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#### **Statistical Physics Problems in Adaptive Resolution Computer Simulations of Complex Fluids**

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**Abstract** Simulating complex fluids or in general complex molecular systems requires approaches covering decades of time and length scales. This usually cannot be achieved within one simulation model. Over the years many different methods and models have been developed ranging from rather generic models, representing most efficiently the universal statistical mechanical properties of e.g. polymers, to all atom models and even quantum mechanical treatments. While these allow for scientifically very important studies in their own right, only a combination and close link between models of different levels allows for a truly quantitative description of materials and processes. In the present contribution we discuss an adaptive resolution approach where different levels of detail are treated within one simulation and the molecules are free to diffuse between different regions in space, where the molecules interact with different interaction potentials.

Keywords Coarse-graining · Multiscale simulation · Adaptive resolution · AdResS

#### 1 Introduction

Soft matter or complex fluids are abundant in nature as well as in modern technology as they include all biological tissues as well as synthetic macromolecular materials from simple plastics to high tech materials in electronics. Despite their importance still many basic properties are only purely understood. These properties might resemble structural and dynamical aspects or, on a more complex level, function such as light harvesting to name one

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of the most complicated ones. In almost all cases these properties are determined by a variety of processes and interactions originating from a wide range of time and length scales. Of course eventually everything can be traced back to atomistic interactions based on quantum mechanics. This however is neither practically possible nor—in most cases—useful when it comes to complex (macro-)molecular systems. Instead different properties require different levels of detail in the theoretical investigation of soft matter systems. Global conformational fluctuations for instance are very slow and coupled to diffusion processes while at the same time local fast conformational degrees of freedom determine function or drive phase transitions. Thus a description which bridges scales can be very helpful if one wants to study specific systems and if one wants to make the step from a rather qualitative or scaling type of description to a more system/material specific quantitative result or prediction. In order to achieve such a goal, there has been intense research over the last years employing a number of different approaches [1, 23, 29, 49, 51].

Scale bridging or multiscale simulations in most cases work sequentially. That means a system is treated by independent simulations runs on different levels of detail. Starting from an all atom description a coarse grained model can be parameterized in different ways in order to reproduce the (to be defined) essential properties of the underlying microscopic model. Typically coarse models are derived by a structure based ansatz [10, 13, 14, 19, 24, 25, 42, 44, 46, 50] focusing on reproducing structural aspects or based on free energy mappings [20, 21]. For the first one aims at reproducing for instance characteristic polymer conformations and molecular packing so that atomistic simulations analyzed within the coarse grained framework match as closely as possible the same structural properties (e.g. radial distribution functions, chain radius of gyration etc.) of the coarse grained simulations. These approaches have been quite successful for the study of different polymer melts in bulk and close to surfaces as well as liquid crystalline systems and more recently small aggregating biomolecules in solution [28, 52, 53]. Though quite successful, it is very difficult to study phase transition by such a method, since the equation of state of the coarse grained and the underlying all atom model usually are different. The reason is quite simple, as in a practical renormalization group step a coarse graining step integrates out degrees of freedom and includes necessary approximations. These approximations are state point dependent and give rise to problems in transferability from one physical situations to another. This currently is matter of intense research. On the other hand free energy based methods do better here by the very construction, however there it often is quite difficult if not impossible to keep a close link to conformations and morphology. This problem also sometimes is quoted as representability issue of coarse graining.

Though very successful for many questions even including polymer dynamics, the above short introduction shows that rather inhomogeneous systems or systems subject to strong fluctuations are difficult to deal with on the basis of a sequential multiscale approach. For them it would be of advantage to perform a simulation on a rather coarse level and only focus on "interesting regions" like using a magnifying lens. This is the idea of adaptive resolution simulations, as illustrated in Fig. 1. Following such a concept as closely as possible however requires a number of measures. Taking the magnifying glass analogy everywhere the same Hamiltonian should be used. This however is exactly what one wants to avoid. To treat the microscopic region as if it was embedded in a truly large environment one first has to assure full equilibrium with its surrounding, that is molecules can freely diffuse from one regime to another without experiencing any barrier which might manipulate the fluctuation spectrum. Second, the system should be set up in a way that any analysis of a full microscopic simulation on the very same subvolume. This is achieved by the so called AdResS (Adaptive

**Fig. 1** Adaptive resolution simulation: zooming in/out into a region of interest



Resolution Simulation) scheme [31, 34, 37]. In the following we first explain some basics of the approach and then discuss in some more detail some specific problems of the transition regime, which is needed to interpolate between microscopic and the mesoscopic region.

#### 2 Adaptive Resolution Simulation

To present the underlying idea of adaptive resolution we consider a homogeneous liquid of N molecules in a box of volume V. We divide the box into two equally large domains that freely exchange molecules. In the first domain *ex*, the region of specific interest, we represent molecules on a high resolution level whereas in the second domain *cg* we use a lower coarse-grained representation of the very same molecular system.<sup>1</sup> The two domains are in thermodynamical equilibrium, i.e.,

$$\mu_{ex} = \mu_{cg}, \qquad p_{ex} = p_{cg}, \qquad T_{ex} = T_{cg}, \tag{1}$$

where  $\mu_{ex}$ ,  $p_{ex}$ ,  $T_{ex}$  and  $\mu_{cg}$ ,  $p_{cg}$ ,  $T_{cg}$  are the chemical potentials, pressures, and temperatures of the liquid in the *ex* and *cg* domains, respectively [34, 37, 39]. Based on this together with the condition of free molecular exchange between the regions, each subsystem simulation can be considered as run in the  $(\mu, V_{sub}, T)$  ensemble, with  $V_{sub}$  being the volume of each subsystem. The number *n* of explicitly considered degrees of freedom (DOFs) per molecule differs in the different domains and generally is higher in the *ex* domain than in the *cg* domain.<sup>2</sup> Accordingly, the value of the free energy, which is an extensive quantity, is higher in the *ex* domain than in the *cg* domain. The respective free energy density F = F(x) profile (associated to the DOFs that we explicitly consider in the simulation) therefore is expected to take a form as depicted in Fig. 2. In order to facilitate a smooth

<sup>&</sup>lt;sup>1</sup>This restriction we will later on not need anymore.

<sup>&</sup>lt;sup>2</sup>In the *cg* model we reduce the many body potential of the *ex* representation into a reduced effective potential and retain only two-body terms (higher order terms are omitted for numerical efficiency). We omit the one-body terms, which depend only on the temperature and hence do not contribute to the intermolecular forces [17]. These terms can be viewed as the equivalent of a latent heat. If we kept them the free energy profile in Fig. 2 would be flat.



Fig. 2 Sketch of the free energy density profile across the system: coupling two different resolutions [39]

transition between the two resolutions when molecules pass from one regime to another we introduce a transition hyb regime, filled with hybrid molecules (see Fig. 2), at the interface. Consequently the number of explicitly treated DOFs n for each molecule varies along the x coordinate from  $n_{ex}$  in the explicit region to  $n_{cg}$  the coarse region, respectively, while we have  $n_{hyb} = n(x)$ , as discussed below. The system is in equilibrium and hence:  $\lim_{x \to d^-} \frac{\partial F_{ex}(x)}{\partial x} = \lim_{x \to d^+} \frac{\partial F_{cg}(x)}{\partial x} = 0 \implies \lim_{x \to d^-} \frac{\partial n_{ex}(x)}{\partial x} = \lim_{x \to d^+} \frac{\partial n_{cg}(x)}{\partial x} = 0$ and  $\partial F_{ex}/\partial N_{ex} = \mu_{ex}$  and  $\partial F_{cg}/\partial N_{cg} + \phi = \mu_{cg}$ , where  $\phi$  is the free energy per molecule associated with DOFs, which are integrated out. The free energy density profile allows us to define a weighting function w that determines the level of resolution across the system [34] (see Fig. 3). We introduce w = w(x) in such a way that w = 1 and w = 0 correspond to the ex and cg representations, respectively, while the values 0 < w < 1 correspond to the transition regime. While crossing the transition regime n changes continuously. This leads to a continuous change in the dimensionality of the phase space associated with a particular switching DOF [39, 40]. To describe the continuous change of the phase space dimensionality in a mathematically consistent way we resort to fractional calculus [3, 11, 27, 47, 48]. Any switching on or off of DOFs simply in terms of amplitude would correspond to a cooling/heating of modes in the system, which is not what we want to do here.

#### 2.1 Transition Regime: Fractional Degrees of Freedom

For computing thermodynamic properties, e.g., temperature, the phase space of a fully switched-on DOF with w = 1 has its full dimensionality. On the other hand, if a given DOF is completely switched-off, i.e., w = 0, it does not contribute to any statistical average and its dimensionality is zero. In the transition regime, a partially switched-on DOF contributes to statistical averages according to its weight w, can be interpreted as its fractional dimensionality.<sup>3</sup> To quantitatively determine this contribution, we divide the transition regime into thin slabs each with different but constant values w between 0 and 1.

<sup>&</sup>lt;sup>3</sup>As mentioned before the weight w is not to be confused with an amplitude. If one "froze out or in" DOFs that would literally lead to frozen systems, making the free exchange between the two liquids essentially impossible.



For a quadratic DOF *i* with fractional dimension w and amplitude  $p_i$  we can then write the partition function as:

$$\exp(-\beta F_i) = C \int \exp(-\beta p_i^2/2) dV_w$$
$$= 2C \int_0^\infty \exp(-\beta p_i^2/2) |p_i|^{w-1} \frac{dp_i}{\Gamma(w)}$$
$$= \frac{2^{w/2} C \Gamma(w/2)}{\Gamma(w)} \beta^{-w/2} \sim \beta^{-w/2}, \qquad (2)$$

where  $dV_w = |p_i|^{w-1} dp_i / \Gamma(w) = dp_i^w / (w\Gamma(w))$  is an infinitesimal volume element of the fractional configurational space and  $\Gamma$  is the gamma function [39] and  $\beta = 1/k_B T$  the inverse temperature with  $k_B$  being the Boltzmann constant. Then the average kinetic energy is given as  $\langle K_w \rangle = \frac{d(\beta F_i)}{d\beta} = \frac{w}{2\beta} = \frac{wk_B T}{2}$  for fractional quadratic DOF *i* with the weight *w*. This generalization of the equipartition principle to fractional quadratic DOFs [39, 40] allows to define a temperature in the transition regime and in equilibrium  $T_{ex} = T_{cg} = T_{hyb} = T$  with  $n_w \sim w$ . The precise definition of a temperature in the transition region enables us to employ the local thermostat to control the free energy difference between different levels of resolution. As shown below this is needed in an adaptive resolution scheme.

The kinetic energy part of the free energy for a generic quadratic switchable DOF i is [31]

$$F_i = \mu_i^{kin}(w) = -k_B T \log\left[\int e^{-\beta p_i^2} d^w p_i\right].$$
(3)

The analytical solution of (3) is:

$$\mu_i^{kin}(w) = Ck_B T\left(\frac{w}{2}\right) \log(T) + k_B T \log \frac{\Gamma(\frac{w}{2})}{\Gamma(w)}$$
(4)

where *C* is a constant. Equation (4) is the ideal gas kinetic contribution to the chemical potential coming from the internal DOFs. The second term in (4) is negligible in the temperature regime of interest [31]. The kinetic part of the free energy thus depends in the first

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order linearly on w, which determines the slope of the free energy density profile in the transition regime presented in Fig. 2.

The total contribution of the entire set of switchable DOFs per molecule is

$$\mu^{kin}(w) = \sum_{DOF} \mu_i^{kin}(w).$$
<sup>(5)</sup>

As defined by (3) and (5),  $\mu_{cg}^{kin} = \mu^{kin}(0) + \phi(0)^{kin} = \mu_{ex}^{kin}$ .  $\mu^{kin}(w)$  thus represents only the explicit contribution of the partially switched-on DOFs (with the weight w) to the kinetic part of the chemical potential and thus usually  $\mu^{kin}(0) \neq \mu_{cg}^{kin}$ . The remaining (internal) kinetic part of the chemical potential is included in the kinetic component of  $\phi$ , i.e., the latent heat, defined as

$$\phi(w)^{kin} = \mu_{ex}^{kin} - \mu^{kin}(w). \tag{6}$$

Commonly, in single-resolution simulations the kinetic contribution to the chemical potential is ignored being only a trivial constant depending only on temperature, i.e. the ideal gas contribution [17]. In our case, each DOF in the transition region contributes differently according to the corresponding value of w(x). Hence, the latent heat defined by (6) is crucial for keeping the thermodynamical equilibrium between two levels of resolution in the adaptive resolution simulations.

#### 3 The Adaptive Resolution Scheme (AdResS)

Following the above considerations, we couple the two levels of resolution in a molecular dynamics simulation using a force-based scheme AdResS [34]. The interpolation formula for the pair force between molecules a and b employed in AdResS is

$$\mathbf{F}_{ab} = w(x_a)w(x_b)\mathbf{F}_{ab}^{ex} + \left[1 - w(x_a)w(x_b)\right]\mathbf{F}_{ab}^{cg}$$
(7)

where  $\mathbf{F}_{ab}^{ex}$  is the total intermolecular atomistic force taking all details of the fine grained region into account and  $\mathbf{F}_{ab}^{cg}$  is the total intermolecular force obtained from the effective cgpotential, w(x) is the weighting function and depends on the center of mass positions  $x_a$  and  $x_b$  of the two interacting molecules a and b. The above AdResS scheme allows a molecule to smoothly find its correct orientation in the liquid once it is given a random orientation at the low resolution/transition regime boundary (see Fig. 2). As the molecule approaches exdomain the atomistic interactions are gradually turned-on and the molecule on-the-fly finds its proper orientation based on the interaction with the surrounding.

In (7) forces and not interaction potentials are interpolated. This is crucial for local linear momentum conservation and proper diffusion of molecules across the transition regime. One could, in principle, also define the mixing scheme using the respective potentials instead of forces, which has been attempted in Refs. [7, 26]:

$$V_{ab} = w(x_a)w(x_b)V_{ab}^{ex} + \left[1 - w(x_a)w(x_b)\right]V_{ab}^{eg}.$$
(8)

<sup>&</sup>lt;sup>4</sup>In an isolated *cg* simulation one can omit  $\phi(0)^{kin}$  term because it depends only on temperature and does not enter into pair forces. One can then say the *cg* model has certain DOFs and one starts from there. But if we keep track that this *cg* model was derived from a more detailed one then we have to keep the free energy contribution of those integrated out DOFs because they are still there—we just do not consider them explicitly. This is the internal part—or what one might consider analogous to a latent heat.

However, this approach violates Newton's Third Law [6, 39, 40]. In (8) the potential energies between two particles depend on their absolute positions of the particles and not only on their relative distances. The associated conservative force acting on the molecule *a* is

$$\mathbf{F}_{ab} = -\frac{\partial V_{ab}}{\partial \mathbf{r}_{a}}$$
  
=  $w(x_{a})w(x_{b})\mathbf{F}_{ab}^{ex} + [1 - w(x_{a})w(x_{b})]\mathbf{F}_{ab}^{cg}$   
+  $\left(\frac{\partial w(x_{a})}{\partial x_{a}}w(x_{b})[V_{ab}^{cg} - V_{ab}^{ex}], 0, 0\right),$  (9)

where  $\frac{\partial}{\partial \mathbf{r}} = (\frac{\partial}{\partial x}, \frac{\partial}{\partial y}, \frac{\partial}{\partial z})$ ,  $\mathbf{F}_{ab}^{ex} = -\frac{\partial V_{ab}^{ex}}{\partial \mathbf{r}_a}$ , and  $\mathbf{F}_{ab}^{cg} = -\frac{\partial V_{ab}^{cg}}{\partial \mathbf{r}_a}$ . The expression in (9) for the force differs from the corresponding expression given by (7) by the additional term  $\frac{\partial w(x_a)}{\partial x_a} w(x_b) [V_{ab}^{cg} - V_{ab}^{ex}]$  in the *x* component of the force. The respective force acting on the molecule *b* is in this case

$$\mathbf{F}_{ba} = -\frac{\partial V_{ab}}{\partial \mathbf{r}_{b}}$$

$$= w(x_{a})w(x_{b})\mathbf{F}_{ba}^{ex} + \left[1 - w(x_{a})w(x_{b})\right]\mathbf{F}_{ba}^{cg}$$

$$+ \left(\frac{\partial w(x_{b})}{\partial x_{b}}w(x_{a})\left[V_{ab}^{cg} - V_{ab}^{ex}\right], 0, 0\right).$$
(10)

Using  $\mathbf{F}_{ba}^{ex} = -\mathbf{F}_{ab}^{ex}$  and  $\mathbf{F}_{ba}^{cg} = -\mathbf{F}_{ab}^{cg}$  we obtain

$$-\mathbf{F}_{ba} = w(x_a)w(x_b)\mathbf{F}_{ab}^{ex} + \left[1 - w(x_a)w(x_b)\right]\mathbf{F}_{ab}^{cg} - \left(\frac{\partial w(x_b)}{\partial x_b}w(x_a)\left[V_{ab}^{cg} - V_{ab}^{ex}\right], 0, 0\right).$$
(11)

In order that the force given by (9) satisfies Newton's Third Law, i.e.,  $\mathbf{F}_{ab} = -\mathbf{F}_{ba}$ , we see from (9) and (11) that

$$\frac{\partial w(x_a)}{\partial x_a} w(x_b) = -\frac{\partial w(x_b)}{\partial x_b} w(r_a)$$
(12)

implying that

$$\frac{1}{w(x_a)}\frac{\partial w(x_a)}{\partial x_a} = -\frac{1}{w(x_b)}\frac{\partial w(x_b)}{\partial x_b} = const. = 0.$$
(13)

From (13) it follows that the force defined by (9), although it is conservative, can satisfy Newton's Third Law only for a trivial case of w(x) = const. corresponding to constant resolution simulations. In order that diffusion of molecules between regions with different resolution is not perturbed by the resolution change, the conservation of momentum dictated by the Newton's Third Law is crucial in adaptive resolution MD simulations. Hence, starting with (8) has a clear disadvantage in adaptive resolution MD simulations. Therefore in AdResS we follow the scheme of (7).

Each time a molecule leaves (or enters) the *cg* region it gradually gains (or loses) its e.g. vibrational and rotational DOFs while retaining its linear momentum. Note that in the *cg* domain each molecule represents many orientations and conformations of the corresponding

molecule in the *ex* domain. Because of this, going back and forth between the representations in the transition regime, one does not exactly reproduce the atomistic coordinates and velocities. The reverse-mapping thus destroys time-reversibility in the simulation. Since time reversibility is essential for energy conservation [15], AdResS does not conserve energy. In particular, the force in (7) is in general not conservative in the transition region (i.e., in general  $\oint \mathbf{F}_{ab} \cdot \mathbf{dr} \neq 0$ ) [6, 40]. Hence, to supply or remove the latent heat associated with the switch of resolution (see (6)) a locally acting thermostat is needed, we usually use a DPD thermostat [16, 45]. The thermostat forces do not enter into the AdResS interpolating scheme, (7), instead they are added to the AdResS [34].

Once the above requirements are fulfilled the construction of  $\mathbf{F}_{ab}^{cg}$  does not interfere with the boundary conditions required by (1) in order to keep thermodynamic equilibrium between the coarse grained and the fine grained regime. Note however that the transition region itself will require further consideration. Examples of application of the AdResS scheme (7) are a liquid of tetrahedral molecules [34, 35], a generic macromolecule in solvent [36], and liquid water [22, 41] and the solvation of fullerenes in water [18].

#### 4 Generalizations and Extensions

#### 4.1 Thermodynamic Force

To practically perform adaptive resolution simulations requires not only thermodynamic equilibrium between the coarse grained and the fine grained regime. Also the absence of a barrier is necessary to allow for a free unhindered diffusion between the regions. Such barrier free exchange of molecules over the molecular resolution boundaries is required to properly account for fluctuations. Ideally this is fulfilled if the effective equation of state is the same everywhere. This however is very difficult if not impossible to achieve as various studies on coarse graining have shown and especially holds for the transition regime [37, 38]. In general, even though (1) is fulfilled, there is no guarantee that this also holds for the transition region. Actually our studies have shown that this typically is not the case leading to significant density undulations in the transition region, which in turn can produce diffusion barriers. Ideally there would be a constant density profile throughout the whole simulation box. To overcome this problem recently a generalization of AdResS [31] was introduced. In this generalized approach we extend the original scheme, (7), by subtracting a thermodynamic force  $\mathbf{F}^{TD}$  so that the total force  $\mathbf{F}_a$  acting on particle *a* reads

$$\mathbf{F}_{a} = \sum_{b \neq a} \left( w(x_{a})w(x_{b})\mathbf{F}_{ab}^{ex} + \left[ 1 - w(x_{a})w(x_{b}) \right] \mathbf{F}_{ab}^{cg} \right) - \mathbf{F}^{TD}(x_{a})$$
(14)

where  $F_x^{TD} = -\frac{\partial \mu^{exc}}{\partial x}$  and  $\mu^{exc}$  plays the role of the effective excess chemical potential due to the intermolecular interactions [31]. The aim is to arrive at a totally flat density profile throughout the whole system. Because AdResS however is a non-conservative scheme the potential  $\mu^{exc}$  is not well defined in the transition regime. To circumvent such a problem and to arrive at a first guess of the thermodynamic force we run *m* individual simulations of systems with one fixed value  $w_i$  of the transition function *w* between  $w_0 = 0$ , which corresponds to the *cg* region and  $w_{m+1} = 1$ , which corresponds to the *ex* region, respectively. At any fixed value of *w* a Hamiltonian is well defined up to a constant also for the hybrid system, allowing to calculate  $\mu^{exc}$  by standard particle insertion methods for instance. The excess chemical potential is then  $\mu^{exc}(x_i) = \mu^{exc}_{w_i}$ , where the  $\mu^{exc}_{w_i}$  is the chemical potential of



Fig. 4 The excess chemical potential  $\mu^{exc}$  and the thermodynamic force. The figure is adopted from Ref. [31]



the molecules in a bulk system of the specific representation of  $w_i$ . Repeating this procedure with all values of  $w_i$  leads to a position dependent excess chemical potential  $\mu^{exc}(x)$ , as the first guess for the second contribution to  $\phi$  [31]. In the transition region the value of win the actual simulations varies continuously. Consequently a molecule never experiences a *constant* w environment and the so determined thermodynamic force is practically the initial guess for a further iterative optimization.

As an example the excess chemical potential  $\mu^{exc}$  for a liquid of tetrahedral molecules [31] is depicted in Fig. 4.  $\mu^{exc}(x)$  is the same for w = 1 and for w = 0 because the equations of state are the same in both the *ex* and *cg* domains at the temperature and density of the simulation. Introducing the concept of a thermodynamic force allows to avoid a general problem of coupling two different systems by a simple linear interpolation of forces [35]. Figure 5 shows the original and improved density profiles in such a simulation after applying  $F_x^{TD}$  (see the inset of Fig. 4).





#### 4.2 Extension to Mixtures and Polymer Solutions

Based on the above improvements of the original approach it is possible to systematically extend this methodology to mixtures of different molecular species or polymer solutions [30]. Here the problem of avoiding any drift introduced by the transition regime requires special care and is not always treated in detail [26]. In general let us start from a mixture of two kinds of molecules for which both an all atom and a coarse grained description is available. Further let us assume that we are far enough away from any phase transition and that the coarse grained model has been parametrized by a structure based coarse graining method, so that e.g. appropriately evaluated radial distribution functions in both representations agree to each other. An example of such a system is presented in Fig. 6 for a liquid of tetrahedral molecules, which solvate another species of spherical molecules [31]. We treat the system at temperature  $T = \varepsilon/k$  and a liquid density with an atom density of  $\rho = 0.175/\sigma^3 \approx 1.0/\sigma_{cg}^3$  ( $\sigma_{cg}$  is the excluded volume diameter of the coarse-grained molecule). Here  $\sigma$  and  $\varepsilon$  are the standard Lennard-Jones parameters of length and energy, respectively. For the force field parameters and other modeling details see Refs. [34, 35]. A coarse grained model of both solvent and solute are derived from the pure atomistic simulation [31].

The treatment of a binary mixture deserves a more careful treatment, as it was shown in the previous subsection for the case of the chemical potential. Without any correction through the thermodynamic force, one observes significant density undulations in the transition region. Above we have given a theoretical interpretation of this additional force, which for mixtures would also contain cross terms between the different species. The fastest convergence however in a practical application is found in correcting the thermodynamic force of only one component per iteration, where the force is proportional to the gradient of its own density. The procedure begins from the most concentrated to the most dilute of the species. The proposed iterative formula for the thermodynamic force of component  $\alpha$  is

$$\mathbf{F}_{\alpha}^{TD^{i+1}} = C_{\alpha} \frac{1}{\rho_t} \frac{\partial p}{\partial \rho_{\alpha}} \nabla \rho_{\alpha}^i + \mathbf{F}_{\alpha}^{TD^i}$$
(15)

where  $\rho_t$  is the total particle number density and  $C_{\alpha}$  is a numerical prefactor, between 0 and 1 that will moderate the effects of the force, assuring the numerical stability of the whole process. Such a coefficient is required since the effects of mixing are neglected in

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Fig. 7 Density profiles for solvent (*top*) and solute (*bottom*) using  $C_{\alpha} = 0.3$ 

this approach. For the present example a prefactor of  $C_{\alpha} = 0.3$  turns out to be appropriate and leads in only a few iteration steps to the desired flat density profile as illustrated in Fig. 7. Actually an additional "fine tuning" correction can be applied by reducing the value of  $C_{\alpha}$  for the last iterations. The convergence also can be improved if one compensates the effect of the solvent correction in the solute and takes mixed terms into account. While not affecting the final result, less iterations are needed to obtain the required accuracy of the density profile. In general also the extension of this procedure to systems composed of more than two components is straightforward.





#### 4.2.1 Polymer Solutions: Treatment of Bonded Interactions

While mixtures of relatively small molecules already offer many opportunities for interesting studies applying adaptive resolution schemes, eventually one wants to deal with huge molecules, where only a (small) part of it is treated on an all atom basis and the rest on a more coarse level. To test such a situation we extend the above described framework to the case of a polymer chain made up of the "solutes" of the previous study solvated in a liquid of tetrahedral molecules, as illustrated in Fig. 8. Since the treatment of non-bonded interactions has already been performed for the above two component systems, we here only have to add intra molecular interactions. Because we want to be able to eventually apply this to "real" chemical species, we consider bond length, bond angle and torsion potentials.

The coarse-grained bonded potential was obtained by means of an Iterative Boltzmann Inversion calculation. Starting from the potential of mean force, the procedure converged after three iterations for a polymer composed of N = 20 monomers solvated in 2800 tetrahedral molecules within a cubic box of side length  $25.261\sigma$ . The obtained potential generates a bond distribution that shows very good agreement with a chain of the same length in explicit solvents. Also for chains composed of 50 and more monomers the bond length distribution did not change, indicating that N = 20 was sufficient to parameterize the coarse grained model.

The adaptive resolution simulations then were performed on a chain of 50 monomer beads solvated in 7000 tetrahedral molecules in a box of dimensions  $36 \times 33.458 \times 33.458\sigma^3$ . Since we are especially interested in the influence of the transition region on the average monomer density, we kept the central monomer fixed at the center of the hybrid region. The width of the hybrid region was  $12\sigma$ . The results are compared for AdResS simulations where thermodynamic force was determined previously for a mixture of solutes (monomers) and solvent at the same concentration. These forces can be further refined, particularly on the solute, by applying the iterative procedure described in the previous section. However as the results below display, for most applications that probably is not needed.

First the most simple polymer model with out any bond bending and torsion potential was tested. The static properties are listed in Table 1. There a full microscopic simulation is compared to two versions within the adaptive resolution scheme. The mean squared end to end distances, the radius of gyration as well as the hydrodynamic radius of the chain

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Table 1 Static properties of a System Explicit AdResS AdResS (TF) single freely jointed chain of length N = 50 in a tetrahedral  $\langle R_F^2 \rangle^{1/2}$  $15.5 \pm 0.4$  $16.2 \pm 0.6$  $15.7 \pm 0.6$ solvent for different adaptive resolution setups as indicated  $7.06 \pm 0.2$  $6.7 \pm 0.2$  $6.8 \pm 0.2$  $\langle R_H^{-1} \rangle^{-1}$  $6.09\pm0.09$  $5.9 \pm 0.1$  $5.9 \pm 0.1$ 0.56 0.56 0.54



**Fig. 9** Bond distributions of the model polymer under different representations

**Fig. 10** Form factor of the model polymer under different representations

agree within the error bars. Also the bond length distribution is not altered in the different simulations as shown in Fig. 9. The effective scaling exponent  $\nu$  for the chain extension as a function of chain length N, which asymptotically in good solvent is close to 0.59 in three dimensions agrees within the error bar and shows that the chain is in a good, but not very good solvent, meaning that the asymptotic regime is reached only for significantly larger chains. The exponent  $\nu$  can directly be derived from the intermediate regime of the chains form factor S(q). For  $2\pi/R_E < q < 2\pi/\sigma$  one expects for a self similar fractal  $S(q) \sim q^{-\nu}$  as also shown in Fig. 10.



Not only the average properties of the chain are not affected within the error bars by the transition region, there is, even more important for practical applications, also now tendency for a density variation as Fig. 11 shows, a criterion crucial for the soundness of the method.

So far only two body interactions have been considered. However for many polymer simulations it is important to consider angular interaction potentials as well. For the present first test we consider three and four body interactions, namely a bond and a dihedral angle interaction, which is kept the same for the polymer in both the fine and the coarse grained regime. These angular potentials are given by

$$U^{a}(\theta) = \frac{k_{\theta}}{2}(\theta - \theta_{0})^{2}$$
(16)

with  $k_{\theta} = 3 \text{ rad}^{-2} \epsilon$  and  $\theta_0 = \frac{2}{3}\pi$ , while the dihedrals are defined by

$$U^{t}(\phi) = K_{\phi}(1 + \cos\phi) \tag{17}$$

where  $K_{\phi} = 2\epsilon$ . The angle and dihedral distributions change considerably with respect to the original polymer model. However, in this case, these interactions require no reparametrization in the coarse-grained representation.



Once simulated under the AdResS scheme, the thermodynamic force on the solute requires an additional correction of two iterations. We show the bond, angle and dihedral distributions in Figs. 12, 13 and 14, respectively. Finally, the static properties are listed in Table 2. In all cases, we obtain good agreement with the results of the explicit simulations.

#### 4.3 AdResS-HybridMD: Coupling to Continuum

Recently, the AdResS scheme described in the previous section has been extended to couple to a continuum model of a liquid [4, 5]. We have derived the triple-scale scheme by combining two dual-scale schemes: AdResS, introduced above, and a hybrid flux-exchange based continuum-MD scheme (HybridMD) developed by Delgado-Buscalioni et al. [9]. The resulting triple-scale model consists of a particle-based MD region, which consists of a central *ex* and surrounding *cg* domains, and a macroscopic region modeled by the Navier-Stokes equation. The simulation setup is presented in Fig. 15 for the liquid of tetrahedral molecules. The central idea of the triple-scale method is to gradually increase the resolution as one approaches to the region of interest, i.e., *ex* region. The continuum and MD domains exchange information via mass and momentum fluxes. These fluxes are conserved across the interface between continuum and MD regions.





**Table 2** Static properties of thepolymer with angle and dihedralinteractions

System	Explicit	AdResS	AdResS (TF)
$\langle R_E^2 \rangle^{1/2}$	$16.8\pm1$	$16.4\pm0.5$	$18.2\pm0.6$
$\langle R_G^2 \rangle^{1/2}$	$8.8 \pm 0.3$	$8.9 \pm 0.3$	$9.3 \pm 0.2$
$\langle R_H^{-1} \rangle^{-1}$	$7.5\pm0.2$	$7.6\pm0.1$	$7.7\pm0.1$



Fig. 15 Concurrent triple-scale simulation of liquid of tetrahedral molecules. Reprinted with permission from Ref. [4]. Copyright 2008, American Institute of Physics

To test the momentum flux conservation by the triple-scale scheme we performed simulations of a simple Couette flow and analyzed the resulting steady velocity profile [4]. Since any significant difference in the fluid viscosity as one crosses from one model to another would induce a change in the slope of the velocity profile we matched the viscosities of explicit, coarse-grained, and hybrid models using a Transverse DPD thermostat [16] presented briefly below. The velocity profile displayed in Fig. 16 shows a perfectly linear velocity profile with no slope change and in agreement with the expected Couette flow.

Our triple-scale approach is designed for molecular simulations of open domains with relatively large molecules, either in the grand canonical ensemble or under nonequilibrium conditions.



4.3.1 Tuning the Transport Properties of Coarse-Grained Models

To synchronize the timescales of the all-atom and coarse-grained regimes in the adaptive resolution simulations, where the diffusion constants and viscosities of the coarse-grained models are due to softer interaction potentials typically too high/low, respectively, compared to all-atom simulations, the coarse-grained dynamics has to be slowed down. In the first attempt we have achieved this by increasing the effective friction in the coarse-grained system using the position dependent Langevin thermostat [22]. Since the Langevin thermostat does not reproduce the correct hydrodynamics, i.e., the hydrodynamic interactions are nonphysically screened, in order to tune the transport coefficient of liquids we exploited the dissipative particle dynamics (DPD) [8, 12]. To this end, we extended the standard DPD thermostat [45] by including the damping of the transverse components of the relative velocity [16]. Our basic assumption is that in contrast to the standard DPD the viscosity is very sensitive to the damping perpendicular to the interatomic axis. This damping mimics the shear of those degrees of freedom (DOFs) that were integrated out in the coarse-graining procedure.

We introduce the Transverse DPD thermostat as [16]:

$$\dot{\mathbf{p}}_i = \mathbf{F}_i^{\mathrm{C}} + \mathbf{F}_i^{\mathrm{D}} + \mathbf{F}_i^{\mathrm{R}},\tag{18}$$

where  $\mathbf{F}^{C}$ ,  $\mathbf{F}^{D}$ , and  $\mathbf{F}^{R}$  are conservative, damping, and random forces, respectively [8]. The damping force is defined as

$$\mathbf{F}_{ij}^{\mathrm{D}} = -\zeta \, w^{\mathrm{D}}(r_{ij}) \, \overset{\frown}{P}_{ij}(\mathbf{r}_{ij}) \mathbf{v}_{ij} \tag{19}$$

and the random force as

(

$$\mathbf{F}_{ij}^{\mathsf{R}} = \sigma \, w^{\mathsf{R}}(r_{ij}) \, \overset{\frown}{P}_{ij}(\mathbf{r}_{ij}) \boldsymbol{\theta}_{ij}. \tag{20}$$

Here  $\zeta$  and  $\sigma$  are the friction constant and the noise strength, respectively. The projection operator  $\vec{P}$  is symmetric in the particle indices  $(\vec{P}_{ij} = \vec{P}_{ji})$ . On the other hand, the noise vector  $\boldsymbol{\theta}_{ij}$ 

$$\boldsymbol{\theta}_{ij}(t) \otimes \boldsymbol{\theta}_{kl}(t') = 2 \widetilde{T} (\delta_{ik} \delta_{jl} - \delta_{il} \delta_{jk}) \delta(t - t'), \qquad (21)$$

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is antisymmetric in the particle indices according to the fluctuation-dissipation theorem. The projection along the interatomic axis between particle *i* and  $j \vec{P}_{ij}(\mathbf{r}_{ij}) = \hat{r}_{ij} \otimes \hat{r}_{ij}$  retains the standard DPD thermostat while  $\vec{P}_{ij}(\mathbf{r}_{ij}) = \vec{I} - \hat{r}_{ij} \otimes \hat{r}_{ij}$  yields the Transverse DPD thermostat.

Results of our simulations have revealed that the transport coefficient are indeed pretty much insensitive to  $\zeta^{\parallel}$  for damping the central relative velocities. On the other hand, they are very sensitive to  $\zeta^{\perp}$  for damping the transverse relative velocities used in the Transverse DPD thermostat as Fig. 17 shows for the diffusion coefficient of liquid water [16].

#### 5 Conclusions

In this contribution we have shortly reviewed some theoretical concepts which current adaptive resolution molecular dynamics simulations are based on. The basic idea is to employ a simulation scheme, where depending on the problem requirement, the local resolution of the simulation can vary, while keeping the full equilibrium between the different regions. Unlike in solid state systems [2, 43] for soft matter or complex fluids in general the free exchange of molecules or parts of molecules between the different regions is essential, as these fluctuations are characteristic for many properties and functions of these systems. This requires special attention to the transition region, which interpolates between more coarse and more fine grained regions of resolution. The transition of hybrid regime has to assure the free exchange without any kinetic barrier. In addition in general the equations of state of the more coarse and the more fine grained parts are not identical and special measures have to be taken. First, as shown, one cannot interpolate the Hamiltonians of the two regions but the forces derived from these Hamiltonians, second a thermostat is needed to take care of the "latent heat" related to the DOFs which are changed throughout the transitions. For that the concept of fractional degrees of freedom is needed in order to have a well defined temperature. Still this interpolation usually will lead to (strong) density undulations within the transitions regime, which can be eliminated by the thermodynamic force introduced. Within this framework a number of model systems have been studied so far. Most recently this setup was used to investigate the influence of bulk water on the solvation shell close to the surface of a series of  $C_{60}$  to  $C_{2160}$  icosahedral fullerenes for two different frequently employed water carbon potentials [18]. By coupling the AdResS scheme to continuum first steps towards open systems molecular dynamics simulations are introduced.

Taking these considerations into account in the present paper we extended the adaptive resolution simulations to mixtures of model systems and polymer solutions, where the polymer chain spans through all three regions. By fixing the center bead to the middle of the transition region we could demonstrate that the appropriately iterated thermodynamic force cancels any remaining drift of the polymer beads into or out of any region, unlike it would be in the uncorrected case. Currently we are extending these studies in general to couple rather different systems and to explore solvation free energies of a variety of hydrophobic solutes, where either experimental or theoretical date or both are very difficult to obtain otherwise. In another recent very interesting extension Poma and Delle Site extended the above concept towards a central quantum mechanical region, where the quantum degrees of freedom are considered on a path integral level [32], which currently also has been extended for a first adaptive resolution study of para hydrogen [33].

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