COMPUTATIONAL MODELING From Chemistry to Materials to Biology

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SESSION 3: MODELS AND EXPERIMENTAL DATA ON WATER DYNAMIC COMPLEXITY OF SOLID/LIQUID INTERFACES

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Discussion among the panel members

Joanna Aizenberg: Well, let us first discuss among ourselves to see whether there is anything that we can learn in addition to discussions that we already had in the presentations; and in some way I honestly want to say that my own take on many projects that I do is trying really hard, in pretty much every case, to develop analytical models. And with that I want to address the first question to David Quéré. If we talk about analytical models, regarding the phenomenon that you described. How much of that can be actually done?

David Quéré: Thank you for asking this question which somehow corrects a little bit my presentation, which I chose to be extremely qualitative, based on images and movies. So you might have the feeling that all of that was just a description of things, which in many cases is enough actually. We are very happy to see phenomena and to try to understand them qualitatively, but of course we need also to develop models. I could have a general answer and a particular one here. The general answer is that in soft matter at large — and I am very flattered to be among you because I am more physicist —, in the physics of soft matter where we have to face complexity, we like very much to use scaling laws. Which is a very powerful tool for describing things in a quantitative way. This is something which allows us to face questions that we could not solve really analytically, or at least it is a first step. In all what I showed, there is a way to solve things by scaling laws. So, they are laws, they are models, which are describing all these facts. Modelling could be also using computers, which personally I do not, but we had many evidences in this conference that this is a fabulous approach, in particular when you go to the limit of microscopic systems. Because we tend to reach smaller and smaller scales when for instance I discussed textures and solids. And the question of reducing the size was obviously something very interesting because it produces new facts. Here, of course we converge with computing because the size of the systems that we are

dealing with is such that molecular dynamics, for instance, provides quantitative answers which very nicely complement what we can do. So, modelling we love it and we need it!

Julia Yeomans: I think we can go a long way with the continuum models, they really seem to work very well down to length scales, maybe even to ten nanometers, maybe a bit less. And we know what the equations are, and so the hard thing is that sometimes they are a bit tricky to solve in a complicated geometry but I think at that level the equations are right. It is an interesting question just where you need to cross over to molecular dynamics.

Mischa Bonn: I completely agree and I think continuum models are extremely powerful and, if we talk about water at interfaces for instance, there are many very straightforward intuitive physically extensions of the Poisson-Boltzmann theory to describe water interfaces, to account for molecular level effects and to take those into account in a more or less phenomenological way. On the other hand, I think it also depends which approach you use, it depends on the question you want to answer. Because if you want to talk about energetics of interactions, as Angelos pointed out, continuum models simply don't give you anything that resembles an answer. So you will need to go to molecular level descriptions.

Eugene Shakhnovich: I am a big fan of continuum models as well. On that, aside, besides dynamics, there is of course thermodynamics. There are a lot of things that we can learn from usual continuum model thermodynamics studying chemical potentials or water effects on solutes, and all of that. It works to a great extent and even for smaller systems. But there are of course cases when this kind of molecular nature of water becomes very important. One aspect of that is related again to biological systems where water plays a structural role. There, continuum models naturally break down and we have to consider explicit energetics. Because in term of just energetics even on the interfaces in some cases you can use simple thermodynamical analyses to estimate or to get these numbers, these parameters from continuum models. We do not always need energetics on the interfaces which are microscopic, molecularly resolved. There are cases when water is molecularly resolved by Nature, in a sense, by its structure. In this case of course we have to treat water obviously as a kind of a single molecule rather than a continuum.

Joanna Aizenberg: I want to continue on that and I was trying to present this as a multi-scale problem when there are solutions and ways we can address a phenomenon on one scale but not on the other. Some macroscopic functions depend on molecular structure and potentials and others do not. So, if we think about challenges associated with scales, what are the best practices of multiscale or reduced order models. Do you want to answer?

Sinan Keten: I think there are usually benefits of continuum models — I'm trained as a mechanician —, so from our perspective you always start with the simpler analytical model that gives you some physical intuition into the problem. But oftentimes you realize the exceptions that come from heterogeneities, chemical features that the small scales are difficult to explain with the simple models. The exceptions are often the most interesting things you see. From things like transport problems *etc.* Then, the question becomes, as you incorporate these details from the molecular scale to higher scale models, how do you pass the information across the scales? In the context of molecular dynamics, we have atomistic models, we have *ab-initio* models, we have coarse-grain models, which are even one scale above. We have many challenges on how to describe the dynamics at these different scales. In the case of transport: how do I coarse-grain, for instance, a membrane? How do I capture the dynamic features that I think are important in those types of systems? This is a big challenge and I think one has to think about ways to enrich in a systematic way to capture the chemical details. There is a lot of work on systematic coarse-grain techniques like that but few have been really applied to things like transport and there is a lot to be done in that field I think.

Joanna Aizenberg: I am an experimentalist most of the time, so if I will be provocative then can you tell me: in addition to a general description of water in particular in this case, are simulations useful? If so, which ones? And if they are useful, how do you link results of your simulations to the scale of experiments? Is there a crossover of scales? Just convince me as an experimentalist that you can do something that I can then take and expend on that experimentally.

Angelos Michaelides: I think that these systems are very challenging, we have heard that a lot already, and you need a very well-defined molecular level understanding to describe a lot of macroscopic phenomena. Mischa showed a nice example on silica, of how specific functional groups can alter the macroscopic properties. We have worked on it. Another example is the wetting of a copper substrate, where the experimentalists saw that under specific conditions the substrate wetted, it was hydrophilic, but they could not understand why. It came down to us doing simulations at the molecular level, understanding that continuum models broke down, in this case, because the water is dissociated and there were specific hydroxyl groups that were acting as nucleation sites. It was only through getting this well-defined information at the molecular scale that we could describe the larger scale macroscopic phenomena. I think the value of theory and simulations, in this area, is providing insights and understanding that can help and interpret the larger scale experimental data.

Julia Yeomans: I think that you need both because simulations can give ideas and then you do the experiments and find out what is wrong with the simulations. In my view, trying to do simulations which look exactly like experiments is a bit

pointless because you can do the experiments. But doing simulations which help to understand the basic ideas is often helpful to suggest new experiments.

Joanna Aizenberg: I cannot agree more because honestly the way I try to address many of my questions is first to see whether the simulations can repeat my results but this is not that interesting. But then actually to find interesting features that we have never observed experimentally and be guided by these simulations and knowledge that can be drawn from theory. Can you give me a couple of examples where things that you have done with simulation of water was actually helpful in highlighting new behaviour and then shown experimentally?

Julia Yeomans: An example from the droplet work is that we looked at drops bouncing on a surface which was a superhydrophobic surface but with large holes and these drops spread out like a pancake and then jumped without retracting. It took us ages to work out why. It turns out it was very simple. The thing acts like a trampoline because the water goes in into the holes and back out again. The only reason we have got it in the end (maybe if we had been clever we would have figured it out sooner) was to do the simulations to see what was happening. The simulations did not really match the experiments but the physics behind it matched and then we could do the theory right.

Angelos Michaelides: There was a movie that I was tempted to show but I did not have enough time. There have been nice experiments with STM looking at the diffusion of water clusters across surfaces. Interestingly, when the rates of water monomers diffusion were compared to rates of water dimer diffusion, the STM experiments showed the dimers moved more rapidly than monomers. This was an interesting observation and given the relative mass it was unexpected. We did a lot of simulations to try and understand this effect and we realized that the key to this was the fact the hydrogen bond in the water dimer was exchanging, and it was exchanging through the tunnelling process. We could then predict that if you go off and do the measurements with deuterated water, you would not see more rapid diffusion. Also, we went further and we screened a wide variety of substrates and we made predictions: this substrate tunnelling is possible and we would get fast diffusion or on this other substrate tunnelling is not possible and we will not get fast diffusion. Those predictions were followed up with experiments and verified.

Mischa Bonn: I think there are two useful interplays of simulations and experiments. One is where the simulations explain the experiments. An example that I showed you is that water interacting with the soft charge interfaces behaves differently than water interacting with hard charge interfaces, like mineral charge interfaces. This is simply because you need a molecular understanding of the deformation that can occur at high charge densities for the soft interfaces which is not possible for the hard interfaces. I have also had similar experience to Angelos, where in fact the

simulations were predictive. Theory collaborators came to me and said "you know I have been looking at the water/air interface for a long time and if you partially deuterate your water — so you look at mixtures of H_2O and D_2O and HDO —, my quantum simulation predicts that you will have preferentially OH groups sticking out the surface into the gas phase. It is going to be a non-statistical distribution of free OH groups or dangling OH groups" and I have "this is the quantum nuclear effect for sure. We are never going be able to see that." He did the calculations, quantified it and we could see it. It was actually quite significant. For me, it was a very nice example of where simulations predicted an effect that I would have never tried to do the experiments, ever. I would never have believed it is possible. But it worked.

Eugene Shakhnovich: Another example where simulations were quite important was like about six or seven years ago, we were trying to design an inhibitor believed to be implicated in Alzheimer's disease. No luck, nothing worked but then at some point one of the post-docs did simulations very carefully (all-atoms simulations with explicit water), and he predicted that there is one structural water which was not seen crystallographically which slightly changed the conformation of the loop and the close form by, I would say, 1.5 Å probably. And then the design was done against this predicted conformation and this design worked. And then later on there was a high-resolution structure which showed the structural water in the structure. Basically sometimes of course it is a super high-resolution approach that continuum methods cannot reproduce by definition, but this is an example where atomistic water in structural simulation played a really important role.

Joanna Aizenberg: One or two minutes left and I do want to ask another question that nobody touched. I like crystallization, as you probably understood from my presentation. A subject that nobody talked about, not only water at interfaces, about minerals. If you deposit minerals, a majority of things is driven by hydrated ions and their ability to release the hydrated shell. What is done in term of simulations of how hydrated ions, when incorporated into crystalline phases, release their hydrated shell and how this controls crystallographic features and types of minerals that can form. A particularly interesting system is of course carbonates, and carbonates are of interest to Solvay all together. Nobody has ever looked at that.

Angelos Michaelides: We have been interested in understanding the wetting properties of clays. In collaboration with Rahul Nair's group in Manchester, contact angles of water droplets on clay substrates have been measured. They were able to show that the contact angle was a function of the counter-ion that was present in the clay. So, we went about trying to understand what was going on. We could relate the hydration of the counter-ions, comparing different counter-ions to correlate what was observed with the experimental observation.

Joanna Aizenberg: I want to finish this — coffee is waiting — by challenging you, by looking at hydration of ions, somehow it is not done enough and there is a lot of interesting things especially in biological systems, thinking about magnesium with an hydrated shell, calcium with a shell and what is happening due to the fact that water is so tightly bound to some ions but not to others and how that affects the interactions and the ability to control all ranges of phenomena. We know this experimentally but there is a lack of theoretical and simulation data on this subject. And with that, I would like to finish our discussion, have a little bit of coffee, and try to take difficult questions from the rest of the audience.

General discussion

Joanna Aizenberg: This session is open for questions.

Bernd Hartke to Angelos Michaelides: Concerning the nuclear quantum effects in water, would you expect that it is possible to incorporate that into a coarse-grain model that does not do the nuclear quantum motion explicitly? Like, for example, in force fields, I would say force fields coarse-grain the electrons away and this gives you a five-order of magnitude in performance enhancement. Would you expect it to be possible to incorporate nuclear quantum effects into an empirical water model so that you do not have to treat them explicitly?

Angelos Michaelides: In many empirical water models, if they are trained against experiments, then they are implicitly accounting for nuclear quantum effects. If we want to include them explicitly in empirical potentials, then the most widely used approach is path integral techniques. Traditionally, path integrals have been very expensive but there has been a lot of work using clever thermostats that actually make the cost of a full path integral simulation only one or two times more expensive than a traditional classical molecular dynamic simulation. So, those are my answers. They are implicitly included if we are fitting to experiment and if we want to account for them explicitly they were very expensive, but this is not as expensive as it was.

Bernd Hartke: The obvious follow-up question is, is there any need to ever?

Angelos Michaelides: It depends on what you are interested in. There has been a big debate about the properties of liquid water and how nuclear quantum effects alter their radial distribution function, density, diffusion coefficient. It is all on the level of a few percents. That does not necessarily excite me. Also the lattice constants of ice do not change very much. But where nuclear quantum effects are very important and need to be accounted for is if the water is dissociating and we have free protons. That can happen in the bulk, and that can happen at the interface. There, nuclear quantum effects can have a very significant impact and need to be accounted for.

Alán Aspuru-Guzik: I actually have a paper on that topic that I think is relevant. We developed a theoretical force field factor theory which is the equivalent to density functional theory for force fields. It shows the following: there is always a unique classical potential that reproduces the quantum distribution at a fixed temperature and pressure. This basically means that, for each point in the phase diagram, you can have a classical potential that would reproduce the quantum distribution with classical dynamics. This is my opinion how you can do a force field that includes the quantum effects. The theorem is there. We have shown basic examples for van der Waals type potentials but this can be extended to a full water potential. There is theory for that and it is called force field factor theory.

Joanna Aizenberg to Alán Aspuru-Guzik: But the temperatures and pressures that you are developing with, are they relevant to actually reasonable conditions?

Alán Aspuru-Guzik: The way to do it is simple: to develop the force fields you would do a path integral simulation at a particular temperature and pressure. Again, the theorem shows that the force field is not transferable to other temperatures formally. But once you have run the simulation, you can find that force field and the theorem says it would be exact for that particular path integral distribution.

Bert Weckhuysen to Mischa Bonn: I enjoyed very much your talk and I have a first question on your silica and your water. Did you ever have considered to do an experiment where you do silica with ^{18}O and the water with ^{16}O, or the other way around, to try to distinguish, with your method, what is happening so you can really distinguish what you showed in one of your first slides?

Mischa Bonn: That is a very good question. Indeed, one cannot do the isotopic exchange for the deuterium or the hydrogen because that exchanges too rapidly (the surface hydroxyls with the water) to distinguish that. Those two make it impossible. But indeed, that is a very good idea and it is an idea that we implemented after thinking much longer than you thought about it. We did the experiment for $H_2^{18}O$ to show indeed that there is an isotopic shift in the OH that can be assigned to the water and not to the silica.

Bert Weckhuysen: My second question is about silica. Silica is used a lot as a catalyst support and one silica is not the other. You can make silicas in different ways, and I assume your zero point of charge is around two. Do you have ever considered to put heteroatoms in it like aluminium and then try to increase or vary that? And then, what is the effect on it?

Mischa Bonn: That is also an excellent question. Indeed, depending on the source of silica, the silica surface will have different types of surface hydroxyls each with different pKa's. Indeed, the point of zero charge will vary depending on the source

of the silica and the way it is made and the way it is purified. We have seen sort of batch to batch variations in the quantitative details. The qualitative trend is always the same. We have not thought about using that chemistry to tune the surface properties to a desired goal but that is a very nice idea.

Joanna Aizenberg: I want to add to this comment and maybe suggest that, in addition to silica with other oxides attached to it, you may try to look at the biological form of silica where different species would have a very nice range of hydroxyls on the surface. All these silicas would have different levels of hydration, not all the OH bonds are actually fully condensed in these systems. You will have a really broad range of surfaces that Nature created from glass surfaces, where OH distributions are quite well described by now. Just to see how that may affect the interaction with water as a function of dangling OH bonds.

Bert Weckhuysen: My last question is about silica. In the introductory comment, it was already mentioned about electrocatalysis. It is very important to know that in electrocatalysis what is really happening at the interface and what is happening with the charges. I was wondering if you can device this as an operando system, where you could look at this first real monolayer under these conditions. What would then happen? Do you believe that your method could establish that?

Mischa Bonn: Yes, that is also again a very good idea that we are working on. The challenge is to actually have the optical beams reach the interface. The infrared beam, when it goes through water, is absorbed over a very short length scale, microns roughly. The trick that we are now developing, and we have some initial work that has just been published, is to use graphene as an electrode. It is optically thin and allows us to access the interface. So, great idea.

Wilhelm Huck: I was wondering, the rearrangement of you interface near lipid bilayers, what do you think the impact is of that on the adhesion of proteins to lipid bilayers?

Mischa Bonn: That is an excellent question. Thank you. Honestly, I don't know. I would certainly expect that there must be an effect because this reorganisation occurs at physiological charge densities. I expect that the effect would depend very much on a protein to protein basis. I think it is very difficult to predict *a priori* if there is a general rule but I honestly do not know. That is a very good question.

Joanna Aizenberg: Just to comment a little bit from the experimental side of things. There is a duality in this effect: when proteins are attaching to biologically-formed silica, you see reorganisation in both. The structure of a protein is affected by the structure of silica to which it attaches. Then, you see changes in both, these proteins affecting hydration of the silica. But then silica changes periodicity, or

distances between its charges in correspondence with those in the protein. There is a really interesting dynamical reorganisation when proteins interact with silica, at least in Nature.

Eva Nogales to Julia Yeomans: Could you tell us more about your modelling of these nematic systems applied to the biology? I do not remember your particular example. Was it the microtubules motors or the epithelial layer? Assuming that you are not entering the molecular details of how these things are moving one with respect to the other into your models, what goes into them so that you are able to ultimately represent that kind of motion?

Julia Yeomans: I am talking as a physicist here so I am looking at the generic properties of these active systems. The sort of model I am writing down should apply to all the systems but of course condense all the questions about them. It is like using the Navier-Stokes equation, it works for all fluids (or simple fluids) but it does not tell you about the molecular things that we have been talking about. So, what goes in, is symmetry of the system, as a continuum model. We are doing more coarse-grained models where we are putting more details. We are sort of starting from the large end and other people have done models starting from the small end.

Eva Nogales: The second part of my question. This has to do with the case of the epithelial layer. I found it very interesting that you said that defects correspond with apoptotic cells but you put them as the defects that generate tension, which then make the cells go into apoptosis. But I would have changed the cause and the effect. Because apoptotic cells round up and they lose contact, that would be more what would coincide with that moving defect, rather than what comes first, in a way. I don't know what you think.

Julia Yeomans: Yes, that is what I thought to start with, but what I have said is based on experiments, experiments done in Benoît Ladoux's group where they actually looked at the chemistry behind it. The experiments showed that — they are bio-experiments so there are lots of error bars —, but the experiments showed that what happen is: stress moves YAP (Yes-associated protein), and YAP signals cell death. The stress on the cell moves the YAP from the nucleus to the cytoplasm. This is a known signal for cell death.

Kurt Wüthrich: I think this is a follow-up to Eva's question. Do I understand correctly that all the processes we have been dealing with in this session are stochastic? And what are the frequency ranges covered? I am sure that surface hydration is a stochastic process. I am not so sure whether this is true for turbulence-like motions that you described or for the topological defects.

Julia Yeomans: I think this is a lengthscale story again. So, I think anything molecular is going to be a stochastic process because of fluctuations. The sort of scale

I was looking at is less so because we are looking at larger things and therefore fluctuations are less important. So, the topological defects, no.

Kurt Wüthrich: What are the frequencies?

Julia Yeomans: I can tell you about the velocities but I do not understand frequency in this context. These things are moving at microns per minute.

Todd Martinez to Angelos Michaelides: There was this question that came up about whether or not theory had predicted anything. Before that Angelos showed us the attraction curve for water to graphene with a bunch of different density functionals and showed that they got different results. Clearly whenever you predict anything you have to validate it first. First you have to figure out what density functional should you use, which one is right. What I would like to ask is an open question: how do you know, when you do predict something, whether you have actually already baked the answer in for the validation process? In other words, how do you assess how difficult a particular prediction was, after the facts?

Angelos Michaelides: This is a very difficult and very important question. I think, in the case of density functional theory, as you would know, as many people would know, there are sort of two strategies to developing new functionals. One is about trying to satisfy constraints and the other is about fitting to large data sets, either from experiments of from higher-levels theories. If you take the latter route, then you will implicitly be including some physical effects that you are probably subsequently trying to capture. The route that we have been taking to get more well defined, more reliable *ab-initio* data is not through density functional theory. In these particular systems, the one slide I skipped quickly through was quantum Monte-Carlo. So, I think that quantum Monte-Carlo is a much more promising approach for the types of problems we are interested in, where we have weak interactions when we are talking about wetting on substrates. There are no empirical parameters in that and there is no real scope for including empiricism in that approach. So, that is what I think is a more useful *ab-initio* way for it. Like I have said, in DFT, there is a level of empiricism that is hard to avoid.

Laura Gagliardi to Angelos Michaelides: We have discussed about maybe DFT or quantum Monte-Carlo and then force fields and Alán suggested a high way of doing more advanced force fields. Probably what has not been discussed extensively are *ab-initio* molecular dynamics methods and Car-Parrinello techniques. I would like to have your opinion and also discussion about where do you think these methods are going? Are they useful for these kinds of approaches? Or the time-scale of the simulations is too short? Or the fact that the quantum in DFT is still too much of a simplification?

Angelos Michaelides: There is certainly a big role for *ab-initio* molecular dynamics (MD). We have used it a lot. In particular, where bonds are being made and bonds are being broken. For a lot of these wet surfaces, you have a mixture of intact molecular state and a dissociated water state. If the barrier between these states is close to zero, then you could sample this with any equilibrium *ab-initio* MD simulation. There are lots of scenarios where you might want to look at a chemical reaction. We looked at, for example, the dissolution of salt crystals. We did it with *ab-initio* MD but we enhanced the dynamics with meta-dynamics. Thinking longer into the future, it could be that machine learning comes along and squeezes out *ab-initio* MD from existence. That is a completely foreseeable future. We are working on disposable machine learning potentials where you run an *ab-initio* MD trajectory and you then train a potential based on that trajectory. It does not enable you to go outside the parameter space in which you have trained but to run a longer trajectory and a bigger system.

Sinan Keten: I think it entirely depends on the problem you look at, and in the particular case of reactions certainly there are benefits of a more quantum level, a higher-level treatment. In the case of pressure-driven flow, it might be relevant when you are looking at things like proton transfer *etc.* but I think for the transport of water molecules through a membrane we can get away perhaps with classical treatments. I think the impact on the time-scaling that you have might introduce other errors such as having to run much larger pressures or having to run much smaller size systems. I suspect in those cases the advantages you get from chemical accuracy would be counterbalanced with the errors you introduce from trying to scale the problem to smaller scales and then trying to extrapolate to actual experiments.

Veronique Van Speybroeck: I have a question regarding also the confinement in nanoporous materials for water. We have done now quite some water simulations on various types of nanoporous materials. It was discussed that of course they can interact with an OH group, so that is interesting. But how about hydrophobic materials, where we do not have it and where they actually, sort of, "rip out of the wall" and how do they organize? We also have seen that they then start to make ice-like structures sometimes. It depends also on the confinement and the typical topology of your material. In extension to that, if you, for example, go to metal organic framework materials, there you have the mixture of hydrophobic and hydrophilic sites. What is your opinion about the structural organization of water in these types of materials? How should we tackle it? Maybe both from experimental and theoretical points of view? To get more insight in that, because I have the feeling that it is not completely well understood in my opinion. But I might be wrong.

Sinan Keten: I think it is a really great question. Polarity is not necessarily a necessity for order in confined systems. People have studied carbon nanotubes and

you do get all the structures and all kind of complexity, I am sure everyone is aware. The challenge also there is that you change the dimensions of your pore a little bit and then the structure changes and you get complexities that come with that. I think that is a really rich question. There are other aspects that come from not just polarity but even how you restrain a pore. Whether it is dynamics or restrains, or if it is a stiffer system, and that changes again the fluctuations of water with changes of structure, I do not have a good answer for all the things, but I think it is a very worthwhile direction of investigation.

Veronique Van Speybroeck: My question is basically because I also think it is a very broad and open question. So, how should we tackle it also to obtain structural information in these materials and so on? It would be also interesting to know how, also from an experimental point of view, we can learn from that from a theoretical point of view, how we can simulate that? Maybe we can look at symmetry functions also to see what kind of structures are formed. And then, compare to more water-like structures that we know in other environments. Maybe we have to do it somewhat like that — we have some ideas. But then the question also, how do we compare to experimental insights? So, for me, I do not know, is there any suggestion on how to proceed there? It will be very useful.

Mischa Bonn: I am a molecular spectroscopist. I think that the answer to your question is to do molecular spectroscopy. This is of course not completely straightforward because it means that we have to translate the structures that we obtained from simulations, be they MD or DFT or even higher-level, to somehow translate them to get the molecular response function that we measure in the spectroscopy from those structures. In my experience, that works remarkably well. This allows to translate structures into spectroscopic observables, it allows a direct connection to experiment in precisely the type of systems that you mentioned where you really do not know much and we do not know what is good theory. It is also difficult to do good experiments, of course.

Miquel Solà: Just a methodological question. In the same way that QM/MM are used to analyse proteins or something like that, is it possible to mix QM/MM and these physical methods that you are using, these nematic models, and this kind of things? Is it something that has been done, or possible? Maybe you can analyse better the interactions of some molecules with the surface or something like that with this possible method? I don't know whether this exists.

Julia Yeomans: I think this is a question which has been hanging around for about 40 years and people have tried to do multiscale methods and, up to now, I think it is probably true to say that they do not work. What seems to work better is when you identify the question you are asking and then choose the right lengthscale model to use it. The way the molecular details go into the continuum models is in

coefficients like viscosity or parameters for the free energy. You have to realize how limited and useless that is for some sort of questions but maybe right for others. Coarse-graining is really hard when you get to do dynamics.

Ben Feringa: In the last ten years, in the synthetic community, there was a lot of debate and discussion about on-water chemistry. So, the acceleration of reactions on water. Barry Sharpless introduced this concept and nowadays there are a lot of people that are very intrigued by this reactivity at interfaces with water or even in water *etc.* What do we know about it? Can you simulate what is going on? Or why you see such tremendous acceleration effect in some reactions, like for example the Diels-Alder reaction? Or is it just hydrophobic effects and whatever the orientation of the water? I am intrigued by that because we are so much puzzled and people get very exciting results without having explanations, as far as I know, but can somebody comment on that?

Wilhelm Huck: Actually, we have looked at these on-water effects. What we have found is that most people did not study the kinetics, they only studied the yield after certain time. And so, if you look at the kinetics and the changes between on-water and in-water, the differences are often really small. I think, for the Diels-Alder it is big, for maybe a few others it is reasonable to assume that there are some hydrogen bonds to the transition state. For, I think, the vast majority of the reactions, there is hardly any difference. In our experience, at least.

Joanna Aizenberg: I am actually quite surprised because, generally speaking, when we think about what can happen in monolayers, things on water see two environments: there is the hydrophobic environment of air and the hydrophilic environment of water. In principle, your reactions can reach different states that are not necessarily accessible in water. At least, things can happen; again I do not want to bring it again as a crystallization thing, but crystallization on water is always better than crystallization in water. I would say this duality of the interface, having these two media, contributes in many cases, probably not in all reactions, as an accelerating feature.

Wilhelm Huck: One comment on that. The tricky bit is that they are typically not done on air/water interfaces but on oil/water interfaces, so organic solvents. In a lot of cases it is unclear where the reaction actually reaction takes place because these molecules might be soluble in either phase as well. So, it is very difficult to distinguish exactly what is going on in these systems.

Ben Feringa: May I add to that? I agree with that because we do not know absolutely for sure how much organic material is at the interfaces. In some of these reactions, there might be some solvent *etc.* I will tell you why we are so puzzled. Because recently we have found, and not only we but also Italian groups and some

groups in England, that when you have butyl lithium or metal lithium, avoid any molecule of water, because it reacts spontaneously immediately with water. Now, we do reactions on water with butyl lithium with very high yields and other groups are also working on this. It is amazing. There must be something special. It could be that there is a monolayer of organic material prevented from reaching the water or whatever, but there is something special there with the hydrophobic interfaces of water or the air/water interface. And I am puzzled.

Eva Nogales to Angelos Michaelides: It concerns your STM studies of the structural organization of water on these atomically-flat metals. I was a little puzzled by the fact that you were not telling us anything about the details of the surface, or lattice parameters and whether that had any effect. I wanted to understand: in the first layer of water, every molecule of water is only interacting with metal, not with itself, is that correct? In the second layer, do they do both, interact with the metal and with other water molecules or just with water? Why is the lattice of the metal not relevant? Or, is it?

Angelos Michaelides: It is relevant. The point of showing that was to give an overview. Explaining every one of those images, each one would have taken ten minutes. It was just to make the point that these are flat substrates and you get this rich variety of behaviour. The variety and the structures that emerge, they entirely do come down to the balance of the lattice structure, of the reactivity of the substrate, so the strength of the bond with the substrate. In all of them, water molecules are hydrogen-bonded to each other. In the contact layer, these are fully hydrogen-bonded structures. In the second layer, the interaction to the substrate is essentially zero. It is screened out so that you have hydrogen-bonding within the contact layer bonding to the substrate; in the second layer it is bonding within the layer and to the layer below. But we spent a lot of time trying to understand why do specific structures form and when, and we have a set of rules. We have a set of two-dimensional rules to predict these structures. But that is not something that I had time to go into.

Tomas Cech: Those of us who work in the molecular macromolecule biological area choose our systems from Nature. But what I saw today was a variety of systems to look at the interface with water, such as these atomically flat metals and silica. It seems to me that there are perhaps a million or several million different surfaces that one could look at. What we have seen is that you probably will get a different answer with each system. You spent, many of your students spent, many years looking at one particular system. Had you looked at a different system, they would have spent a decade looking at that system. How do you choose the systems to look at? What is the rational?

Angelos Michaelides: The metal systems that I showed, there are not any single crystal metals floating about in the atmosphere. One area of our interest is

understanding ice formation on atmospheric airborne particles. But we do not know the composition of those atmospheric particles. So, our work on metals is motivated by a desire to understand: are there any general principles that we can extract from these model well-defined systems where people can do very good measurements, getting molecular scale information and we could do good quality calculations? So, it is to extract insights, it is to validate and benchmark the calculations and it is a route to these more complex, more interesting systems.

Joanna Aizenberg: My problem with that unfortunately is that, especially if you talk about ice crystallization on small particles where curvature is extremely important, there would be no connection to crystallization of ice on an absolutely flat surface. Curvatures introduce problems to crystallinity. If it is an extremely curved environment, you can even form amorphous ice. There are some many things, so that I actually agree with this question. Is there relevance? If you tell me that these metal surfaces are important for some industrial application, it would be one thing. But if this is about understanding and trying to address the question of ice nucleation on small particles in a completely different composition of the environment, I have a problem even with the approach *a priori*.

Eugene Shakhnovich: Another system that I think may be interesting to biological applications, which probably you are sort of alluding to, is water in narrow capillaries with hydrophobic surfaces. There has been a lot of work, including our work in the 90's and several work from David Chandler. It is for sure that there are very peculiar behaviours applied in this type of narrow kind of slits/capillaries where you can have even a kind of evaporation under certain conditions at normal temperature, *etc.* The water will escape the capillary and evaporate and there is a definite — again in this story about dry molten globule — connection to what people see experimentally and in simulations, and what is predicted from this type of water. My point is whatever the question you are asking, what systems you are analysing, the surface should correspond to exactly the system you are curious about and I hope this is an example of that.

David Quéré: The question is so general that it should have as many answers as people here on the panel. It is a little bit like considering abstract painting, for instance. You have something which is *a priori* a huge field of freedom. I think that if you are an abstract painter, the first thing you have to do is to frame the things, to add constraints. Because you cannot face this infinity of possibilities, and so we heard already different answers. Another way to face it, which I think we share with Joanna, for instance, is to consider real systems. These systems are existing so we are not facing something which is infinite. But these natural systems, if we think about the surfaces of bugs and leaves that we showed, are amazingly different however. Instead of being infinite, it becomes at least one hundred types of surfaces. Then, there is a very open question there, which is: why do we have

this variety? Does it correspond to different ways of facing water, for instance? It should be in some cases. Just the fact that we ask the question opens a very interesting box. In a very few cases we have answers, but I think it is a way to answer your question which is to say: well we have to select and we select in the real world.

Mischa Bonn: I completely agree and I think this also goes for some of the molecular level studies that I have showed. For lipid/water interfaces, of course it is very easy to exchange lipids and look at the effects of different types of lipids. The different lipids behave more similarly than they behave differently. So, there are certainly rules that one can infer there. The same is true for the minerals. Of course, if I talk about oxides, many of the oxides behave similarly. Yes, there are differences but, again, there are more similarities than there are differences. Even the same is true for protein/water interfaces. We study anti-freeze proteins and ice nucleating proteins. Both of these proteins have the same structural surface to both inhibit and trigger ice nucleation. There are all different sorts of anti-freeze proteins but they all have the same structural properties that allow you to extrapolate by studying one. You have to study a few to show that there is this generality, but once you have shown that, it is clear.

Joanna Aizenberg: So, in other words, one should ideally choose a group of representative surfaces that make sense, that are interesting and relevant, and hoping that the entire group would have similar features that can be captured by the model or by the experiments.

Mark Ellisman: Judging from the time, I think this may be the last discussion, but again I will come back to something Tom started, and Eva also communicated on that. The biological systems that you choose could be more evolved. When you use the example of nano-capillaries, I think that there are examples in biology, in the nervous system for example, dendritic spines and the necks, and instead of thinking of these things as hydrophobic because the molecules there are extremely acidic, actin, they are charged, they would organize water. One of the properties that I was waiting to hear about and now I will shut up and try to stimulate you to tell me about. Are there examples that you are promoting your students to work on where you look at organization and disorganization of water within microdomains? Because that is what looks like biology does within the nucleus, with acidic chromatin, within the cytoplasm. You have local domains where water is highly organized but putting it into the Brownian energetic pool does work. Biology figures out probably how to make that work vectoral. There are lots of systems of organizing and disorganizing water with moving cations, which are usually controlled. There is no free calcium in the cell. You may not realize that, that is a misinterpretation of what dyes tell you. There are thieves, they just look at calcium when it is being handed from one molecule to another. When cations enter, they

kick water out of bound surfaces into the free pool. What does that do, if you did it locally or vectorally?

Joanna Aizenberg: Who is brave enough to take this question because actually I had asked similar questions at the end of our discussion. I think that this release of water from hydrated states, and what the role of ions is in that is extremely interesting to me, but any answers?

Mischa Bonn: I think that is an extremely excellent point. While we have done work on cells at different levels of hydration to look at water properties, these are still ensemble averages measurements so they contain some information and they show heterogeneity. But, of course, the dream is to be able to develop techniques that allow you, without labels, to look at water as it moves through a cell at the molecular level on the time-scale that it moves. I am afraid that that is a movie that I have yet to produce. It is certainly the holy grail and the dream.

Joanna Aizenberg: That is the last question that we take but I hope that the way to answer this question is while we do not know now but maybe 50 years from now there would be another Solvay conference on water where we will be able to try to address that in more details. Maybe we will hear more about biological systems, including water and other things, in this session that is still to come.

Tomas Cech: Please let us know what happens in 50 years.

Joanna Aizenberg: We will! Don't worry! So, I have to close this session, I am very sorry because picture taking is extremely important and apparently everybody is extremely hungry. Thank you so much!