CECAM Workshop Scientific Report

Workshop: **Tackling Complexity of the Nano/Bio Interface - Computational and Experimental Approaches**

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I. Summary

The workshop "**Tackling Complexity of the Nano/Bio Interface - Computational and Experimental Approaches**" was held at the University of Bremen, Germany from June 12th to 16th 2017. In total, 72 participants from Belgium, Brazil, Finland, Ireland, Luxemburg, The Netherlands, Portugal, Slovenia, Spain, Sweden, Switzerland, Russia, France, Germany, UK and US attended the workshop.

The programme consisted of 28 invited lectures, one poster session presenting 27 posters and many events (reception / conference dinner) to allow for informal exchange. The lectures were scheduled to last 40 min, including 5-10 min discussion time. In addition to this extended time for discussion, the chairpersons were instructed to introduce the subject of the session and to actively participate in the discussion. This "Gordon-conference-style" was essential to guarantee a vivid discussion. The organizers ensured that well-established scientists acted as invited speakers and chairpersons.

Concerning the poster session, we accepted only 27 posters to allow for an intense exchange of ideas at each single poster. Here, we encouraged in particular the young scientists to ask questions. The participation of PhD students was supported by partly covering local accommodation costs.

Due to the compact organization and accommodation in one hotel only all participants had to stay together for the whole time of the conference, which additionally enforced the scientific discussion which was mandatory since scientists from various separated fields, i.e. advanced quantum chemistry, many-body perturbation theory, DFT and QM/MM-techniques, nanoparticle synthesis, environmental and health risk management, nanomedicine, etc. attended the meeting to merge ideas and formulate a common goal for future directions and collaborations of theory groups with experimental groups.

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II. *Scientific content, main outcome of key presentations, selected discussions*

Various sessions were related to the topics (a) nano-bio interfaces and interactions (b) nanoparticle synthesis, (c) nanoparticle-membrane interaction (d) computational analysis of solid/liquid interfaces, (e) multi-scale computational methods, and (f) experimantal characterization of interface properties. These topics are interrelated leading to stimulating discussions between researchers from different fields.

On the technological side, nanotechnology has already led to numerous applications in the areas of batteries, electronics, water desalination, drug/gene delivery, and diagnostics and energy production. Considering these trends, there is little doubt that the impact of nanotechnology will only increase in the future.

Given the tremendous impact of nanotechnology, it is also important to consider the sustainability of nanotechnologies, particularly the potential for nanomaterials to elicit detrimental biological outcomes. The small size and often reactive nature of nanomaterials raise concern about their potential environmental, health and safety (EHS) impacts. This has been realized, for example, from the very beginning of the National Nano Initiative in the US, which encouraged programs that systematically analyze EHS issues of nanotechnology. However, the interactions between nanomaterials and biological systems are complex and involve physical, chemical and biological processes that span broad length and spatial scales. These facets were presented and discussed during the workshop. To properly address the EHS issues of nanotechnology, it is essential to understand the mechanistic details of nanomaterials/biological system interactions; i.e., it is essential to establish causality, rather than correlations, in how nanomaterials impact biological outcomes. Only with this level of understanding can we design the next generation of nanomaterials that are functional yet with minimal deleterious EHS impacts.

The workshop was kicked off with two broad overview talks by the directors of two national centers supported by the US National Science Foundation, A. E. Nel from the UCLA Center of Predictive Nanotoxicology and R. J. Hamers from the UW-Madison Center for Sustainable Nanotechnology. The two talks highlighted complementary strategies to tackle EHS concerns of nanomaterials. The UCLA led center focused on mechanism-based *in vitro* assays and *in silico* predictive tools for expedited screening of the hazard potential of broad classes of chemical substances and engineered nanomaterials. The CSN effort led by UW-Madison focused on understanding the molecular transformations of nanomaterials (e.g., metal oxides used for energy storage) under simulated environmental conditions, as well as understanding the potential for these materials to induce toxicity in single-celled and multi-cellular organisms. Nanomaterials can also be introduced into cells in a site-selective manner to enable their participation in desired cell metabolic functions, forming a basis for new tools for biomedicine and biotechnology. Striking examples were given by T. Rajh from the Argonne National lab where photoinduced charge separation in TiO_2 was employed to create reactive oxygen species and induce apoptosis in tumor cells.

Synthesis and characterization of nanomaterials for specific properties are essential to both application and mechanistic analyses. Cathy Murphy from UIUC described the synthesis and surface chemistry of gold nanoparticles, and a series of biophysical measurements that quantify the composition and even orientation of biomolecules on the nanoparticle surface; the talk also highlighted opportunities for theory and computations for better understanding several key mechanistic issues concerning the biological exposure to these nanomaterials. Since nanoparticles potentially can perturb cellular redox processes, which in turn may lead to the formation of damaging reactive oxygen species, characterizing the “flat band potential” is essential to describe the electrochemical behaviour of nanoparticles in aqueous biological environments. Lutz Madler described a novel approach based on porous electrode and electrochemical impedance spectroscopy.

Since lipid membranes form a natural barrier between cells and the environment, understanding the interactions between nanomaterials and lipid membranes represents a major topic of the workshop and was covered by two sessions. The studies involved diverse experimental analyses of model membrane systems of increasing complexity (J. Pedersen of UW-Madison), polymeric materials (W. H. Briscoe from Bristol) and interaction of high aspect ratio materials with cells (R. Hurt from Brown). The observations and analyses highlighted the complexity of such interactions and the roles of membrane phase behaviors and mechanical properties. To help tease out physical factors that dictate nanoparticle/membrane interactions, computational studies are highly valuable, as demonstrated by several talks. Electrostatic interactions between charged ligands of nanoparticles and lipids were shown to be important by both atomistic (I. Vattulainen from Helsinki) and coarse-grained (G. Rossi of Genoa) molecular dynamics simulations. More subtle effects were also seen on the lipid phase behavior (L. Monticelli from Lyon and Z. Cournia from Academy of Athens): for example, polypropylene disfavors lipid phase separation, polystyrene stabilizes it, and polyethylene modifies the topology of the phase boundaries and causes cholesterol depletion from the liquid ordered phase. Therefore, different hydrophobic ligands also have major effects on the properties of lipid membranes, which in turn modulate the assembly behavior of nanoparticles on membrane (shown by both Z. Cournia and F. Stellacci) calling for further investigations on model systems and cell membranes. These studies may also shed lights on other problems that implicate assembly of materials, such as biominerialization, as discussed by L. Ciacchi from Bremen.

The complexity of the nano-bio interface calls for the development of novel computational methodologies across different scales. These start with electronic structure methods at the DFT level, which have been well established for molecules but involve significant complications when applied to reactions at solid/liquid interfaces, as discussed by J. Bennett (U. Iowa), A. Gross (Ulm) and M. Sprik (Cambridge) using different examples of metal oxides and surface reactions. To expand the length and time scales of computations of solid/liquid interface, robust hybrid QM/MM models and classical force fields need to be developed, as discussed by Q. Cui (UW-Madison), H. Heinz (U. Corolada) and U. Kleinekathoefer (Jaobs). To further enhance the scale accessible to computations, coarse-grained models that faithfully describe not only structural and energetics properties but also dynamic characteristics are required; initial efforts along this line have been discussed by R. Hernandez (Johns Hopkins). Given the importance of electrostatic interactions to nano-bio interfaces, methods that are able to predict charge of functionalized nanoparticles are required; different strategies were presented by Q. Cui and G. Groenhof (Jyväskylä), and methods for describing other relevant properties such as hydrogen-bonding network of complex proteins (A. Bondar) and charge transport (T. Kubar) were also discussed. Finally, to ensure reproducibility and to minimize technical errors of simulations for complex systems, W. Im discussed recent advances in the popular Web-based tool CHARMM-GUI, which was initially developed for biomolecular simulations but recently extended to treat complex materials and nano-bio interfaces. Ultimately, it is essential to integrate these computational advances with experimental studies to tackle the mechanism of processes at the nano-bio interface; such integration was already demonstrated in several presentations, such as the analysis of metal oxide dissolution (R.J. Hamers and J. Bennet) and peptide/silica interactions (C. C. Perry and H. Heinz).

III. Assessment of the results and impact on future direction of the field

The foremost objective of the proposed workshop was to bring together leading and active researchers who work on nano-bio interactions in both experiment and theory and to discuss about the environmental implications and risks of nanotechnology. Aiming for a focused meeting with 70-80 participants we have stimulated exchange, awareness of challenges, approaches and achievements in the respective fields. Moreover, we emphasize to strengthen the links between experimental and computational groups in this fast-developing field and to interconnect current multi-scale classical and first-principles descriptions.

The workshop became a forum to discuss the particular potential of nanomaterials, to learn about nano-bio interactions and to control the environmental implications of nanotechnology. We have been able to achieve the following key objectives:

1. On the experimental side, we have invited leading researchers in the area of nanoparticle synthesis and characterization, including those who develop and apply cutting-edge non-linear spectroscopies (e.g., sum frequency and second harmonic scattering) and imaging techniques (e.g., super resolution fluorescence imaging) that provide molecular level information at complex soli-liquid interfaces. Other invite speakers reported about the impact of nanoparticles on both model (e.g., supported lipid bilayers) and actual biological systems. Although the primary focus of the workshop was to understand mechanisms at a molecular level, the program included a number of researchers who characterize the impact of nanoparticles at the whole organism levels (e.g., gene transcription, protein expression, small molecule secretion) to help put the molecular level investigations into proper context.
2. On the theory/computation side, we have invited researchers who develop techniques that bridge scales from electronic through atomistic to coarse-grained levels. Although many techniques at these three scales have been well developed, how to integrate information at these scales in a robust and smooth fashion is not trivial, and has been discussed widely. Most importantly, we have encouraged discussions between experimentalists and theorists to identify the pressing challenges and opportunities for better understanding processes at the nano/bio interface. We hope we could stimulate new collaborations between two or more research groups that will help answer key mechanistic questions that will impact the design of the next generation of nanomaterials. In the organization of our workshop, we have tried to balance researchers at different stages of their career and from different geographic regions (Europe, the US and Asia).

IV. Infrastructure requirements to make advances in the field

As discussed above, the advancement of theories and computational techniques to describe and understand nano-bio interfaces requires the development of novel theories and codes which can i) capture the inherent complexity of realistic interfaces and ii) contain sufficiently accurate description of physico-chemical processes involved with the environment, including photon-electron interactions, electron-hole coupling, electron-phonon coupling, etc. The development of such theories and the resulting computer software will benefit the broad community of theoretical researchers, but also have important impacts on experimental studies and industry. However, to achieve this, a continued investment is required, as method and code development usually occur on a longer time scale compared to the study of applications. This also requires the training of masters and PhD students not only in physics, materials science or biology, but also in computer programming (including parallelization of software) and use of high-performance computing resources.

V. *Impact to address the need of industry in driving economic growth*

Progress in the field of nano-bio interactions and interfaces, is fundamental to many European nanotechnology industries connected to high-tech materials design and device applications. Examples are

- Nanomaterials for energy conversion and environmental waste management
- Photo-catalytic processes in energy storage and pollutant degradation
- Hybrid nano/bio-systems for medical applications
- Nanomedicine and cancer treatment using nanomaterials

Such directions can be strengthened by focused research projects for the development of new materials and devices in key enabling technologies. The field of nanodevices is currently opening to new materials, especially metaloxide nanoparticles and 2D nanomaterials. The EU flagship on graphene and 2D materials is indeed expected with the aid of computational predictions to produce several new outcomes. However, technological innovation is not limited to these materials.

July 12th 2017

The Organizers