interfaces" has successfully taken place from May 9th to 12th 2011. It has been organized by Sandro Scandolo (ICTP), Lucio Colombi Ciacchi (Fraunhofer IFAM), Alessandro De Vita (KCL), and Holger Röhl (SCHOTT) and hosted by the Abdus Salam International Centre for Theoretical Physics. Scientists and students from all countries that are members of the United Nations, UNESCO or IAEA were invited to participate. The topics addressed included: structural and mechanical properties of oxide interfaces, classical potentials for oxide systems, DFT for oxides, the “Learn On The Fly” method, multiscale methods, spectroscopical methods, chemical methods, crack propagation experiments, technological applications of oxide interfaces (see appendix for complete programme). The purpose of the workshop was to impart an understanding of the properties of oxide interfaces since it has widespread implications in materials science, engineering, electronics, and physics. Ceramic coatings used in modern structural glasses, oxide films used in smart fuel cells or in the basic components of advanced biomedical devices used in orthopaedics and dentistry, all rely on the optimal performance of oxide interfaces in aggressive chemical environments. The mechanical and electronic properties of oxide interfaces are tightly connected to their atomistic structure, which is in turn the result of a complex interplay between the properties of the different phases involved (e.g., crystalline or glassy) and the chemical nature of the bonding between the relevant ionic species across the interface. Atomistic modelling plays a fundamental role in this area. It complements experimental efforts by providing an atomistic interpretation of the results. Moreover, modelling can be used as a guide in the design of new materials with enhanced properties, desirable for practical applications. The atomistic modelling of oxide interfaces requires chemical accuracy and at the same time must be able to treat large systems, up to several thousand atoms. It is thus an ideal playground for the development of atomistic methods capable of bridging length and time scales with *ab initio* accuracy, as done in particular within the ADGLASS Consortium. Altogether, 67 participants attended to the workshop.

b. We have organised a **Science-Industry Workshop** with the specific purpose of bringing together European research institutions and private companies. A further aim was the thematic cross-linking of disciplines (spanning from measurement devices to software production). The workshop, entitled "Atomistic Modelling for Industrial Product Development", has successfully taken place from November 14th to 16th 2012. It has been organized by Lucio Colombi Ciacchi and Dorothea Stübing (Fraunhofer IFAM) and Gianpietro Moras (Fraunhofer IWM). The venue was the Swiss Hotel Bremen, Germany. Representatives of renowned German and European companies, scientists and students from European countries and members of the United Nations, UNESCO or IAEA were invited to participate. The topics addressed included: lifetime and fracture, methods and principles, materials processing as well as surfaces and interfaces. Altogether, 56 participants attended to the workshop.

c. We have organized a training activity on the application of atomistic modelling techniques for the knowledge-based design of novel materials. The “**ADGLASS Winter School on Advanced Molecular Dynamics Simulations**” has been held from February 18th-21st 2013 and was hosted by the ICTP in Trieste, Italy. Since the training included extensive practical application of the

atomistic models developed within ADGLASS, computer access was indispensable for the participants. This was readily available at the ICTP; up to 50 computer work places could be provided. Altogether, 43 participants attended to the school, together with the two organizers and the 11 lecturers. In the focus of the school were advanced Molecular Dynamics (MD) techniques, as in large part developed within the Consortium during the course of our project. More specifically, the first two days were devoted to combined quantum/classical (QM/MM) techniques. The training session comprised simulations of brittle fracture in silicon and silicon oxide by means of LOTF techniques, as implemented in the computer code developed in WP1 and tested in WP3. The second two days were devoted to the calculation of free energies in MD simulations. In particular, the free energy of adsorption of small organic molecules (amino acids) at solid/liquid interfaces has been calculated in the training sessions, which were almost totally based on the novel knowledge developed in WP1, WP2, and WP4.

The ADGLASS Consortium has been advertised in the initial stage of the project via a printed flyer (available for download at http://www.adglass.eu/docs/Adglass_Flyer.pdf). A Webpage has been created and constantly updated, in particular including a full list of publications and the main events concerning the Consortium's work (http://www.adglass.eu/).

4.1.5 Project website:

http://www.adglass.eu/