



Original Article

Molecular modeling in confined polymer and biomembrane systems

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Received 18 November 2008; Accepted 22 February 2009

Abstract

The computational study of soft materials under confinement for bio- and nanotechnology still poses significant challenges but has come a long way in the last decade. It is possible to realistically model and understand the fundamental mechanisms which are at play if soft materials are confined to nanometer dimensions. Here, we present several recent examples of such studies. Thin polymer films are abundantly used as friction modifiers or steric stabilizers. We show how systematic modeling can shed light on the interplay between entropic and energetic interactions. Thin glassy films are critical for the success of nanolithography. For that we have to understand the effect of confinement on the glass transition behavior in order to guarantee the stability and integrity of the lithographic masks. Simulations aim to understand the fundamental differences in the densities of states of glass formers in bulk and under confinement. With the advent of bionanotechnology the structure and phase behavior of lipid membranes as models for cellular membranes at the nano scale length is of importance due to implications in understanding the role of the lipids in biochemical membrane processes.

Keywords: molecular simulation, confinement, soft materials

1. Introduction

Molecular modeling has established itself as the third leg of science complementing experiments and analytical theory in recent decades. This is especially true in the field of nanotechnology where the relevant length scales are ideally suited for molecular modeling and the direct comparison to experiments is often possible. On the other hand it is also a very important area of modeling as analytical theory becomes hard if one (or more) of the system length scales is on the same order or at least comparable to molecular length scales. In this realm bulk methodologies and even the system bulk behavior can break down as the system essentially consists only of surface and subsurface particles. It is, thus, crucial to

study these systems computationally in order to learn to understand the limits of the bulk description and to describe any new physics which may emerge by this interplay of length scales. No other theoretical technique can be reliably used in this endeavor. Of course there are several caveats here as well, mainly based on the reliability of the underlying molecular models and on the question of proper equilibration and sampling of the systems.

In this contribution we discuss several recent modeling approaches of soft matter in confinement (Ghosh and Faller, 2006a, b; Hatakeyama and Faller, 2007; Träskelin *et al.*, 2008; Xing and Faller, 2008). We will be discussing three specific examples: The first one is the effect of confinement on the glass transition in thin films on model and real glass formers, second we discuss the influences of surfaces on various polymer systems and we finish with a study on the influence of surfaces on biomembranes.

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2. Thin glassy films

The glass transition in confinement is one of the most interesting open questions in soft matter physics with tremendous importance for technological applications. Polymeric glasses are the main materials applied in the semiconductor industry as photoresistive coatings, or photoresists for short (May and Spanos, 2006). If the material properties of these glassy photoresists fail the whole chip making process cannot proceed. It has been reported that with decreasing line width the stability of photoresists becomes questionable (Kim *et al.*, 2003) and this has been linked to a change in the glass transition temperature of the film. The glass transition changes due to confinement area a wide open area and far from completely understood (Jackson and McKenna, 1991); we discuss here some small model compounds to increase our understanding.

Ortho-terphenyl is a small organic glass former and an excellent model system to study the glass transition (Greet and Turnbull, 1967). The molecule consists of three connected benzene rings. The two outer ones are connected in ortho positions to each other onto the central ring. It is a fragile glass former in Angell's nomenclature due to the lack of directional bonding forces (Angell, 1995). We first discuss simulations of two structurally linked models of ortho-terphenyl on different length scales in bulk and a freestanding film to examine the differences in behavior due to confinement effects. We address the heterogeneity in dynamics in dependence of distance from the film center. Finally we compare the confinement effects to a more generic model, the Kob-Andersen binary Lennard-Jones glass (Kob and Andersen, 1994).

2.1 Atomistic molecular dynamics of Ortho-terphenyl

We presented earlier the first simulation of a small organic glass former in a freestanding film (Ghosh and Faller, 2006a) where a widely used approach to set up a thin film the "elongation and expansion method" (Rane *et al.*, 2004) was applied to form a freestanding film starting from the bulk glass. We used freestanding films of about 7 nm thickness in vacuum. The box size perpendicular to the film had to be chosen large enough in order to avoid any interaction of the films with its virtual neighbors as we want to keep three dimensional periodic boundary conditions for efficiency reasons.

Based on measurements of density and specific volume as a function of temperature as well as the diffusion coefficients we obtained a glass transition temperature of 260 K for the bulk system (Ghosh and Faller, 2006a). This is in reasonable agreement with the experimental value of 243 K. In simulations one expects the apparent glass transition temperature to be higher than in experiments due to the inherently faster effective cooling rates and the limitation on relaxation times. All atomistic simulations (not only for this project but also the other ones discussed below) were carried

out using the GROMACS (Van Der Spoel *et al.*, 2005) software package versions 3.2 and 3.3 as the simulations were performed on different systems including supercomputers.

Deep below the bulk glass temperature, around 230 K, freestanding OTP films are stable and a well-defined density profile can be observed. Increasing temperature leads to instability of the film by evaporation below the bulk glass transition temperature. At the bulk glass transition the freestanding film is no longer glassy and a liquid freestanding film decays. We therefore conclude that the glass transition temperature is reduced for a freestanding OTP film from the bulk value. There are, however, no experimental data on freestanding OTP films to directly validate this finding.

We expect the behavior of the film to be heterogeneous due to different distances from the surface and also different local densities. To characterize such heterogeneities we analyzed systems in the stable regime below the bulk glass transition. In order to describe the heterogeneity in the freestanding film we divide the film into different regions depending on the distance from the center of the film. We determined the dynamics in these regions separately and find that in the center the dynamics is very similar to bulk behavior; there is a weak decrease of dynamic localization or "caging". On the surface, however, there is a significant speedup of the dynamics. At long times all molecules move at the same rate but up to about 1 ns we find an inhomogeneity in molecular motion and as a whole a higher mobility in the film.

2.2 Coarse-graining of Ortho-terphenyl

Atomistic models like the one discussed above are very powerful in order to describe molecular motion and behavior in highest possible detail. However, there are severe limitations on the reachable time and length scales. To alleviate these problems several so-called coarse-graining techniques have been devised to develop systematically larger scale models (Ayton and Voth, 2002; Reith *et al.*, 2003). In order to describe the model on the larger scale we first need to introduce the interaction centers on that scale. In the meso-scale model of Ortho-terphenyl to be used here each benzene ring is replaced by a single interaction center (a super-atom). It satisfies the basic requirements (Faller, 2007) that the distances between super-atoms described well-defined single peak (ideally Gaussian) distributions. The bonds between such super atoms can then be simply modeled using a harmonic potential. For OTP three bonds are adequate, i.e. the angle between the two outer rings is modeled as a bond as well. For the non-bonded potential we use iterations based on the potential of mean force (PMF) obtained by Boltzmann inversion of the radial distribution function between different super-atoms. Let us briefly summarize this technique called Iterative Boltzmann Inversion (IBI). For further details the reader is referred to the original description (Reith *et al.*, 2003) or recent reviews (Faller, 2007; Müller-Plathe, 2002). Based on atomistic simulations

one can measure Radial Distribution functions (RDF) of the superatoms. In the first step, we now produce a potential by Boltzmann inversion of the RDF; i.e. the free energy difference is assumed to be the potential energy difference. We now perform a simulation using this potential as an initial guess. The RDF on the meso-scale and the target function, calculated in the atomistic simulation, are subsequently compared. After the first meso-scale simulation the difference between the simulated RDF and the atomistic target is determined and added as correction V_{corr} .

$$V_{\text{corr}} = -k_B T \ln(RDF_{\text{meso}} / RDF_{\text{atom}}) \quad (1)$$

This procedure is iterated until the difference between the target structure and the modeled meso-scale structure is negligible. The resulting potential is completely numerical. The DL_POLY parallel molecular dynamics simulation package was applied for the meso-scale simulations (Smith and Forester, 1996).

One of the main results of this procedure was that the ensuing potential is strongly temperature dependent (Ghosh and Faller, 2007). It is fundamentally clear that any structurally coarse-grained potential is temperature dependent due to the explicit appearance of temperature in the inversion procedure. But one hopes of course that the potential derived at a certain set of conditions is reasonably transferable to other conditions. This has been shown to apply in the polymer case (Carbone *et al.*, 2008; Sun and Faller, 2007). But in the case of this low molecular weight glass this is not the case. It turns out that the model developed in the liquid range crystallizes under cooling whereas the model developed in the glass behaves correctly. So essentially we would need to develop a model for every set of conditions which somewhat defeats the idea of coarse-graining.

2.3 Density of states modeling

Molecular Dynamics as discussed up to now has the advantage that it follows the system dynamics and by that produces always a physical trajectory which can be analyzed dynamically. On the other hand it is also hampered by this tie-in with the real dynamics. Monte Carlo techniques can here be more creative as they only need to produce correspondingly member of the physical ensemble but not in any particular order as Monte Carlo is based on a Markov chain approach.

Wang-Landau Density of States Monte Carlo is a novel modeling approach to directly calculate the density of states of a system (Wang and Landau, 2001b). In contrast to standard Monte Carlo simulations it uses an inverted approach. If the density of states of a system would be known the complete thermodynamical behavior could be derived from this knowledge. Additionally, if we would bias a Monte Carlo simulation with the inverse of the Density of States the

probability of visiting different energy states $p(E)$ would be homogeneous based on the fundamental Monte Carlo equation.

$$p(E) = W(E)\Omega(E) \quad (2)$$

where $W(E)$ is the weighting factor normally dictated by the ensemble. This equation is true for any Monte Carlo calculation, in the standard flavor of the canonical ensemble the weighting factor becomes the Boltzmann factor $W(E) = e^{-\frac{E}{kT}}$ and we obtain the fundamental probability distribution tied to the Helmholtz free energy. If W and Ω are now the inverse of each other p becomes a constant and the probability of visiting states becomes homogenous. It has to be said that a direct simulation in such an "ensemble" cannot be analyzed in the standard way by just averaging over the simulation as the relative weight of the energy states is not physical. However, as we obtain the Density of States we can analyze the system in any ensemble (Ghosh *et al.*, 2006). Technically Density of States Monte Carlo is again an iterative process where uniformity of the probability distribution is approach by an optimization strategy. For details the reader is again referred to the original literature (Wang and Landau, 2001a, b).

We used Wang-Landau Density of States Monte Carlo to study a binary Lennard-Jones glass-forming mixture of big and small particles (Kob and Andersen, 1994) in bulk and films between noninteracting impenetrable walls (Ghosh and Faller, 2008). The interactions are inspired by mixed metallic glasses but are not meant to produce any specific glass formers but have been carefully selected to avoid crystallization and phase separation. Thermodynamic properties are calculated using two different ensembles and the film data is compared with the bulk (Ghosh and Faller, 2008). Bulk properties are found to be in good agreement with previous simulations (Faller and de Pablo, 2003). We confirm the formation of a glass by analyzing a wide variety of properties including energy, heat capacity, and pressure as functions of temperature for both bulk and film. We find a change in slope in the energy per particle and pressure as a function of temperature which we identify as a glass transition as we do not find any crystal structure. There is, however, a preference for the bigger particles to be at the surface with respect to the smaller ones. The density profile for particles individually has been plotted against the Z-coordinate in Figure 1. Based on all properties we find overall a higher glass transition temperature is for the film.

In connection with the OTP data above this shows that it is very relevant how exactly the glass formers are behaving. These two models behave drastically differently even under very similar conditions in freestanding films. We find that the glass transition temperature is shifted in opposite ways for the two models discussed here.

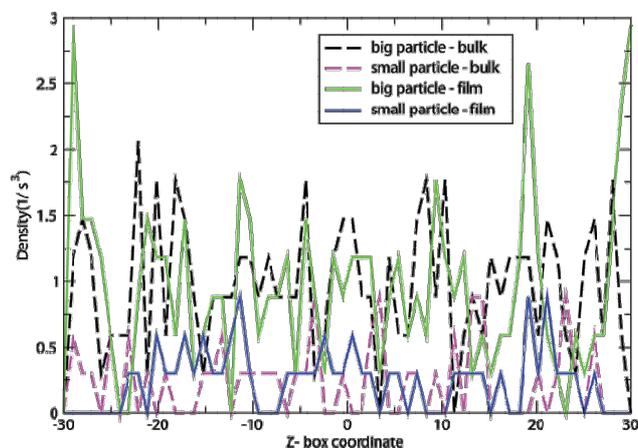


Figure 1. Density profile of binary Lennard-Jones particles in a freestanding film in comparison to bulk

3. Polymers in confinement

A very important class of soft materials encompasses polymeric systems. As polymers are omnipresent in our daily lives we have ample motivation to study their behaviors. Here we present two examples of polymers under confinement,

3.1 Amphiphilic triblock copolymers

The conformation and behavior of copolymers in strongly confined systems depend on the type of wall interaction and concentration. Polyethylene oxide-polypropylene oxide-polyethylene oxide (PEO-PPO-PEO) tri-block copolymers are widely used for industrial applications, such as detergents, stabilizers, emulsifiers, and drug delivery systems (Anderson *et al.*, 2000; Bergstrand and Edwards, 2004). PEO-PPO-PEO tri-block copolymers are non-ionic surface active agents commonly known as Pluronic (trade mark by BASF Corp.). It is very interesting to study the interaction of the copolymers with biological membrane in relation to drug delivery system (Hatakeyama and Faller, 2008). It is computationally not yet feasible to study the direct complex interaction between Pluronics and biomembranes or other wall systems in atomistic detail. So again a coarse-grained approach is required.

We first study PEO₁₀PPO₂₀PEO₁₀ in water under confinement (Hatakeyama and Faller, 2007) where we focus on the influence of simple walls on the morphology of the ensuing self-assembled structures. The coarse grained model of Pluronics is based on the MARTINI model for lipids (Marrink *et al.*, 2004) in which we model PPO monomers as hydrophobic superatoms, whereas PEO are hydrophilic superatoms. The wall particles are simple hydrophilic or hydrophobic centers as well.

The hydrophobic parts of the copolymers adsorb preferentially to hydrophobic walls and the hydrophilic ends to hydrophilic walls. This does not necessarily lead to simple layer structures but more complex assemblies like surface

hemimicelles are found as well. These structures are known from experiments (Brandani and Stroeve, 2003). They are characterized by the fact that some polymer chains form bridges between the surfaces or they form loops where both ends are connected to the same surface. This shows that even such relatively simple systems can give rise to complex self assemblies. If we are able to tune this assembly behavior for nanotechnological applications we can construct complex systems from the bottom up rather than the top down.

3.2 Polymer brushes

Polymer brushes are another class of confined nanotechnological system with wide ranges of applications from adhesion modification to controlled release of drugs. They are formed when flexible macromolecules are attached at one end to a substrate, and the density of the anchor-points is high enough for the grafted chains to stretch away from the substrate surface. The structure of a given polymer brush is critically dependent on the absence or presence of a solvent. While in the absence of a solvent the polymer chains typically prefer to curl up at the surface, addition of a “good” solvent can cause stretching of the chains. The physical driving force for this transition is the competition between configurational entropy and the energy gained by optimizing the polymer chain-solvent interface. Here, we briefly discuss the structural and thermodynamic properties of polystyrene brushes under confinement. Polystyrene chains have been grafted at graphite substrates at various grafting densities. The behavior of brushes in toluene solvent solutions is then investigated. In order to simulate a polystyrene melt, 48 atactic polystyrene chains of length 15 monomers were constructed. Subsequently the melt was enclosed between two graphite surfaces each consisting of two immobilized graphene sheets (snapshot in figure 2). Both solvent particles and monomers interact with the wall atoms with a Lennard-Jones potential. Systems of various densities were created by varying the distance between the surfaces. Using molecular dynamics the systems were

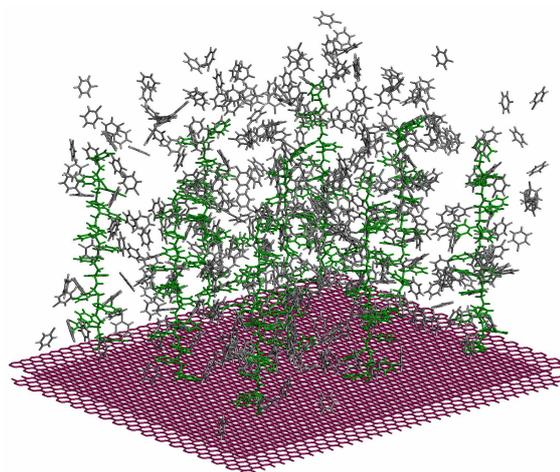


Figure 2. Snapshot of a polystyrene brush in toluene

equilibrated for 1 to 5 ns. Since the initial polystyrene melt was constructed under pressure, the polystyrene molecules are well separated from the graphite surfaces. The construction of polymer brushes with various grafting densities began with the extraction of polystyrene chains from the bulk melt. The curled chains were stretched by molecular dynamics simulations. Arrays of stretched polystyrene chains were then grafted onto a surface of two graphene sheets, forming polymer brushes of various densities with graphite surface. This end-grafting was achieved by restraining the position of one end of the chain at a short distance (2.5 - 3.0 Å) above the graphite layer. Systems with 3x3, 4x4, 5x5, 6x6, and 7x7 polystyrene chains have been investigated.

During the simulation the chains in brushes without solvent are contracting. In order to investigate the effect of a good solution, toluene molecules in various amounts were added to all systems. With increasing toluene density the radius of gyration of the chains increased rapidly showing tenability of yet another nanosystem.

4. Supported lipid bilayers

Supported Lipid Bilayers (SLBs) are abundantly used as models for the cell membrane (Sackmann, 1996) or in biosensors although it has been realized that protein function within them is often somewhat limited (Tanaka and Sackmann, 2005). In order to understand the differences between supported bilayers and their real cell membrane counterparts, computer simulations are an ideal tool. It is therefore surprising that these simulations are relatively rare (Heine *et al.*, 2007; Hoopes *et al.*, 2008; Xing and Faller, 2008; Xing *et al.*, 2009). A model which is very appropriate to study such systems is the MARTINI model of lipid bilayers (Marrink *et al.*, 2004; Marrink *et al.*, 2007) where 3-5 non-hydrogen atoms are represented by one interaction site allowing simulations of systems of several thousand lipid molecules for several microseconds. To simulate supported lipid bilayers the model has to be slightly adapted in order to avoid freezing of water at the surface (Bennun *et al.*, 2007). Experimentally it has been found that there is a thin water cushion between a support surface and the bilayer (Miller *et al.*, 2005). The structure and thickness of this layer are a matter of debate.

We simulated a bilayer of DPPC lipids as these are among the most abundant in cell membranes. The initial configuration was derived from a study of a pure unsupported DPPC bilayer (Marrink and Mark, 2004). The temperature was 323 K, above the main phase transition temperature of DPPC which is $T_c = 314$ K. The area per molecule is fixed at 62 \AA^2 the value found from simulations of unsupported DPPC bilayer. The amount of water on either side of the lipid membrane equilibrates within a few microseconds.

Due to periodic boundary conditions the system is effectively a slab of water and lipids between two identical surfaces; we do not exclude water-water or water-lipid interactions through the support as long as they are within the

cutoff. We showed that this does not significantly change the behavior (Xing and Faller, 2008). In order to keep the interaction density of the support constant, the lateral area of the simulation box and consequently the bilayer is kept constant.

We find strong effects of the support on the density and pressure profile. In a free bilayer there is a clear minimum density area in the middle and symmetry around that lowest density plane. There is not much structure otherwise. In the supported bilayer all these features change. There is no symmetry plane in a supported system as the symmetry is broken and we see a significant difference in the structure of the two leaflets. There is significant localization of both, headgroups and tails. There is significant ordering in the proximal leaflet and much less in the distal leaflet. Especially the proximal headgroup is highly localized and we find strong interaction with the support. The plane of lowest density is not necessarily the middle of the bilayer. The proximal leaflet is thicker than the distal as the tails are more elongated. It probably is much closer to or even in the gel state. In comparison to the well characterized density profiles of free bilayers it appears that the proximal leaflet is significantly altered whereas the distal leaflet is apparently very similar.

The influences on the pressure profile are very severe as well. There is an increase of at least a factor of three in local lateral pressures (Xing *et al.*, 2009). This is highly significant as lateral pressure has been connected to the dysfunctionalization of proteins (Cantor, 1997). We suspect that this pressure change is one of the fundamental reasons of protein configurational changes in supported membranes.

5. Discussion and outlook

It is clear that computational modeling is inevitable for understanding the complex interplay of many length scales in nanoscopic systems. We presented several examples which illustrate the strengths and limitations of such modeling approaches. It is clear that still a lot of work is ahead of us.

The main challenges lie clearly in the correct choice of the appropriate model for the application under study. As length and time scales vary considerably we always have to be aware which model characteristics are reliably representing real phenomena and which are arbitrary.

The main strength of this kind of modeling is not so much the quantitative comparison to experiments although that often succeeds as well but rather the unearthing of the underlying mechanisms. There is no other technique available to date to accomplish this task. And on the nanoscale molecular modeling is the ideal partner for experiments as the length scales are closely matched.

Acknowledgements

Many discussions with Samuli Ollila, Ilpo Vattulainen, Dennis Mulder, Margie Longo and Tonya Kuhl are gratefully acknowledged. This work was partially supported by the US Department of Energy through the Office of Advanced Scien-

tific Computing, under grant DE-FG02-03ER25568 (for the work on glasses) as well as through the Office of Basic Energy Sciences under grant DE-FG02-OGER46340 (polymer brushes) and the US National Science Foundation through grant CBET 0506602 (supported lipid bilayers). PT acknowledges support from the Academy of Finland. This research used resources of the National Energy Research Scientific Computing Center, which is supported by the Office of Science of the U.S. Department of Energy under Contract No. DE-AC03-76SF00098.

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