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Adaptive Resolution Schemes

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The Adaptive Resolution Scheme (AdResS) is a simulation method, which allows to perform Molecular Dynamics (MD) simulations treating different regions with different molecular resolutions. The different scales are coupled within a unified approach by changing the number of degrees of freedom on the fly and preserving the free exchange of particles between regions of different resolution. Here we describe the basic physical principles of the algorithm and illustrate some of its relevant applications.

1 Introduction

Multiscale techniques are becoming standard procedures to study systems in condensed matter, chemistry and material science via simulation. The fast progress of computer technology and the concurrent development of novel powerful simulation methods has strongly contributed to this expansion. This led to the result that detailed sequential studies (modeling) from the electronic scale to the mesoscopic and even continuum are nowadays routinely performed (see e.g.[1–8]). However, sequential approaches still do not couple scales in a direct way. Their central idea is to employ results from one scale to build simplified models in a physically consistent fashion, keeping the modeling approximations as much as possible under control; next, in a separate stage, a larger scale is considered. A step beyond these sequential schemes is represented by those approaches where the scale are coupled in a concurrent fashion within a unified computational scheme. Problems as edge dislocation in metals or crack of materials where the local chemistry effects large scale material properties and vice versa, are typical examples where the idea of concurrent scale methods has been applied. In this case quantum based methods are interfaced with classical atomistic and continuum approaches within a single computational scheme[9–11]. A further example is the Quantum Mechanics/Molecular Mechanics (QM/MM) scheme[12]; mainly used for soft matter systems it is based on the idea that a fixed subsystem is described with a quantum resolution while the remainder of the system is treated at classical atomistic level. A typical example of application of the QM/MM method is the study of the solvation process of large molecules; for this specific example the interesting chemistry happens locally within the region defined by few solvation shells and thus it is treated at a quantum level while the statistical/thermodynamical effect of the fluctuating environment (solvent) far from the molecules is treated in a rather efficient way at classical level. In the same fashion there are several more examples (see e.g. Refs.[13, 14]). All of these methods, although computationally robust, are characterized by a non-trivial conceptual limitation, i.e. the region of high resolution is fixed and thus the exchange of particles among the different regions is not allowed. While this may not be a crucial point for hard matter, is certainly a strong limitation for soft matter, i.e. complex fluids, since relevant density fluctuations are arbitrarily

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suppressed. The natural step forward to overcome this problem is the design of adaptive resolution methods which indeed allow for the exchange of particles among regions of different resolution. In general, in such a scheme a molecule moving from a high resolution region to a lower one, would gradually lose some degrees of freedom (DOFs) until the lower resolution is reached and yet the statistical equilibrium among the two different regions is kept at any instant. Recently some schemes based on this idea, for classical MD, have been presented in literature[15–19]. They are based on different conceptual approaches regarding the way the scales are coupled and the way the equilibrium of the overall system is assured. For the quantum-classical case there are instead several conceptual problems to be solved before a proper scheme can be designed; this is briefly discussed in the next section.

2 Classical and Quantum Schemes

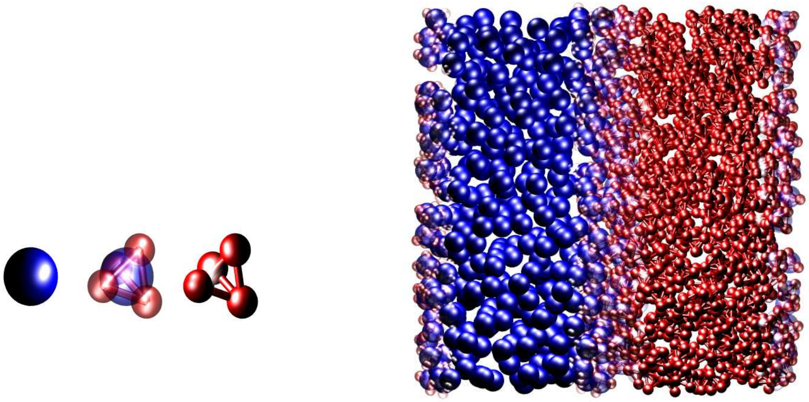
As stated before, many problems in condensed matter, material science and chemistry are multiscale in nature, meaning that the interplay between different scales plays the fundamental role for the understanding of relevant properties as reported in the examples above. An exhaustive description of the related physical phenomena requires in principle the simultaneous treatment of all the scales involved. This is a prohibitive task not only because of the computational resources but above all because the large amount of produced data would mostly contain information not essential to the problem analyzed and may overshadow the underlying fundamental physics or chemistry of the system. A solution to this problem is that of treating in a simulation only those DOFs, which are strictly required by the problem. In this lecture, in particular, we will illustrate the basic physical principles of the Adaptive Resolution Scheme (AdResS) method, where the all-atom classical MD technique will be combined with the coarse grained MD one (for a general discussion about coarse graining see the contribution of C. Peter and K. Kremer), and briefly discuss the difference with other methods. In the AdResS method the combination of all-atom classical MD and coarse grained MD leads to a hybrid scheme where the molecule can adapt its resolution, passing from an all-atom to a coarse grained representation when going from the high resolution region to the lower one (and vice versa), and thus changing in a continuous manner the number of DOFs on the fly. In this way the limitation of the all-atom approach in bridging the gap between a wide range of length and time scales is overcome by the fact that only a limited region is treated with atomistic DOFs (where high resolution is necessary) while the remaining part of the system is treated in the coarse grained representation and thus loses the atomistic (chemical) details but retains those DOFs relevant to the particular property under investigation. This means that one can reach much longer length and time scales and yet retain high resolution where strictly required. In principle the same concept may be applied for quantum-classical hybrid adaptive schemes. Here for quantum is meant that the nuclei are classical objects but their interaction is determined by the surrounding electrons obeying the Schrödinger equation. In this case, however the level of complexity is by far much higher than the hybrid all-atom/coarse grained case. In fact it involves not only a change of molecular representation but also of the physical principles governing the properties of the system. One of the major obstacles is that of dealing with a quantum subsystem where the number of electrons changes continuously in time, that is the wavefunction normalization varies in time. In this case one deals with a different Schrödinger problem at each step unless one introduces some artificial creation and annihilation terms in the Hamiltonian in order to allow a continuous fluctuation of the electron number in a consistent way. Although not trivial, this may still be feasible but the physics of the system could be dramatically modified by the presence of such technical artifacts. One should be also careful in not confusing a proper adaptive scheme, where the DOFs (classical and quantum) change continuously on the fly, with the straightforward approach of running a QM/MM-like simulation and at **each step** modify the size of the quantum region. In this case one has a brute force, by-hand adaptivity which does not allow the system to properly relax both the classical and quantum DOFs. A possible solution to the problems above may be that of treating the electron in a statistical way within a macrocanonical ensemble where their number is allowed to fluctuate, along the same line of thinking of Alavi's theory in the Free Energy MD scheme[20], or by mapping the quantum problem of the subsystem into a classical one in a path integral quantum mechanical fashion (see e.g.[21]) so that the idea of adaptivity can be applied between two (effective) classical descriptions. A possible further approach may be along the lines of coupled quantum-classical MD schemes where the classical bath provides the average environment for a quantum evolution of a subsystem via the use of Wigner transformations[22]. However at this stage these are only speculations and up to now no proper quantum-classical procedures where the adaptivity occurs in a continuum smooth way have been proposed.

3 AdResS: General Idea

The driving idea of the AdResS is to develop a scheme where the interchange between the atomistic and coarse level of description is achieved on the fly by changing the molecular DOFs. In order to develop this idea a test model for the molecule has been built. Fig. 1 gives a pictorial representation of the tetrahedral molecule used and its corresponding spherical coarse grained representation, derived in a way that it reproduces chosen all-atom properties. The tetrahedral molecule consists of four atoms kept together by a spring-like potential with a Lennard-Jones intermolecular potential; specific technical details of the model as well as of the coarse grained procedure for the spherical representation are reported in Appendix. As Fig. 1 shows, the atomistic molecule when passing to the coarse grained region, slowly loses its vibrational and rotational DOFs, passing through different stages of hybrid atomistic/coarse grained representation and finally reducing its representation to a sphere whose DOFs are solely the translational ones of the center of mass with a proper excluded volume. A crucial point to keep in mind is that the different resolutions do not mean that the molecules are of different **physical** species. The basic underlying physics is in principle the same in all region and thus the process of exchange has to happen in condition of thermodynamical and statistical equilibrium which means pressure balance $P^{\text{atom}} = P^{\text{cg}}$, thermal equilibrium $T^{\text{atom}} = T^{\text{cg}}$, and no net molecular flux $\rho^{\text{atom}} = \rho^{\text{cg}}$. This conditions must be preserved by the numerical scheme and thus represent the conceptual basis of the method[17], next the effective dynamical coupling between the scales must be specified; this is reported in the next section.

3.1 Scale coupling

Once the effective potential is derived on the basis of the reference all-atom system (see Appendix 8) then the atomistic and the coarse grained scales are coupled via a position



(a) On-the-fly interchange of a molecule (b) Snapshot of the simulation box

Figure 1. (a) The on-the-fly interchange between the atomic and coarse grained levels of description. The middle hybrid molecule is a linear combination of a fully atomistic tetrahedral molecule with an additional center-of-mass particle representing the coarse grained molecule. (b) Snapshot of the hybrid atomistic/mesoscopic model at $\rho^* = 0.1$ and $T^* = 1$ (LJ units). The red molecules are the explicit atomistically resolved tetrahedral molecules, while the blue molecules are the corresponding one-particle coarse grained molecules. (Figure was taken from Ref.[15])

dependent interpolation formula on the atomistic and coarse grained force[15, 16]:

$$\mathbf{F}_{\alpha\beta} = w(X_\alpha)w(X_\beta)\mathbf{F}^{\text{atom}}_{\alpha\beta} + [1 - w(X_\alpha)w(X_\beta)]\mathbf{F}^{\text{cg}}_{\alpha\beta} \tag{1}$$

where α and β labels two distinct molecules, $\mathbf{F}^{\text{atom}}_{\alpha\beta}$ is derived from the atomistic potential where each atom of molecule α interacts with each atom of molecule β, and $\mathbf{F}^{\text{cg}}_{\alpha\beta}$ is obtained from the effective (coarse grained) pair potential between the centers of masses of the coarse grained molecules. In the region where a smooth transition from one resolution to another takes place, a continuous monotonic ”switching” function $w(x)$ is defined as in Fig. 2 (where X_α, X_β are the x-coordinates of the centers of mass of the molecules α and β). A simple way to think about the function $w(x)$ is the following: $w(x)$ is equal to one in the atomistic region and thus the switchable DOFs are fully counted, while $w(x)$ is zero in the coarse grained region and thus the switchable DOFs are turned off, while in between takes values between zero and one and thus provides (continuous) hybrid representations of such DOFs (i.e. they count only in part). In general, Eq. 1, allows for a smooth transition from atomistic to coarse grained trajectories without perturbing the evolution of the system in a significant way. More specifically the formula of Eq. 1 works in such a way that when a molecule passes from the atomistic to the coarse grained region, the molecular vibrations and rotations become less relevant until they vanish so that $w(x)$ smoothly “*freezes*” the dynamical evolution of these DOFs and their contributions to the interaction with the other molecules. Vice versa, when the molecules goes from the coarse grained region to the atomistic one, $w(x)$ smoothly ”*reactivates*” their dynamics and their contributions to the intermolecular interactions. In the case of tetrahedral molecules, being characterized by pair interactions, we have that all the molecules interacting with coarse grained molecules interact as coarse grained molecules independently of the region

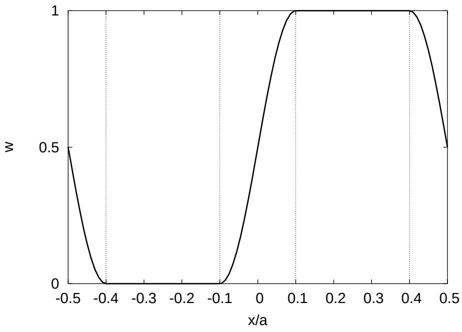


Figure 2. The weighting function $w(x) \in [0, 1]$. The values $w = 1$ and $w = 0$ correspond to the atomistic and coarse grained regions of the hybrid atomistic/mesoscopic system with the box length a, respectively, while the values $0 < w < 1$ correspond to the interface layer. The vertical lines denote the boundaries of the interface layers. (Figure was taken from Ref.[15])

where they are (the coarse grained molecule does not have any atomistic detail, thus the other molecule can interact with this molecule only via the center of mass), two atomistic interact as atomistic, while for the other couplings, the interactions are governed by the $w(X_\alpha)w(X_\beta)$ combination. A very important point of Eq. 1 is that, by construction, the Newton's Third Law is preserved. The diffusion of molecules between regions with different resolution must not be perturbed by the resolution change. Thus the conservation of the linear momentum dictated by the Newton's Third Law is crucial in adaptive resolution MD simulations.

3.2 Thermodynamical equilibrium

Eq. 1 cannot be derived from a potential and thus a scheme based on it, would not have an energy to conserve. The natural subsequent question is how to then control the thermodynamic equilibrium. The conceptual problem for an adaptive scheme is that the free energy density is formally not uniform since the number of DOFs varies in space, however being the system uniform by construction (and being the **underlying physical** nature of the molecules the same everywhere), this would be only an artifact of the formalism used. This non uniformity leads to a non-physical preferential direction of the molecular flux. In fact, as numerical tests show, there is a preferential tendency of the atomistic molecules to migrate into the coarse grained region and change resolution in order to lower the free energy of the system (the free energy is an extensive quantity, that is proportional to the number of DOFs). A simple qualitative way to picture this diode-like aspect is the following: when a molecule goes from an atomistic to a coarse grained region it loses vibrational and rotational DOFs and thus in its interactions with the neighboring (coarse grained) molecules it must accommodate only its excluded volume (i.e. find space). This becomes more complicated if a coarse grained molecules moves into an atomistic region, in this case the molecule acquires rotational and vibrational DOFs and tries to enter into a region where other molecules are already locally in equilibrium. This means that in order to enter this region, the molecules should accommodate both rotational and vibrational DOFs according to the neighboring environment. Most likely the molecule would enter with vibrational and rotational motions which does not fit the local environment and this would lead to a perturbation of the local equilibrium. This means that for such a molecule the **way back** to the coarse grained region is more convenient, and thus this free energy barrier works as a closed door (probabilistically) for the coarse grained molecules and opened door for the atomistic ones so that a preferential molecular flux from the atomistic to the coarse grained region is produced. In thermodynamic terms, as an artifact of the method, the different regions are characterized by a different chemical potential, however, since this aspect does not stem from the physics of the system but only from the formalism, we have to amend for this thermodynamical unbalance. This means that the use of Eq. 1 alone cannot assure thermodynamical equilibrium and further formal relations, linking the variables of the problem, should be determined in order to obtain equilibrium. This can be obtained, as shown in the next sections, by analyzing the meaning of the process of varying resolution in statistical and thermodynamical terms.

4 Theoretical Principles of Thermodynamical Equilibrium in AdResS

In this section we analyze the idea of describing thermodynamical equilibrium for a system where, formally, the number of DOFs is space dependent and yet the molecular properties are uniform in space.

4.1 The principle of geometrically induced phase transition

The space dependent change of resolution can be seen, to have some similarities to a physical phase transition, as a fictitious geometrically induced phase transition. In simple words, the concept of latent heat is similar to that of a molecule which, for example, goes from the liquid to the gas phase and in doing so needs a certain energy (latent heat) to activate those vibrational states that makes the molecules free from the tight bonding of the liquid state. In the same way, a molecule in the adaptive scheme that passes from a coarse grained to an atomistic resolution, needs a latent heat to formally (re)activate the vibrational and rotational DOFs and to reach equilibrium with the atomistic surrounding. Vice versa the heat is released when the molecule goes from gas to liquid and so the bond to the other molecules becomes tighter, in the same way in the adaptive scheme, the molecule passing from atomistic to coarse grained, formally releases DOFs and thus automatically the associated heat. This concept can be formalized as: $\mu^{\mathrm{atom}} = \mu^{\mathrm{cg}} + \phi$, where μ^{cg} is the chemical potential calculated with the coarse grained representation, μ^{atom} that of the atomistic one, and ϕ is the latent heat[23, 17]. Possible procedures for a formal derivation of an analytic or numerical form of ϕ and how to use it in the AdResS scheme is still a matter of discussion and subject of work in progress and will be briefly discussed later on. For the time being, a simpler and practical solution is used, that is the system is coupled to a thermostat (see Appendix 8) which automatically, as a function of the position in space, provides (or removes) the required latent heat assuring stability to the algorithm and equilibrium to the system. The coupling of the system to a thermostat leads to the natural question of how to define the temperature in the region of transition where the number of DOFs is space dependent.

4.2 Temperature in the transition region

In the atomistic and coarse grained region the temperature can be defined without a problem employing the equipartition theorem: $T^{\text{atom/cg}} = 2\frac{<K^{\text{atom/cg}}>}{n^{\text{atom/cg}}}$, where $< K^{\text{atom/cg}} >$ is the average kinetic energy of the atomistic/coarse grained region and $n^{\text{atom/cg}}$ is the total average number of DOFs. In the atomistic/coarse grained region, such a quantity is a well defined number, however it is not so in the transition region where $n^{\text{trans}} = n(x)$. The question arising is how to define T^{trans} and above all what $< K^{\text{trans}} >$ means. To address this question we make the following observations: the switching procedure implies that a DOF, in calculating average statistical quantities, **fully counts** in the atomistic region, which formally means that an integral over its related phase space is performed ($\int ....\text{d}q$; q being a generic switchable DOF). On the other hand in the coarse grained region, q is not relevant to the properties of the system and thus it **does not count at all**, that is no integration over its related phase space is required. In the transition region the situation is something in between and thus by switching on/off the DOF q we effectively change the dimensionality (between zero and one) of its related phase space, that is of its domain of integration. In simple words q in the transition region contributes to statistical averages with a weight. The mathematical tool which allows to formalize this idea is provided by the technique of the fractional calculus, where for a fixed resolution w the infinitesimal volume element is defined as[26]:

$$\text{d}V_w = \text{d}^w q\, \Gamma(w/2)/2\pi^{w/2}\Gamma(w) = |q|^{w-1}\text{d}q/\Gamma(w) = d\text{q}^w/w\Gamma(w) \tag{2}$$

with $\Gamma(w)$ the well-known Γ function. Employing such a formalism to calculate the average energy for quadratic DOFs one obtains:

$$< K_q >_w = \frac{\int_0^\infty e^{-\beta q^2} q^{w+1}\text{d}q}{\int_0^\infty e^{-\beta q^2} q^{w-1}\text{d}q}. \tag{3}$$

The solution of Eq. 3 is found to be[26]:

$$< K_q >_w = \frac{w}{2}\beta^{-1}. \tag{4}$$

This is nothing else than the analog of the equipartition theorem for non integer DOFs. Here $< K_q >_w$ is the average kinetic energy of the switchable DOF q for the fixed resolution w. One can then think to use w as a continuous parameter and thus obtaining the definition of kinetic energy for the switchable DOFs in the transition region. A further point needs to be explained, that is, we have implicitly used a Hamiltonian to perform the ensemble average and this would contradict the statement of the previous section about the non existence of an energy within the coupling scheme used. To clarify this aspect we have to say that the coupling formula on the forces is not directly related to the derivation of the statistical average performed here. Here we have interpreted the process of changing resolution as the process of partially counting a DOF contribution into the statistical determination of an observable, under the hypothesis that the underlying Hamiltonian is the same all over the system. This is justified by the fact that the underlying physics is in principle the same all over the system but the formal representation and thus the analysis of the DOFs of interest and their contributions differs. This in practical terms means that the derivation of the temperature and the principle of coupling of forces via spatial interpolation are two aspects of the same process but one cannot formally derive both from a single general principle so that the connection between them, at this stage, must be intended as only qualitative. However, we will use the numerical tool of simulation where both Eq. 1 and Eq. 4 are employed in connection to each other to prove that they are numerically consistent. At this point the obvious question arises about why to choose the approach based on the interpolation of the forces and not to choose the more natural one based on the smooth interpolation of the potential. This problem is treated in the next section.

5 Coupling the Different Regimes via a Potential Approach

The coupling scheme analog of Eq. 1 using potentials instead of forces would be:

$$U_{\alpha\beta} = w(x_\alpha)w(x_\beta)U^{\text{atom}}_{\alpha\beta} + [1 - w(x_\alpha)w(x_\beta)]U^{\text{cg}}_{\alpha\beta}. \tag{5}$$

This approach leads to a series of problem whose solution is not trivial. In particular if one derives the forces from Eq. 5 obtains an extra term, which here we will name **drift force**, of the following form:

$$\mathbf{F}^{\text{drift}} = U^{\text{atom}}\frac{\partial w}{\partial x} + U^{\text{cg}}\frac{\partial w}{\partial x} \tag{6}$$

There are two options at this point, one accepts this force as a result of a definition of a new force field in Eq. 5, or one tries to remove it by a specific choice of $w(x)$ or by modifying $U_{\alpha\beta}$ in Eq. 5. In the first case one has to be aware that, because the derivative of $w(x)$ enters into the equations of motion, the evolution of the system becomes highly sensitive to the choice of the form of $w(x)$. This means that different functions $w(x)$ may lead to complete different results, and being the choice of $w(x)$ made on empirical basis, the dynamic becomes arbitrary and thus, most likely, unphysical. The limitation above applies in principle to the approach proposed by Heyden and Truhlar[19], where the scales are coupled by an interpolation of Lagrangians via a space dependent function. Moreover, the force obtained from Eq. 5 does not preserve the third Newton's law[23,26].

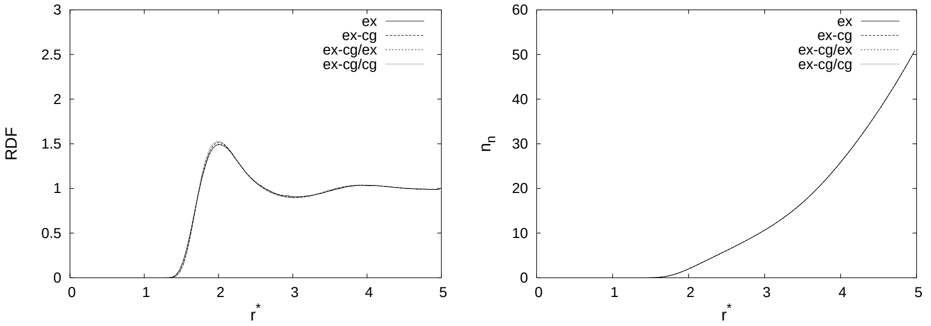
Instead if one tries to follow the second possibility, that is removing $\mathbf{F}_{drift}$, one encounters heavy mathematical difficulties[24,25] since the condition $\mathbf{F}_{drift} = 0$ leads to a system of partial differential equations of first order:

$$\begin{aligned} U^{\text{cg}}\frac{\partial f(X_\alpha, X_\beta)}{\partial X_\alpha} + U_{atom}\frac{\partial g(X_\alpha, X_\beta)}{\partial X_\alpha} &= 0 \\ U^{\text{cg}}\frac{\partial f(X_\alpha, X_\beta)}{\partial X_\beta} + U_{atom}\frac{\partial g(X_\alpha, X_\beta)}{\partial X_\beta} &= 0. \end{aligned} \tag{7}$$

Here $f(x)$ and $g(x)$ are the most general switching functions one can think of. For the system of Eqs. 7 each equation is characterized by two boundary conditions, thus the system is **overdetermined** and thus in general a solution **does not exist**. This is valid also if one tries to generalize Eq. 5 as:

$$U^{\text{coupling}} = f(X_\alpha, X_\beta)U^{\text{cg}} + g(X_\alpha, X_\beta)U^{\text{atom}} + \Phi. \tag{8}$$

The extra potential Φ does not improve the situation because in this case the overdetermination is shifted from f and g to Φ. These sort of problems, in principle, occur for the conserving energy method proposed by Ensing *et al.*[18], where the difference between the



(a) Radial distribution functions (b) Average numbers of neighbors

Figure 3. (a) Center-of-mass radial distribution functions for all molecules in the box of the all-atom ex and hybrid atomistic/mesoscopic ex-cg systems at $\rho^* = 0.1$ and $T^* = 1$. Shown are also the corresponding center-of-mass radial distribution functions for only the explicit molecules from the explicit region ex-cg/ex and for only the coarse grained molecules from the coarse grained region ex-cg/cg . The width of the interface layer is $2d^* = 2.5$. (b) The corresponding average numbers of neighbors $n_n(r^*)$ of a given molecule as functions of distance. The different curves are almost indistinguishable. (Figure was taken from Ref.[15])

true (full atomistic) energy of the system and the one of the hybrid scheme is provided during the adaptive run via a book keeping approach while the forces are calculated with a scheme similar to that of AdResS. The problem of the overdetermination reported above in this case would mean that the conserved energy is not consistent with the dynamics of the system. In comparison, the AdResS method has the limitation of not even attempting to define an energy but on the other hand the overall scheme is robust enough to keep the dynamics and the essential thermodynamics under control without the problem of energy conservation. The next step consists of using the information gained so far and apply the principles of the previous section in a numerical experiment to prove the validity of the scheme.

6 Does the Method Work?

In order to prove that such a computational approach with the theoretical framework presented so far is robust enough to perform simulations of chemical and physical systems we have carried on studies for the liquid system of tetrahedral molecules where the results of the AdResS approach are compared with the results obtained with full atomistic simulations. First we have shown that global and local structure can be reproduced. This means, we have determined the center of mass-center of mass radial distribution function for the whole system (global), and for only the atomistic part and only for the coarse grained part (local) and compared it with the results obtained in a full atomistic simulation. This comparison for a medium dense liquid are reported in Fig. 3; the agreement is clearly satisfactory since the various plots are all on top of each other. However the radial distribution function is based on an average over the space, this means that cannot describe possible local and instantaneous fluctuations due to some possible artifact of the method. These latter may not be negligible but, by compensating each other, they would not appear in the

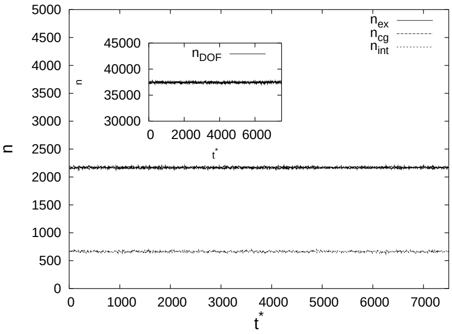


Figure 4. Time evolution of number of molecules in explicit $n_{\rm ex}$, coarse grained $n_{\rm cg}$, and interface regions $n_{\rm int}$ in the hybrid atomistic/mesoscopic model with the 2.5 interface layer width. The time evolution of the number of degrees of freedom in the system $n_{\rm DOF}$ is depicted in the inset. (Figure was taken from Ref.[15])

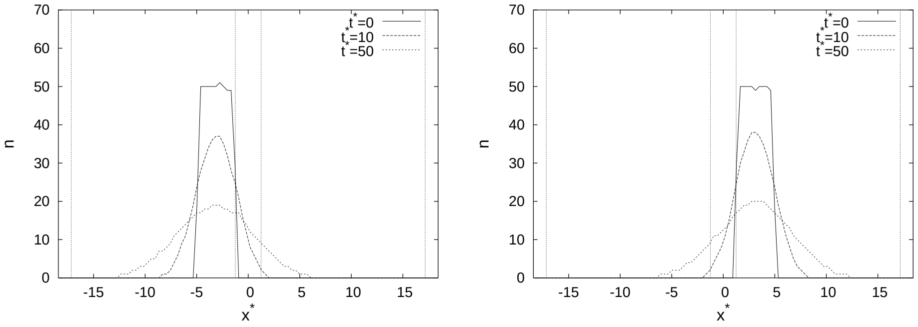


Figure 5. Time evolution of diffusion profiles for the molecules that are initially, at time $t^* = 0$, localized at two neighboring slabs of the mid-interface layer with $2d^* = 2.5$ (n is the number of these molecules with the center-of-mass position at a given coordinate x^*). The width of the two slabs is $a^*/10$. The vertical lines denote the boundaries of the interface layer. (a) The diffusion profile, averaged over 500 different time origins, at $t^* = 0$, $t^* = 10$, and $t^* = 50$ for the molecules that are initially localized at the slab on the coarse grained side of the interface region. (b) The same as in (a) but for the molecules that are initially localized at the slab on the atomistic side of the interface region. (Figure was taken from Ref.[15])

plot of Fig. 3. In this sense the study above is not sufficient to infer about the validity of the method. Therefore, we also studied the evolution of the number of DOFs as a function of time. This should make us aware of possible non-negligible artificial fluctuations of the system. Fig. 4 shows that the number of DOFs is conserved at any time during the run and thus there is no net flux through the border of the two regions. Again, this study is not sufficient to prove the validity of the scheme, because still one should prove that indeed there is a true exchange of particles from one region to another. In fact it may happen that the equilibrium among the different regions is due to a reflection mechanism without exchange of particles between them. Fig. 5 shows that indeed a sample of molecules from the atomistic region diffuses into the coarse grained one and vice versa a sample from the coarse grained region diffuse into the atomistic one. It is however only a coincidence that

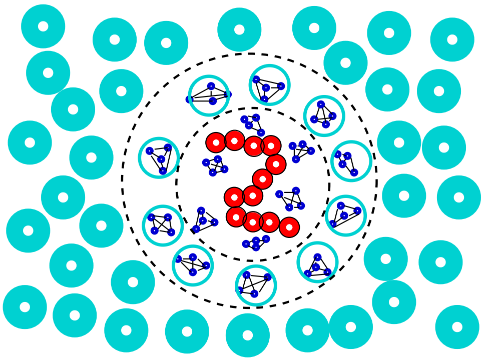


Figure 6. A schematic plot of a solvated generic bead-spring polymer. The solvent is modeled on different levels of detail: solvent molecules within a certain radius from the polymer's center of mass are represented with a high atomistic resolution while a lower mesoscopic resolution is used for the more distant solvent. The high resolution sphere moves with the polymer's center of mass. The polymer beads are represented smaller than the solvent molecules for presentation convenience; for details see text. (Figure was taken from Ref.[27])

this happens in a symmetric way, because the system in question has basically the same diffusion constant in the atomistic and coarse grained representation. In general the profile is not symmetric. To remove this unphysical effect the system is coupled with a position dependent thermostat to match the diffusion constants of the atomistic and coarse grained molecules (see Appendix 8). The data reported in the plots above are for a medium dense liquid[15], but the same satisfactory agreement was found for high density liquid[16].

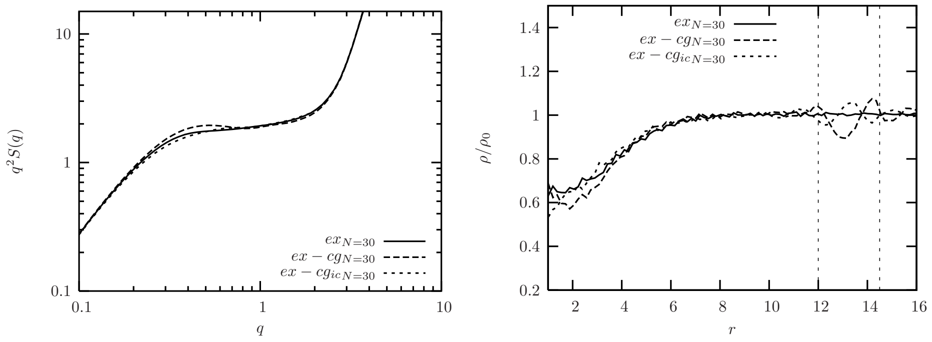
7 Further Applications

7.1 Solvation of a simple polymer in the tetrahedral liquid

An extension of the approach above to a solvation of an ideal bead and spring polymer in tetrahedral liquid was then performed in Ref.[27]. Here the solvation shell is defined as the atomistic region, and outside the solvent is represented with its coarse grained spheres. The solvation shell, centered at the center of mass of the polymer is always large enough that the polymer is contained in it. This region can diffuse around with the polymer and all the molecules entering the solvation area become atomistic and those leaving the region become coarse grained. As for the cubic box before, between the atomistic and the coarse grained regions there is a transition region (see Fig. 6). Two examples of comparison with a full atomistic simulation are reported, these are the calculation of the static form factor (left panel Fig. 7) and the shape of the solvation region as a function of the distance from the center (of the region) in terms of particle density (right panel Fig. 7). These two plots show very good agreement with the full atomistic simulation and thus prove that the method is indeed robust for such a kind of system.

7.2 Liquid water

The first application to a real chemical and physical system is that to liquid water. Several new technical issues arise, the most relevant of which are the presence of the charges and



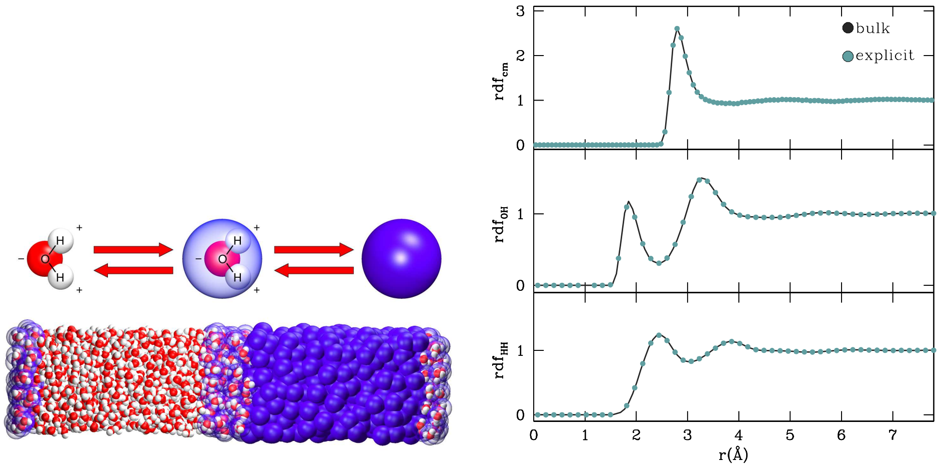
(a) Structure factor (b) Correlation hole

Figure 7. (a) The static structure factor of the polymer with $N = 30$ in the Kratky representation for all three cases studied: the fully explicit, the AdResS scheme with and without the interface pressure correction. (b) The correlation hole for the same systems as in (a) . (Figure was taken from Ref.[27])

the different diffusion coefficients in the atomistic and coarse grained representations (see Fig. 8)[28,29]. These technical problems have been solved and the approach used is reported in the appendix, here we report only the results showing that indeed the adaptive simulation can reproduce in a satisfactory way the results of the full atomistic ones. This is shown in the right panel of Fig. 8(b), where several radial distribution functions calculated in the full atomistic simulation and in the adaptive case (for the atomistic region) are plotted . Moreover, not shown here, results of the study show that the system remains indeed uniform. Several other properties were calculated showing the robustness of such an approach for liquid water and they are reported in Refs.[28,29].

7.3 Triple-scale simulation of molecular liquids

Recently we succeeded in developing a triple scale approach where the atomistic is interfaced with the coarse grained description and the latter with the continuum[30,31]. This multiscale approach was derived by combining two dual-scale schemes: our particle-based AdResS, which links the atomic and mesoscopic scales within a molecular dynamics (MD) simulation framework, and a hybrid flux-exchange based continuum-MD scheme (HybridMD) developed by Delgado-Buscalioni *et al.*[32,33]. The resulting triple-scale model consists of a particle-based micro-mesoscale MD region, which is divided into a central atomistic and a surrounding mesoscopic domain, and a macroscopic region modeled on the hydrodynamic continuum level as schematically presented in Fig. 9 for the example of the tetrahedral liquid. The central idea of the triple-scale method is to gradually increase the resolution as one approaches to the atomistic region, which is the “region of interest”. The continuum and MD region exchange information via mass and momentum fluxes, which are conserved across the interface between continuum and MD regions (for details see Refs.[32,33]). The combined approach successfully solves the problem of large molecule insertion in the hybrid particle-continuum simulations of molecular liquids and at the same time extends the applicability of the particle-based adaptive resolution schemes to simulate



(a) Mapping scheme (b) Radial distribution functions

Figure 8. (a) On-the-fly interchange between the all-atom and coarse grained water models. Top: the explicit all-atom water molecule is represented at the right, and the coarse grained molecule at the left. The middle hybrid molecule interpolates between the two (see text). Bottom: a schematic representation of the full system, where a hybrid region connects the explicit and coarse grained levels of description. All the results presented in the paper were obtained by performing N V T simulations using ESPResSo[34] with a Langevin thermostat, with a friction constant $\zeta = 5\text{ps}^{-1}$ and a time step of 0.002ps at $T_{\text{ref}} = 300$K and $\rho = 0.96\text{g/cm}^{-3}$ (the density was obtained from an NPT simulation with $P_{\text{ref}} = 1$bar). Periodic boundary conditions were applied in all directions. The box size is 94.5 Å in the x direction and 22 Å in the y and z directions. The width of the interface layer is 18.9 Å in the x direction. (b)The center-of-mass, OH and HH RDFs for the explicit region in the hybrid system dots, and bulk line systems. (Figures were taken from Refs.[28] and[29])

open systems in the grand-canonical ensemble including hydrodynamic coupling with the outer flow.

8 Work in Progress: Towards an Internally Consistent Theoretical Framework

The AdResS method has been shown to be numerically rather robust, however further developments of the theoretical framework, on which the method is based, would be highly desirable in order to improve the structure and the flexibility of the algorithm. One relevant point regards the concept of latent heat introduced via the theoretical analysis about the meaning of changing resolution in thermodynamical terms. This has been so far implemented numerically by using a thermostat; such an approach is numerically very convenient to stabilize the algorithm and drive the system to equilibrium but at the same time does not permit the detailed control of the physical process occurring while the change of resolution happens. To this aim we are making an effort to formalize the concept of latent heat on the basis of a physical ground by employing first principles of thermodynamics or statistical mechanics. In this way an explicit analytic or semi-analytic description of the latent heat, would allow to avoid the use of a stochastic thermostat and automatically

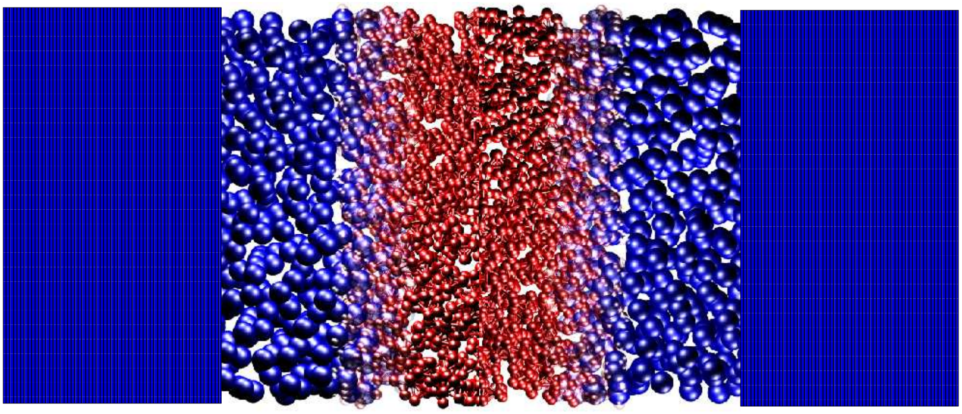


Figure 9. The triple-scale model of the tetrahedral liquid. The molecular particle-based region is embedded in the hydrodynamics continuum described by Navier-Stokes equations (solved by the finite volume method). The molecular region is divided into the central explicit atomistic region with all-atom molecules (red tetrahedral molecules) sandwiched in between two coarse grained domains with the molecules represented on a more coarse grained level of detail (one particle blue molecules). (Figure was taken from Ref.[30])

provide thermodynamic equilibrium. With that the dynamics and the essential thermodynamics can be taken explicitely under control and provide equilibrium despite the fact that still we do not define an energy as in standard simulation schemes. For this purpose we reformulate the problem of the latent heat in terms of an additional thermodynamic force. Such a thermodynamic force is represented by the gradient of a scalar field whose task is that of assuring the balance of the chemical potential in all regions. Such a field can be derived by calculating numerically the chemical potential or the free energy density in the various region of different resolution. Numerical as well as analytic work on this subject is in progress.

Appendix A: Tetrahedral Fluid

In the atomistic representation every molecule of this model fluid consist of 4 atom. All of these have the same mass m_0 and interact via purely repulsive Lennard-Jones potential:

$$U_{\text{LJ}}^{\text{atom}}(r_{\alpha i\beta j}) = \begin{cases} 4\epsilon\left[\left(\frac{\sigma}{r_{\alpha i\beta j}}\right)^{12} - \left(\frac{\sigma}{r_{\alpha i\beta j}}\right)^{6} + \frac{1}{4}\right] & : r_{\alpha i\beta j} \leq 2^{1/6}\sigma \\ 0 & : r_{\alpha i\beta j} > 2^{1/6}\sigma \end{cases}, \tag{9}$$

where $r_{\alpha i\beta j}$ is the distance between the ith atom in the αth molecule and the jth atom in the βth molecule, note that we also consider the Lennard-Jones interactions between the atoms of the same molecule. Additionally the atoms in one molecule are bonded by FENE potential

$$U_{\text{FENE}}^{\text{atom}}(r_{\alpha i\alpha j}) = \begin{cases} -\frac{1}{2}kR_0^2 \ln\left[1 - \left(\frac{r_{\alpha i\alpha j}}{R_0}\right)^{2}\right] & : r_{\alpha i\alpha j} \leq R_0 \\ \infty & : r_{\alpha i\alpha j} > R_0 \end{cases}, \tag{10}$$

with a divergence length $R_0 = 1.5\sigma$ and stiffness $k = 30\epsilon/\sigma^2$.

Appendix B: Mapping Scheme/Coarse Grained Potentials

In coarse grained representation we replace a molecule by a bead located at the position of the center of mass of the atomistic molecule. The interaction between the coarse grained beads is determined by the iterative Boltzmann inversion[35] and it is such that the radial distribution function (RDF) of the coarse grained system fits the RDF of the atomistic system. In summary this procedure works as follows (for a detailed presentation see the lecture of C. Peter and K. Kremer). After starting with an initial guess of the pair interaction $V_0(r)$, the interaction of the $(i+1)$th step is given by:

$$V_{i+1}(r) = V_i(r) + \mathrm{k_B}T \ln \left[\frac{g_i(r)}{g^{\text{target}}(r)} \right] , \tag{11}$$

where $g^{\text{target}}(r)$ is the RDF we want to fit, usually given by atomistic simulation and $g_i(r)$ is the RDF of the ith step. Commonly the potential of mean force is used as an initial guess:

$$V_0(r) = -\mathrm{k_B}T \ln g^{\text{target}}(r) \tag{12}$$

Appendix C: Interface Correction

In the switching region the density profile is not uniform, instead it is characterized by some evident fluctuations. Such fluctuations are due to the fact that for hybrid interactions the corresponding effective potential is not the same as the full coarse grained one for matching the structure and the pressure of the atomistic system. Technically this means that we need to derive first an effective potential between hybrid molecules with a fixed weight, which reproduces the RDF and the pressure of the atomistic one, and then, in order to suppress the density fluctuations, use it for an interface correction. Here we report the case $w = 0.5$, however the extension to other weights (and other points) is straightforward. The newly derived effective potential with $w = 0.5$, $V^{\text{ic},0.5}(R_{\alpha\beta})$ is determined via the iterative Boltzmann procedure (as before, see Appendix 8). Then, one replaces the forces between the coarse grained beads by[16]:

$$\mathbf{F}^{\text{ic}}_{\alpha\beta} = s[w(R_\alpha)w(R_\beta)]\mathbf{F}^{\text{cg}}(R_{\alpha\beta}) + (1 - s[w(R_\alpha)w(R_\beta)])\mathbf{F}^{\text{ic},0.5}(R_{\alpha\beta}) , \tag{13}$$

where $\mathbf{F}^{\text{ic},0.5}(R_{\alpha\beta})$ is the force coming from the potential $V^{\text{ic},0.5}(R_{\alpha\beta})$ and

$$s[x] = 4(\sqrt{x} - 0.5)^2 , \tag{14}$$

is a function $s \in [0, 1]$, which is zero for both weights being 0.5 ($s[(0.5)^2] = 0$) and one for the product of the two weights being 0 or 1 (s[0]=s[1]=0); this means that one has the ”exact” force when both molecules have $w = 0.5$. For other weights the force is smoothly interpolated between the corrected and the standard coarse grained force, and thus one obtains an improvement at the interface. In principle if one repeated this procedure for each combinations of $w(R_\alpha)w(R_\beta)$, in the switching region one would have always the exact force. We have noticed that numerically is enough to have a correction for the worst case ($w = 0.5$).

Appendix D: Charged Molecules

Electrostatic interactions are long-ranged and must be calculated over several periodical images of the simulation box. This leads to some problems in the adaptive resolution method because, on one hand, molecules become uncharged in their coarse grained representation and on the other hand the long-ranged character of electrostatic interactions leads to self interaction of all periodical images, for example the interaction of the explicit regions of two image boxes. Additionally, standard approaches like particle mesh Ewald or P3M will always lead to an all-with-all interaction of the molecules, due the involved Fourier transformation, and thus making the switching of the degrees of freedom not possible.

Luckily, in the case of dense and homogeneous fluids (like water) one can use the reaction field approach[36]. The latter assumes that outside a sphere with radius r_{cut} the charges are distributed homogeneously, and thus it makes it possible to replace the interactions outside the sphere with that of a continuum with a dielectric constant ϵ_{rf}. This scheme has been frequently used for liquid water[37], and, in this case, it allows to treat charged molecules in the adaptive resolution method, where one deals with pair interactions:

$$U(r) = \begin{cases} \frac{q_i q_j}{4\pi\epsilon_0\epsilon_1}\left[\frac{1}{r} - \frac{Br^2}{2r_c^3} - \frac{2-B}{2r_c}\right] & : r \leq r_c \\ 0 & : r > r_c \end{cases} \tag{15}$$

with $B = 2(1 - \epsilon_1 - \epsilon_{\text{rf}})/(\epsilon_1 + 2\epsilon_{\text{rf}})$. The ϵ_{rf} is the dielectric constant outside the cut-off. r_c, which can be estimated from a particle mesh Ewald calculation or determined in a recursive manner.

Appendix E: Thermostat

In general a thermostat is always needed to perform a NVT simulation. Specifically, in the case of the adaptive resolution scheme the thermostat is also needed to compensate for the switch of the interaction between the molecules, since it ensures that the atoms of a molecule have the correct velocity distribution when entering the switching region from the coarse grained side. We use the Langevin idea or stochastic dynamics[38] to ensure the correct ensemble by adding a random and a damping force

$$\dot{\mathbf{p}}_i = -\nabla_i U + \mathbf{F}_i^{\text{D}} + \mathbf{F}_i^{\text{R}} \tag{16}$$

The damping force is Stokes-like force

$$\mathbf{F}_i^{\text{D}} = -\zeta_i/m_i\, \mathbf{p}_i \tag{17}$$

To compensate for this friction one adds a random force

$$\mathbf{F}_i^{\text{R}} = \sigma_i \eta_i(t)\ , \tag{18}$$

where η_i is a noise with zero mean ($< \eta_i(t) >= 0$) and certain correlation properties ($< \eta_i(t)\eta_j(t') >= \delta_{ij}\delta(t - t')$. And ζ_i, σ_i are the friction and the noise strength. The corresponding Fokker-Planck operator[39] for the stochastic part of the Langevin equation (Eq. 16) is given by:

$$\mathcal{L}_{\text{SD}} = \sum_i \frac{\partial}{\partial \mathbf{p}_i}\left[\zeta_i \frac{\partial \mathcal{H}}{\partial \mathbf{p}_i} + \sigma_i^2 \frac{\partial}{\partial \mathbf{p}_i}\right]\ , \tag{19}$$

where the sum goes over all particles. By assuming that the equilibrium distribution is a Boltzmann distribution, one has:

$$\mathcal{L}_{\mathrm{SD}} \exp(-\mathcal{H}/\mathrm{k_B}T) = 0 \tag{20}$$

and from that one obtains:

$$\sigma_i^2 = \mathrm{k_B}T\zeta_i \; , \tag{21}$$

which is also known as the Fluctuation-Dissipation theorem (FDT)[39]. At this point we are left with one free parameter to choose, namely the friction strength ζ_i. The drawback of this thermostat is its lack of Galilei invariance and the strong dependence of the dynamics from the friction strength. Therefore, it is in many cases more appropriate to use the Galilei invariant and hydrodynamics conserving DPD thermostat[40], which leaves the dynamic nearly unchanged for wide range of ζ.

Applying the thermostat in AdResS

To obtain the FDT from Eq. 20 a Hamiltonian is needed and, as discussed above, in the AdResS method it is not possible to define a Hamiltonian. For this reason one has to couple the thermostats acting on the explicit and coarse grained molecules. One could make, for example, a linear combination of the thermostat forces (as in Eq. 1 for the deterministic forces). However, this would violate the FDT because the ratio of “random force squared to damping force” would not be conserved (see Eq. 21). Consequently, the temperature would not be correctly defined. Another possibility is to apply the linear scaling to the friction coefficient of the damping force (from the atomistic friction coefficient at the all-atom/transition regime interface to the coarse grained one at the transition/coarse grained boundary) and adjust the noise strength σ to satisfy the FDT[29,30] (see also the next section). The thermostat is then applied to the explicit particles in the atomistic and transition regions and to the center of mass interaction sites in the coarse grained regime. In addition, the explicit atoms of a given molecule, which enters the transition regime from the coarse grained side, are also assigned rotational/vibrational velocities corresponding to atoms of a random molecule from the atomistic region (where we subtract the total linear momentum of the latter molecule). By doing this we ensure that the kinetic energy is distributed among all DOFs according to the equipartition theorem. For practical reasons, the thermostat can act always on the underlying explicit identity of the molecules even if they are in the coarse grained region (keeping a double resolution)[15]. The explicit forces are then added up to determine the force acting on the center of mass of the coarse grained molecules. In this way the coarse grained particles have the correct velocity distribution.

Diffusive processes

The application of the AdResS method as reported in the previous sections may lead to the fact that one has different diffusion constants in the atomistic and in the coarse grained region. This will lead to an asymmetric diffusion profile for molecules whose coarse grained representation is much simplified with respect to the atomistic one (for example for water). However, while a faster dynamics of the coarse grained molecules may even be an advantage for sampling purposes, for dynamical analysis this is not ideal. A way to circumvent

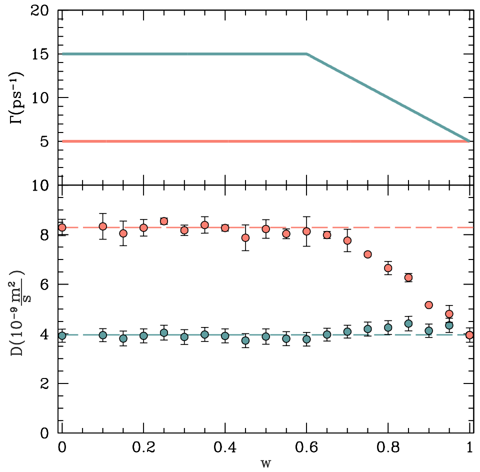


Figure 10. Top figure: The upper curve indicates the dependency of the friction coefficient as a function of the particle identity w when a position-dependent thermostat is used. The straight (lower) curve shows the constant value of the friction coefficient when a regular thermostat is used. Bottom figure: The dots at the upper part indicate the diffusion of the molecules when the regular thermostat is used. The dots of the lower part indicate the diffusion of the molecules when the position-dependent thermostat is used. (Figure was taken from Ref.[29])

this problem is that of slowing down the dynamics of the faster coarse grained molecules. The Langevin thermostat (see above) allows for the changing of the dynamics (and the diffusion constant) by modifying the strength of the friction ζ. As the Langevin thermostat is a local thermostat one can easily make the friction space dependent (or weight dependent). In this case one has to simply tune $\zeta(w)$ in a way that the diffusion constant is the same all over the system. This has been done for the tetrahedral fluid (see Fig. 10).

Recently[41] the DPD thermostat has been extended to change the dynamics of the system; the basic idea is to add an additional friction (and noise) to the transversal degrees of freedom, which allows to conserve hydrodynamics keeping Galilei invariance.

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