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Multiscale simulation of soft matter systems

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This paper gives a short introduction to multiscale simulation approaches in soft matter science. This paper is based on and extended from a previous review.[1] (1. C. Peter and K. Kremer, *Soft Matter*, 2009, DOI:10.1039/b912027k.) It also includes a discussion of aspects of soft matter in general and a short account of one of the historically underlying concepts, namely renormalization group theory. Some different concepts and several typical problems are shortly addressed, including a (more personal) view on challenges and chances.

1   Introduction

Material properties of soft matter systems are determined by processes and interactions on a wide range of length and time scales. While these mutually influence each other, it is not straight forward to provide quantitative information and understanding without taking this properly into account. Although this holds for many physical systems, it is of special importance for soft matter, where the characteristic energy scale is the thermal energy $k_B T$. Unlike for electronic properties, where typically energies are measured in eV (1 eV $\approx$ 40 $k_B T$ at $T = 300$ K), such low energies give rise to significant conformational and structural fluctuations. The materials are "soft" because of a characteristic low (non-bonded) energy density, which to a very first rough approximation resembles the elastic constants of the material. The locally relevant length scales of a few Å to a few nm, lead to the very low energy densities allowing for large thermally driven fluctuations. Thus simulating soft matter automatically means dealing with large spatial and/or conformational fluctuations, making equilibration in many cases particularly difficult. To put the energy scale in perspective and provide a guide for comparison of different experiments and simulation approaches, we present in Table 1 the thermal energy in different units, as they are typically used in different fields.

A typical covalent bond, *i.e.* carbon–carbon, has an energy of about 80 $k_B T$. If no chemical reaction comes into play, it can be considered as stable. In contrast, for

Table 1 The thermal energy $k_B T$ at $T = 300$ K in a variety of units as they are frequently used in different fields of physics an chemistry

Research field	$k_B T \cong 4.1 \cdot 10^{-21}$ J
Electronic properties	$2.5 \cdot 10^{-2}$ eV
Quantum chemistry	$9.5 \cdot 10^{-4}$ E_H
Biophysics	4.1 pNnm
Spectroscopy	200 cm^{-1}
(Phys.) chemistry	0.6 kcal/mol
(Phys.) chemistry	2.5 kJ/mol

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typical hydrogen bonds, energies vary between about 6 and 10 $k_B T$, respectively. Thus they can break and reform on a rather short time scale, yet fairly long for a molecular simulation. As a consequence one usually deals in soft matter simulations with systems of moderate size, *i.e.* usually less than about a million atoms, however for very long time periods. We here give a short introduction related to the many different approaches and concepts, which have been discussed during the recent Faraday Discussion. A complementary introduction focusing on biopolymers can be found in the Faraday Discussion 139.[2]

Molecular simulation approaches to soft matter problems that are determined by a wide range of scales demand for an equally wide range of simulation methods at various levels of resolution including a varying amount of degrees of freedom.[3,4] A variety of quantum mechanical methods are used to address electronic/energetic properties on a high-resolution microscopic level, however they are limited to short length and time scales. Classical atomistic force field methods as well as particle-based coarse grained approaches are capable of sampling microscopic to mesoscopic scales. Especially the latter which is also able to access large conformational fluctuations, yet these approaches still fail to cover many macroscopic phenomena. For this, one needs to go beyond (purely) particle based approaches and use for example the Lattice Boltzmann[5] or DPD[6,7] methods or other mesoscopic methods to include hydrodynamic effects. Fig. 1 illustrates the characteristic different regimes and the level of details the models include.

Many questions regarding soft matter systems can be studied with a single numerical approach on a single level of resolution. However, when it comes to a quantitative understanding of complex materials, approaches with a single level of resolution do not frequently suffice since the different levels of resolution are more intimately interwoven. "Multiscale simulation" refers to methods where different simulation hierarchies are combined and linked to obtain an approach that simultaneously addresses phenomena or properties of a given system at several levels of resolution and consequently on several time and length scales. Multiscale simulation approaches may operate in different ways in terms of combining the individual levels of resolution: (*i*) in sequential approaches the simulation models on different scales are treated separately by simply passing information (structures, parameters, energies *etc.*) from one level of resolution to the next, (*ii*) in hybrid simulations different levels of resolution are present simultaneously, thus requiring direct interaction between them, and (*iii*) adaptive methods allow for individual molecules to
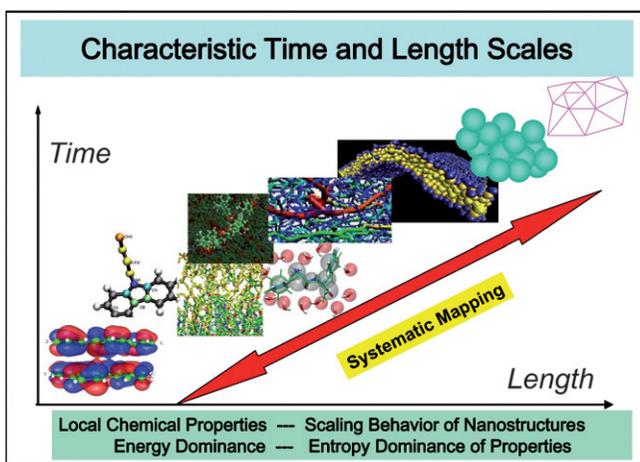
Fig. 1 Examples for characteristic numerical models for various length and time scales in soft matter systems.

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adaptively switch between resolution levels on the fly—for example depending on their spatial coordinates. In either case, the exchange of information, interaction or particles requires a high level of consistency between the individual models.[8–13]

Simplified/generic coarse grained models which only account for a minimal set of properties of the (macro-)molecules of interest such as excluded volume, connectivity and a few basic types of interactions have since long been used and are perfectly well suited to study generic properties of soft matter systems. Since they reduce the computational complexity they allow for much longer effective time and length scales than more detailed models. Good examples are the investigation of scaling properties of polymeric systems,[14] both static and dynamic, as well as the investigation of biomembranes.[15,16] For example, for the problem of polymer melt dynamics such simulations, both molecular dynamics in continuum and Monte Carlo on lattices have been instrumental for a better understanding of the entanglement problem.[17–19] In order to link the results of such coarse grained simulations to real chemical systems one needs to appropriately devise the model parameters and interaction potentials. In multiscale simulations, where one wants to switch between resolution levels or use them next to each other, one has to go beyond scaled or fitted parameters because the levels of resolution need to be linked structurally and thermodynamically consistently. This requires a very careful development of CG models to avoid unphysical effects upon changes between scales. Here, we focus on methodologies to develop CG models based on an atomistic (force field) description.

Before we discuss a few ways to link different levels of resolution, let us shortly go back and mention the physical origin of coarse graining methods.

2   Coarse graining—general aspects

Dealing with the multiscale aspect of soft matter or more generally hierarchically structured materials can be done in many ways. One strategy, which has been followed by many disciplines from engineering to science is to devise independent models, which deal with typical aspects of a given scale. The link between the scales is then essentially given by the parameters characterizing each level. These parameters typically are closely linked to experiments. This is quite successful when it just comes to the description of material properties. A typical example which illustrates these rather complex structures can be studied by such an approach is the numerical investigation of the properties of lobster cuticles.[20] Here we want to go beyond that, however at the price that our systems, though already very complex, remain significantly simpler. In soft matter multiscale modelling the aim is not only to describe material properties but rather to understand the structural organisation and physical mechanisms which lead to morphologies, properties and eventually function. For this the different levels of description have to be much more intimately coupled.

Ideas linked to systematic coarse graining historically were linked to the fact that even for relatively simple systems it was simply not possible to perform all atom simulations. In addition, for many questions of concern, the value of this very detailed information coming from all atom simulations was questionable, since basic conceptional physical information could easily get lost. While physics is used all the time to sort out contributions in terms of small parameters a theoretical systematic link between a more local and a more global view was provided by renormalization group theory. The idea goes back to Kadanoff,[21] who introduced the block spin renormalization concept, which in variants is the basis for real space renormalization group treatments, which can directly be applied to polymers.[21–23] To illustrate this idea, let us look at a spin system as illustrated in Fig. 2.

Take a system of spins, which have only the two states, namely ± 1. When the system is divided into subcells of $(s \cdot a)^d$, a being the nearest neighbour distance and d the dimensionality, we can describe the free energy of the system in terms of cell variables, namely $F_{\text{cell}}(\varepsilon', H') = (as)^d F_{\text{site}}(\varepsilon, H)$, where the prefactor $(as)^d$ comes from the extensivity of the free energy. H is the Hamiltonian of the original system
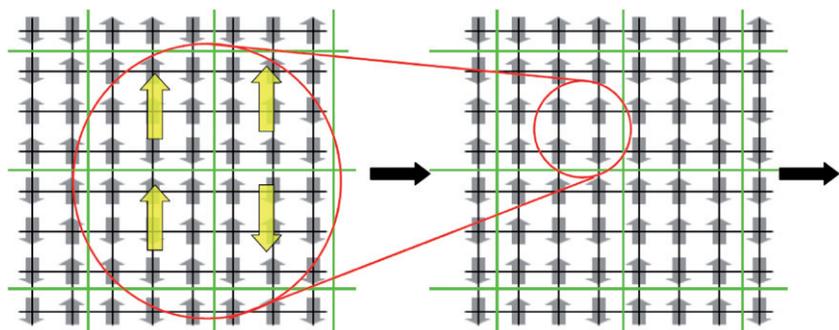
Fig. 2 Illustration of a simple majority rule real space renormalization step of a $d = 2$ Ising system, as it was introduced in the early 70s by L. P. Kadanoff based on the mathematical concepts of K. Wilson.[21,79] Blocks of 3×3 spins are mapped onto a single Ising spin based on a simple majority rule.

and H' the corresponding Hamiltonian on the basis of all cell interactions and $\varepsilon = (T - T_c)/T_c$, the normalized distance from the critical point. So far such a transformation is exact. Then however simple Ising spins (± 1) and nearest neighbour interactions transform into much more complicated longer ranged interactions and spins with many states. In practice usually one has to resort to an approximate treatment, as indicated in Fig. 2. Iterating such a procedure leads to the well known renormalization group flow diagrams. As de Gennes pointed out, polymers are a special case, which naturally suggest a renormalization along the back bone of the chains in a way that groups of monomers are lumped together into one monomer and this then is iterated. Fig. 3 shows a typical example of such a renormalization procedure based on a Monte Carlo simulation[23] of polymers made of hard spheres of diameter d and bonds of fixed length l.

In this context systematic coarse graining can be viewed as just one or two steps in such a renormalization group framework. Since this mapping step in almost all cases
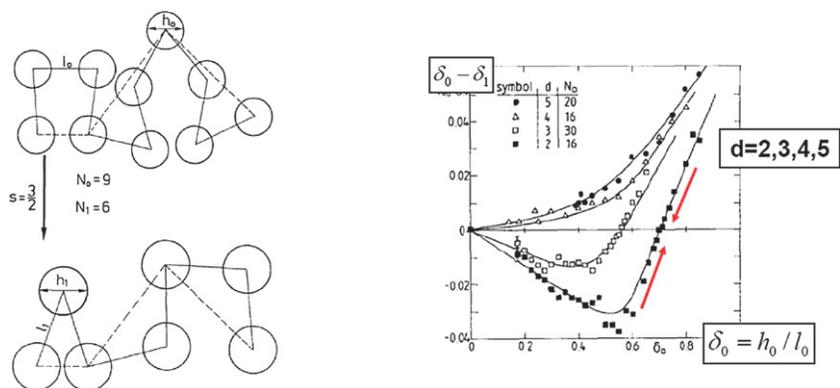
Fig. 3 Illustration of a Monte Carlo Renormalization Group Study of a hard sphere polymer model in spacial dimension $d = 2$ to 5. The relevant parameter is the ratio $\delta = h/l$ of sphere diameter and bond length. By matching the chain extensions (i.e. average squared end to end distance or radius of gyration) a renormalization flux diagram is generated, which leads to a stable fixed point $\delta^* = 0$ for $d = 4,5$ indicating random walk behavior (irrelevance of excluded volume) and non trivial stable fixed points of $\delta^* \approx 0.55$ and 0.7 respectively for $d = 3$ and 2, indicating the self avoiding walk structure. δ^* also indicates the optimal ratio of sphere diameter and bond length to minimize finite size corrections.[80]

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requires significant approximations, it is also obvious that the free energy of a coarse grained system usually cannot be identical to that of the original system. For polymers, universality provides the criteria for which interactions are relevant and have to be properly transformed. This is because a polymer chain can be understood in very close relation to the problem of phase transitions. De Gennes showed that, within the so called n-vector model, a polymer chain of N steps can be seen as a path connecting lattice spins of the so called n-vector model. Since close to a critical point correlation lengths diverge, longer and longer paths, meaning walks of increasing length contribute. Thus there is the correspondence $(T - T_c)/T_c \propto 1/N$ and the conformations of these walks follow for $N \rightarrow \infty$ universal scaling laws leading, for example, to the nontrivial exponents $\nu = 3/(2 + d)$ for the end to end distance $\langle R^2(N) \rangle \propto N^{2\nu}$. For $d = 3$ the best field theoretic renormalization group studies and simulations give $\nu \approx 0.59$ instead of $\nu = 3/5$. While such general considerations give clear guidelines for coarse graining, they also illustrate limitations. Since only a few steps are performed and approximations are unavoidable in almost all cases, coarse grained systems also have to be studied carefully by themselves *i.e.* phase transitions pose special difficulties and there is *a priori* no reason that a coarse grained model, derived on the basis of a given scheme and some approximations, displays phase transitions at the very same temperature, pressure *etc.* as the underlying atomistic model. Second, the power of generic properties based on scaling laws relies on the proximity to asymptotics. While this often is reasonably fulfilled for long chain polymer melts or chains in solution, many of the current systems of interest certainly are not close to the asymptotic scaling regimes. Thus finite size corrections play a crucial role.

Alternatively one can view coarse graining procedures also as a special application of projector operator formalisms. Again the challenge is to define the optimal subspace of parameters, which on the one hand allow for a most efficient treatment of the systems and on the other hand do not exclude any aspect which is crucial for the question under study.

3 Linking levels of resolution: energies, forces and structures

Scale bridging requires systematic development of the individual models which are thermodynamically and/or structurally consistent. Many different approaches have been followed, both from the quantum mechanical to the classical level and from the classical all-atom level to a coarse grained description. For the latter we discuss here a few examples.

The derivation of interaction potentials between the coarse grained particles may be targeted at reproducing thermodynamic properties such as energies or free energies, for example partitioning data.[24,25] This approach has been particularly useful for simulating processes such as lipid membrane association where said properties play a decisive role.[26] On the other hand the energy based coarse graining approach does not *per se* guarantee reproduction of the structure of the system (for example of the underlying atomistic structure).[27] This may potentially cause problems and disruptions if one wishes to reinsert atomistic details into the CG structure. A recent alternative for (so far) rather simple model systems has been developed by Rutledge and Allen,[28–30] where the excess chemical potential of the degrees of freedom, which are averaged out by the coarse graining is properly accounted for.

In simple terms coarse graining methods are characterized by the physical quantities, which the models of different levels are supposed to reproduce as accurate as possible. Generally one can distinguish
- Structure based
- Force based
- Potential energy based

approaches, where the first ansatz most directly allows for a forward and backward mapping of the investigated systems. All three schemes face the problem of

determining the coarse grained interactions based on the underlying more microscopic model. Again there are three methods, which are frequently employed. Based on detailed simulations of the high resolution system, interaction potentials are derived from

- (Iterative) Boltzmann inversion of distribution functions
- Inverse Monte Carlo sampling
- Force matching.

In principle all three methods of calculating interactions can be used for the different mapping schemes. A test comparing them for liquid SPC/E water, liquid methanol, liquid propane, and a single chain of hexane has been recently undertaken.[31]

Generally, structure-based methods provide CG interactions that reproduce a predefined target structure, often described by a set of radial distribution functions obtained from all-atom molecular simulations,[32–34] are well suited to reinsert atomistic coordinates. It is not clear whether they are equally well suited to reproduce thermodynamic properties of the system. Note that there is currently intensive research being carried out to investigate, whether—and if yes how—it is possible to derive coarse grained potentials that are both thermodynamically as well as structurally consistent with the underlying higher resolution description.[28,35]

An at first sight principally different methodology is the force matching method which has been applied to a multitude of soft matter, in particular biomolecular systems.[10,36] Here, the CG force field is determined such that the difference between the (instantaneous) CG forces and the forces in the underlying atomistic system are minimized. It can be shown that this method (in principle) determines a many-body multidimensional potential of mean force describing the CG representation of the system, thus being related to other structure-based CG methods, which usually rely on pair potentials of mean force.[37] The rather global (multibody) structural representation however bears the problem that the link to the underlying structure and the reproduction of local structural properties such as pair distributions may be rather weak. An exact reproduction of the underlying atomistic problem by force matching potentially requires the introduction of higher order interactions and forces.[31]

4 An example: structure-based coarse graining—from polymers to biomolecules

The general aim in structure-based coarse graining is to reproduce structural properties, either determined experimentally or from a higher resolution (atomistic) simulation. Below we will, in addition to references to the literature, give a few examples from work of the Mainz group, which range from classical amorphous polymers to relatively small biomolecules, as shown in Fig. 4. Though the latter are significantly smaller, the complexity compared to a isotropic homopolymer melt is significantly increased.[8,34,38–44]

Often the set of CG interaction functions is separated into bonded/covalent and nonbonded potentials. This approach relies on the assumption that the total potential energy U^{CG} can be separated into the respective contributions

$$U^{CG} = \sum U_{B}^{CG} + \sum U_{NB}^{CG} \tag{1}$$

Following this separation ansatz we will first discuss the derivation of bonded (covalent, intramolecular) interaction potentials and possible implications of interdependet/correlated degrees of freedom. This separation ansatz is also important in the context of transferability of CG models. Assuming such a strict separation means that the intramolecular bonded/covalent CG interactions should be independent of the special scientific problem, i.e. of the surroundings of the molecules.
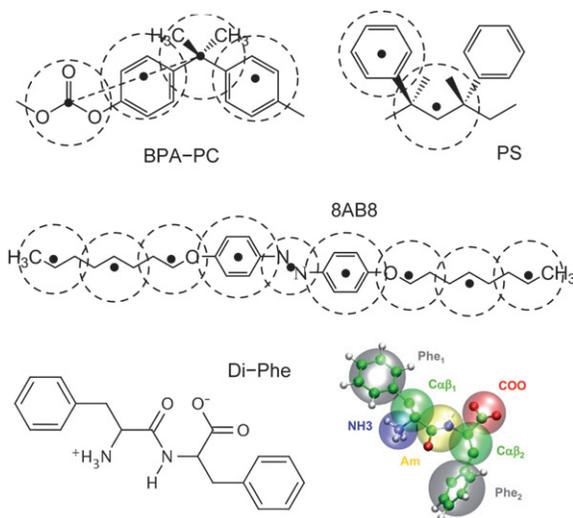
Fig. 4 Chemical structure and mapping schemes of some discussed CG examples: BPA-PC, Polystyrene (PS), the liquid crystalline compound 8AB8, and a small dipeptide (diphenylalanine).

4.1 Bonded/covalent interaction potentials

Bonded interactions are derived such that the local conformational statistics of the molecules is represented correctly in the CG model. These conformational distributions P^{CG} are usually characterized by specific bond lengths r, angles θ, and torsions ϕ between any pair, triple and quadruple of CG beads respectively, i.e. $P^{CG}(r, \theta, \phi, T)$. The assumption that the different CG internal degrees of freedom are uncorrelated, leads to the factorization of $P^{CG}(r, \theta, \phi, T)$ and reads $P^{CG}(r, \theta, \phi, T) = P^{CG}(r, T)P^{CG}(\theta, T)P^{CG}(\phi, T)$. This assumption has to be carefully checked (i.e. often certain combinations of CG bonds, angles and torsions are "forbidden" on the atomistic level). For a detailed discussion of how this can be achieved for the rather complex problem of different stereoregular subunits of polystyrene we refer to a recent study by Fritz et al.[42] The individual probability distributions $P^{CG}(r, T)$, $P^{CG}(\theta, T)$, and $P^{CG}(\phi, T)$ are then Boltzmann inverted to obtain the corresponding potentials:

$$U^{CG}(r, T) = -k_B T \ln (P^{CG}(r, T)/r^2) + C_r \qquad (2)$$

$$U^{CG}(\theta, T) = -k_B T \ln (P^{CG}(\theta, T)/\sin(\theta)) + C_\theta \qquad (3)$$

$$U^{CG}(\phi, T) = -k_B T \ln P^{CG}(\phi, T) + C_\phi \qquad (4)$$

with C_r, C_θ, and C_ϕ being irrelevant constants used to set the minima of the respective potentials to zero. These potentials are in fact potentials of mean force, ergo free energies and consequently temperature dependent (not only due to the prefactor $k_B T$) and are either given in a tabulated form or determined by a fitting procedure.[34,39,40,45] Experience shows that a given parametrization is usually valid over typical temperature range of the order of ±10–20% (if no phase transition is within that range).

It is however also possible to determine the CG internal degrees of freedom based on distributions obtained from an atomistic simulation of the polymer melt.[33] In the latter case one obtains potentials for bonded and nonbonded interactions simultaneously based on the same melt (through iteration as described below).

Consequently all interaction functions are interdependent, *i.e.* there is no clear separation between covalent and nonbonded interaction potentials.

While the above clear separation of bonded and nonbonded interactions is desirable from a statistical mechanical point of view, the derivation of meaningful bonded potentials from an isolated single molecule requires that the conformational sampling of the isolated molecule and in the bulk (or solution) phase do not differ substantially. In biomolecular systems due to the peculiar nature of aqueous solutions (*i.e.* the presence of hydrogen bonds) this assumption can get problematic, as is illustrated by the dipeptide diphenylalanine.[43] For this dipeptide, bonded CG potentials were determined by Boltzmann inversion of the respective distributions obtained from conformational sampling of a single peptide in aqueous solution. Though bonded and nonbonded interactions are not as rigorously separated, covalent and nonbonded interactions were nevertheless separately and sequentially determined. The resulting CG model of the dipeptide (after adding also nonbonded potentials) turned out to very well reproduce the conformational equilibrium of the atomistic peptide.[43,44]

4.2 Nonbonded interaction potentials

Nonbonded interactions can be introduced in a variety of ways, depending of the system and the question one is studying. For amorphous polymers, where the density is known from experimental or atomistic simulations in many cases it is sufficient just to introduce an appropriate excluded volume for the CG beads.[8,38,39] This approach has been successful for studies of polycarbonate and polystyrene. In other cases nonbonded interaction potentials between coarse grained beads are derived based on the structure of isotropic liquids of small molecules (in the case of more complex molecules such as the liquid crystalline compound 8AB8, fragments of the target molecule are used). In the second scheme, the inverse Monte Carlo or the iterative Boltzmann inversion method[32,46] can be used to numerically generate a tabulated potential that precisely reproduces a given radial distribution function $g(r)$. It should be mentioned that the solution to the problem of finding a pair potential which exactly reproduces a given radial distribution function is unique.[47] However there usually exist different pair potentials which reproduce a given structure function within a hardly noticeable error. This can be used to impose additional constraints, *i.e.* to better reproduce thermodynamic quantities[46,48–50] without disrupting the local structure.

For molecules with many different CG beads (for example biological macromolecules) or in the case of liquid crystalline molecules with anisotropic structures the procedure to determine nonbonded interaction functions is slightly more involved. In these cases it is advantageous to split the target molecule into small fragments. Such fragment-based approaches have been successfully applied to the liquid crystalline compound 8AB8[34] (see also Fig. 4) or for the interaction of BPA-PC with metal surfaces.[38,51,52] However, there the problem of transferability of the fragment based potentials to the interactions of the large molecules has to be tested with great care.[52,53] Nevertheless, the procedure to derive CG potentials from chain fragments and low molecular weight liquids does open up the possibility to reuse certain CG potentials for reoccurring building blocks (such as alkyl or phenyl groups).

5 Backmapping

Various approaches have been employed to reinsert atomistic details into a CG structure or simulation trajectory. It should be noted that this "backmapping" or inverse mapping problem has in general no unique solution since every CG structure corresponds to an ensemble of atomistic microstates. For coarse grained polymeric melts it is possible to obtain backmapped atomistic structures by taking rigid all-atom chain fragments obtained from a correctly sampled distribution of all-atom

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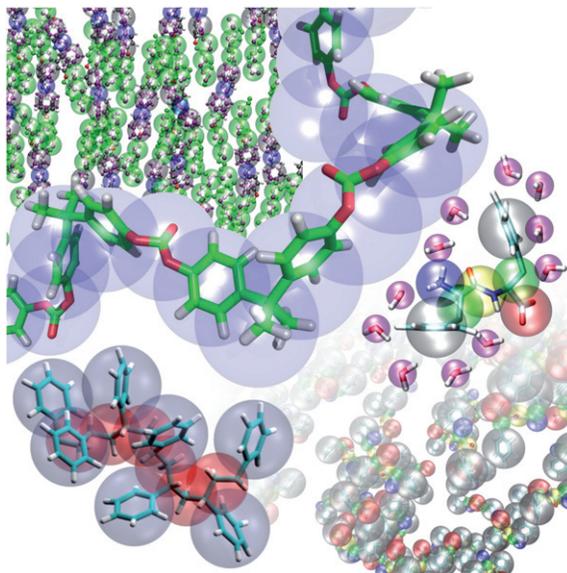
Fig. 5 Coarse grained superimposed with backmapped atomistic structures of a BPA-PC chain and a polystyrene oligomer, of liquid crystalline 8AB8 (upper left corner), of the aggregates formed by diphenylalanine (lower right corner) and a single diphenylalanine molecule with its water shell.

chain structures.[8,39,54–56] This works, if the structural relaxation and diffusion of molecules is slow compared to the local equilibration of the newly introduced atomistic coordinates. The case of more flexible low-molecular weight molecules requires the introduction of constraints in order to avoid the atomistic structure from drifting/diffusing too far from the CG.[34,43,44,57] Fig. 5 shows the result of the backmapping procedure for a few systems: a BPA-PC and a polystyrene chain, a snapshot of liquid crystalline 8AB8, a snapshot of the aggregates formed by diphenylalanine and a single diphenylalanine molecule with its water shell.

The combination of CG simulations with an efficient backmapping methodology is a powerful tool to efficiently simulate long time scale and large length scale soft matter processes and in the end to obtain well-equilibrated atomistic structures and trajectories. For example, the relevant time scale of many NMR experiments requires simulations beyond what is possible with atomistic models. Nevertheless, atomistic coordinates are often necessary to compare with experimental results, an important example for the use of backmapped CG trajectories.[54,58] In a slightly different manner one can also utilize inverse mapped structures in further computation. For example in order to obtain data for solubilities or permeabilities of small molecules in polymeric systems one can combine coarse grained simulations to obtain well equilibrated structures of the polymeric melt with atomistic free energy calculations based on the inverse mapped trajectories.[59–61] In a rather early study of phenol in BPA-PC phenol was introduced into remapped polycarbonate melts at a variety of temperatures. There it could be shown how the diffusion of the phenols coupled to the local fluctuations of the polymeric matrix.[62]

Another promising application of the combination of coarse grained simulations with a backmapping procedure is the possibility to validate the underlying atomistic force field—on time and length scales not accessible to atomistic simulations alone due to sampling problems.

6 Dynamics: coarse grained *versus* atomistic

The construction of a coarse grained model automatically determines the length scaling between the linked models. However, for dynamics this is not the case at all. We want to illustrate this here for the example of polymers. For both simple continuum as well as lattice polymer models it is known that such simulations reproduce the essential generic features of polymer dynamics; that is, the crossover from the Rouse to the entangled reptation regime, qualitatively and to a certain extent quantitatively.[19] Such simple polymer models are, in view of the present discussion, just another set of different polymers. Properly scaled they all follow the same rules. For short chains the longest relaxation time $\tau_R \propto N^2$ and for long chains in a polymer melt we observe a $N^{3.4}$ power law. However, a proper link between the atomistic representation of a system and the corresponding structurally coarse grained system can provide absolute dynamical information without the need to resort to generic scaling laws. Actually, eventually one should recover them as well. Thus one aims at a predictive quantitative modeling of diffusion, viscosity, rates, and correlation times, *etc.* of dynamic events.

This automatically generates the additional question of the minimal time and length scales CG simulations apply to. First it is important to realize that the coarse grained models are, from a simulation point of view, independent models with their own intrinsic dynamics. In the case of the previously discussed polystyrene and BPA-PC simulations one can deduce a typical simulation time scale, as it is traditionally done in MD simulations. Taking the strength of the interaction parameter in the nonbonded excluded volume interaction ε_{CG} (measured in units of the temperature), the average mass m_{CG} of the CG beads and the known length scales σ_{CG} one can determine the intrinsic time scale of the CG simulation[†] from $1\tau = 1(m_{CG}\sigma_{CG}^2/\varepsilon)^{1/2}$. This results for instance in $1\tau = 1.7$ ps for BPA-PC at 570 K and $1\tau = 1$ ps at $T = 463$ K for atactic polystyrene, respectively.[41,63] While these are the natural time scales of the CG model, this does not have to be the time scale of the underlying atomistic model at all. The CG interaction potentials are much smoother, barriers are lower *etc.*, resulting in significantly accelerated dynamics. Beyond the reduction of the number of degrees of freedom this is the main reason for the speed up due to coarse graining.

On the other hand, on length scales above the specific scale of the coarse graining we expect qualitatively the same behavior for the CG chains as for the atomistic chains, certainly on scales where generic properties dominate. This offers a direct way of deducing the time scaling between the CG model and the underlying atomistic model by matching the curves of the mean square displacements of the beads or the center of mass of the whole chain. Since the lengths are fixed by the mapping procedure itself the mean square displacements can be matched just by shifting the time scales. It is however important that the curves of the atomistic and CG mean square displacements not only meet in a point, but rather coincide from a characteristic point onwards, as will be discussed below. Fig. 6 shows a typical result for polystyrene.[64] This procedure leads for the two examples mentioned above to the time scaling of $1\tau = 400$ ps for PS at $T = 463$ K and 30 ps for BPA-PC at $T = 570$ K, respectively. Of course, as this example already illustrates different levels of coarse graining and different CG models lead to different time scales. Also it should be noted that the time scaling factor can be chain-length dependent, since the melt density varies as a function of chain length for polymers below the entanglement molecular weight (see Fig. 6).

The data, on which Fig. 6 is based on, however, reveals more important information. Looking at the displacements of the individual beads, rather than the center of

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† Note that the resulting time scale τ depends on the choice of masses, if the CG model contains different beads. Thus there is some arbitrariness in the value of τ if one wants to use physical units.

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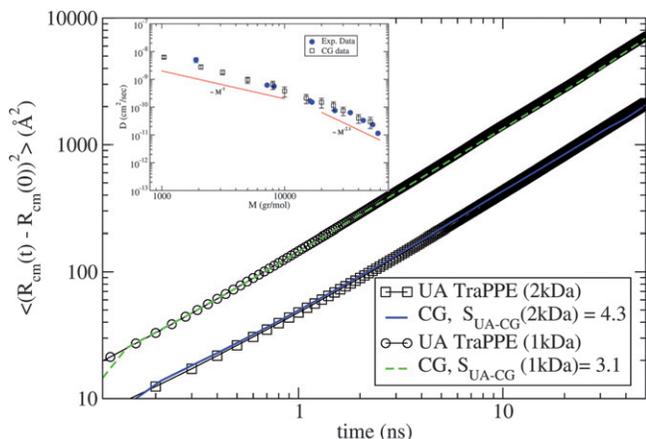
Fig. 6 Mean square displacements of centers of mass of coarse grained and atomistic (united-atom) polystyrene (PS) simulations as a function of time for two different chain lengths. By shifting the CG data along the time axis the time scaling can be obtained. To obtain the real time scaling in another step the united atom (UA; here hydrogens are lumped into carbon superatoms) and the atomistic (AA) simulations have to be compared in the same way. This is necessary since atomistic simulations for PS are extremely time consuming. Because of that two different atom based methods, AA and UA respectively, are needed to obtain a first scale factor from distances, which are too small for CG simulations. The inset shows the diffusion constants for PS obtained from CG simulations based on the resulting AA-CG time scaling in comparison to experiments for a molecular weight of up to M = 50 kDa (after ref. 41,64). Note that there is no adjustable parameter in the simulation data.

mass of the chains, one finds that the motion characteristics down to the characteristic scale of our coarse graining qualitatively and quantitatively, after the appropriate time scaling, agrees to the atomistic simulations. Thus the CG runs can be used to obtain realistic atomistic trajectories. In ref. 54 it was shown for BPA-PC that atomistic dynamic structure factors can be obtained from remapped CG runs in perfect match with short time atomistic data and by this, extend the dynamic information significantly. Recently, we have shown for polystyrene that this also quantitatively predicts correct bond orientation correlation times as obtained from NMR.[64]

Methods like this not only can be used to study the dynamics of homopolymer melts, but also the dynamics of additives in such melts[65,66] and allows quantitative predictions into experimentally extremely difficult to access regions. It should however be kept in mind that the time scaling factor for the additive might differ from that of the host polymer.

7 Variable/adaptive resolution methods

So far we have only mentioned methodologies, where the whole system is studied on a single level of resolution. In many cases, however, this is not desirable or even does not allow the investigation of important problems. To overcome this, methods have been developed over the last years which allow various levels of resolution within one simulation.

A classical problem in this context is crack propagation in solids. There the breaking of a chemical bond is treated by quantum mechanical methods. Beyond the immediate tip of the crack classical force field simulations suffice and beyond that the particles are coupled to continuum finite element like models, which properly can take care of more global stress and strain fields. The hierarchy of modelling is well defined and a given atom might at the beginning be treated quantum
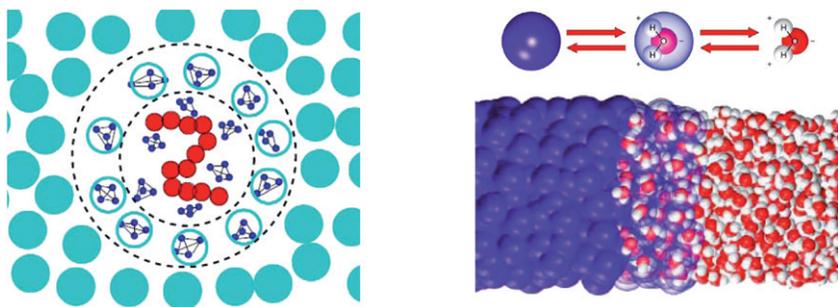
Fig. 7 Illustration of adaptive resolution simulations using the AdResS method. On the left is a small polymer chain in a good solvent of tetrahedral molecules.[81] They adjust their resolution depending on the region they are in, when they cross through the transition regime. The sphere with the "all atom" solvent, which also contains the polymer, diffuses with the chain. On the right the method is illustrated for the simulation of water.[82] The scheme on top indicates the change from an all atom (TIP3P) water to a single sphere model. The water molecules are free to move around and adjust their resolution to the region they are in.

mechanically, then classically and then eventually merges into the continuous description.[67,68]

For soft matter, especially biopolymers, a somewhat different approach has been very successful. Since there is no crystal structure and the systems are more strongly fluctuating it is decided from the very beginning which atoms are treated quantum chemically and which are treated by a classical force field. This so called QM/MM method turned out to very well describe local, quantum-effect dominated phenomena, while the surrounding can be treated classically.[69]

While such methods mark significant progress for a multiscale, or better dual or triple scale, description of materials, they all suffer from the problem that from the very beginning one has to determine, which atom/particle is going to be described on what level. There is no dynamic forward and backward exchange of resolution. Thus it is not possible to study liquids or strongly fluctuating systems by the above methods. One would like to be able to zoom in on demand and treat a dynamic equilibrium between different levels of resolution. Thus atoms/molecules should be allowed to change the level of resolution on the fly. By such a method one can focus on local phenomena, while keeping equilibrium with a greater surrounding, *i.e.* aggregation or adsorption/desorption phenomena. The idea is illustrated in Fig. 7. The condition of equilibrium and free exchange between regions of different levels of resolution poses special difficulties. Recently, an adaptive resolution simulation method (AdResS) has been developed, which allows for adaptive coupling of such different levels.[48,70,71] In a recent extension this method has also been coupled to an outer continuum, devising a way towards open system molecular dynamics.[72]

8 Conclusions and outlook

The general challenge that lies in coarse graining and generally in reducing the number of degrees of freedom of a computational model is to incorporate the (average) effect of the eliminated degrees of freedom into the lower resolution model. We have summarized different developments which are currently pursued with the aim to design coarse grained models that are both thermodynamically and structurally consistent with an underlying atomistic simulation model. This consistency is of particular importance for coarse grained models that are to be used in a multiscale simulation framework where different simulation hierarchies are combined and linked to obtain an approach that simultaneously addresses phenomena or properties of a given system at several levels of resolution and consequently on several time

and length scales. Such multiscale approaches are of great importance in the investigation of complex soft matter systems such as biological and synthetic materials where phenomena on a wide range of scales "team up" to determine the overall (material) properties.

The development of these methods is one of the major methodological efforts in computational chemistry and physics. Scale-bridging approaches can operate on varying levels of "interaction" between the individual scales: the examples shown in the present article mainly combine models on different scales *via* treating them separately and sequentially, *i.e.* they pass information (in the present cases structures) between the levels of resolution. Other resolution exchange methods use the exchange (of the whole system) between simulations at different levels of resolution during the course of the simulation as a means to enhance sampling.[73–75] In the case of hybrid simulations, different levels of resolution are present simultaneously in one system. This is more complex than the sequential approach since interactions between entities at different levels of resolutions have to be devised. Hybrid approaches are widely used in the field of mixed quantum mechanical/classical simulations. The statistically mechanically consistent treatment of such problems has been addressed in methods that allow for individual molecules to adaptively switch between resolution levels on the fly.[48,70–72]

Even though we can now look back at more than a decade of intensive research along the lines discussed above, there are still a number of challenges which require a continued and even stronger effort. Specific problems/challenges are

- Non bonded interactions
- Time mapping
- Efficient and appropriate mapping schemes
- True multiscale simulations of disordered/fluctuating systems.

How delicate the problem of nonbonded interactions is can already be seen for the question of phase segregation in polymer mixtures. In order to hit the transition temperature an accuracy of the interactions of $O(k_BT/N)$ is needed (N being the chain length). This is beyond any predictive theoretical possibilities. Additional problems occur for solvent mediated or directional interactions, which are of special relevance for biomolecules and/or aggregation phenomena. One of the various reasons for these problems lies in the huge abundance of hydrogen atoms for which a classical description even at room temperature often is questionable. Actually, summing up typical uncertainties in the interactions along, *i.e.* a heteropolymer or a protein, one easily arrives at error bars of the size or even larger than the basin of attraction of the folded state.[76] Thus we expect in the future that appropriate coarse grained simulations might even be employed to improve underlying force fields.

The problem of time mapping is a key to understanding dynamical processes. Here however we encounter significant technical and principal problems. As shown for polymers, time scaling between different levels of resolution can be derived and leads to very good results. However such a single scaling factor does of course not work for very short times and is also chain length dependent. Thus the motion of a single additive molecule in a polymer matrix can follow a different time scaling than the matrix itself. This can for instance mean that, mapped back to an atomistic picture, the "different clocks" can lead to diverging time differences. To cure these problems significant further work is needed.

Both previous points are linked to the question of what is the most appropriate mapping scheme. So far groups of atoms are typically lumped together into one coarse grained particle and the appropriate bonded and nonbonded interactions are determined. The grouping is guided by the chemical structure and the question of investigation. For instance for many problems in polymer physics the crossing of chains cannot be allowed, while for some problems that is not crucial at all. So far this very much relies on the intuition and knowledge of the investigator and there are no systematic formal procedures. Here physics based formal concepts could be of tremendous help.

Taking all these aspects together we can expect very significant progress, when it comes to true multiscale simulations of strongly fluctuating and disordered systems. Here we do not only think of biological systems but also of other complex aggregates as they are studied, for example, in the context of organic electronics or of a molecularly based study of non equilibrium phenomena. With the coming new hardware, plain CPU time will probably, for the most part, not be the central issue in the future. However then we are, in a positive sense, back at the beginning, where ideas of coarse graining were more directly linked to the understanding of basic physical phenomena in soft matter physics.

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