Adaptive resolution molecular dynamics simulation through coupling to an internal particle reservoir

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For simulation studies of (macro) molecular liquids it would be of significant interest to be able to adjust or increase the level of resolution within one region of space, while allowing for the free exchange of molecules between open regions of different resolution or representation. We generalize the adaptive resolution idea and suggest an interpretation in terms of an effective generalized grand canonical approach. The method is applied to liquid water at ambient conditions.

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Many (macro) molecular systems display phenomena and properties that are inherently multiscale in nature, and thus particularly challenging for both theory and experiment. Here computer simulations represent a powerful tool of investigation, though truly large all-atom simulations of complex molecular systems are neither possible, because of CPU requirements, nor in many cases very useful, as they often produce an excess of data. To the aim of linking large scale generic properties and local specific chemistry, a variety of scale bridging simulation techniques, ranging from hierarchical parametrizations of models covering different levels of resolution, see, e.g., [1–7], to interfaced layers of different resolutions (see, e.g., [8–18]) have been developed.

As most techniques are sequential—the whole system is treated on one level of resolution at a time—switching between resolutions may be performed only for the whole system. Often, however, it would be desirable to adjust the resolution on the fly only in a smaller well-defined region of space, i.e., considering more details, due to the problem of interest, while keeping the larger surrounding on a coarser, computationally more efficient level. This idea has been successfully employed for problems of crack propagation in hard matter [19]. However, for soft matter or liquids inherent fluctuations pose special challenges. They require molecules or parts of large molecules to be able to cross boundaries between areas of different representation without any barrier, keeping the overall thermodynamic equilibrium intact. While crossing between regions of different resolution, they either become more coarse grained or resume more atomistic detail; i.e., they acquire or lose degrees of freedom (DOFs). In general, for this process the only requirement is that the coarse-grained surrounding supplies or removes molecules and heat in a way that in the atomistic region the thermodynamic state point is the same as in a full atomistic simulation. This can be controlled by keeping thermodynamic and structural properties as radial distribution functions and thus the molecule number fluctuations of the all-atom region the same as in a full atomistic simulation. The adaptive resolution method (AdResS, Adaptive Resolution Scheme), which allows one to couple two systems with different resolution within one molecular-dynamic (MD) simulation [20–25], describes a first step in this direction. Molecules change their resolution and thus their number of DOFs when moving through space and passing from one region through a transition zone into the other. The method has successfully been extended into the quantum [26,27] and the continuum [28,29] region. A different approach based on the interpolation of Lagrangians can be found in Ref. [30].

In the following, we will generalize the AdResS concept and show that the atomistic or fine-grained subsystems can be viewed as a system in contact with a (huge) coarse-grained particle or molecule reservoir, thus effectively representing a μVT ensemble on the level of the high resolution subsystem, while the overall systems remain to be an NVT ensemble. The term "*effective*" points to the fact that AdResS does not allow for a direct specification or control of μ in the atomistic region. However, *a posteriori*, we can conclude that μ must be the same as in a full atomistic system because we match the full atomistic $g(r)$ (and thus molecule number fluctuations) and thermodynamic state point. As a consequence, there is no net flux (molecules or energy) between the regions, while molecules diffuse freely throughout the whole simulation box. Moreover, our reservoir, though large, is finite, and finite size effects might be of concern. To avoid this, an asymptotic μVT setup can be achieved by linking the coarse-grained region in addition to a continuum, as shown in Refs. [28,29]. We now first shortly review the adaptive resolution method AdResS and the concept of thermodynamic force and extend this to a more general coupling scheme. We apply this to the example of liquid water,

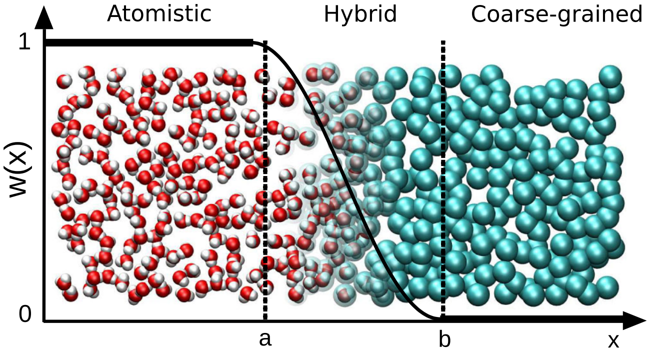

FIG. 1 (color online). Pictorial representation of the adaptive simulation box and local molecular representation. On the right is the low resolution (coarse-grained) region, indicated by B, and on the left is the high resolution (atomistic) region A. In the middle is the transition (hybrid) region H with the switching function $w(x)$ (curve in grey).

where the coarse-grained water model matches the compressibility of the all-atom model, while the pressure is higher by more than 3 orders of magnitude.

In the AdResS method, molecules smoothly change their level of resolution as a function of position by moving through a transition region as illustrated in Fig. 1. In order to accomplish the process described above, two different representations are interpolated by a transition function $w(x)$ with $w = 1$ in region A, the fine-grained more microscopic or all-atom one, and $w = 0$ in the coarse-grained region B, respectively. Further, let us assume that a particle in B is the coarse-grained representation of a (part of a) molecule in region A and the position of the coarse particle is the center of mass of the corresponding atoms. With this in mind, two molecules α, β in region A [fine grained, $w(X_\alpha) = w(X_\beta) = 1$, X_α, X_β being the x coordinates of the centers of mass of the two molecules, cf Fig. 1] interact via the standard forces between all individual atoms of the molecules; in region B [coarse-grained, $w(X_\alpha) = w(X_\beta) = 0$] two coarser molecules interact with each other via central forces; just as in a bulk system of all-atom molecules or coarse-grained molecules, respectively. In all cases of mixed resolution interactions, these two forces are interpolated as illustrated in Fig. 1 so that the total force $\mathcal{F}_{\alpha\beta}$ between two different molecules consist of two parts. The all-atom contribution reads

$$\mathcal{F}^A_{\alpha\beta} = w(X_\alpha)w(X_\beta)\sum_{i,j}\mathbf{F}^A_{\alpha_i\beta_j} \qquad \alpha \neq \beta. \tag{1}$$

While the coarse-grained parts is

$$\mathcal{F}^B_{\alpha\beta} = (1 - w(X_\alpha)w(X_\beta))\mathbf{F}^B_{\alpha\beta} \qquad \alpha \neq \beta. \tag{2}$$

$\mathbf{F}^A_{\alpha_i\beta_j}$ is the force between atom i of molecule α and atom j of molecule β and $\mathbf{F}^B_{\alpha\beta}$ is the coarse-grained center of mass—center of mass interaction. Note that in the transition region the intramolecular atom-atom interactions are left unaffected. For technical details of the implementation we refer the reader to the supporting material [31]. Altogether we simulate a system at constant volume, partitioned in two different (ideally macroscopic) regions (coarse grained and fine grained) by a transition region of finite width. This region facilitates the exchange of molecules and ensures equilibrium between the coarse and fine-grained regions, moreover, by construction (as explained below), should not affect the density fluctuations (i.e., compressibility). Beyond the crucial technical task of assuring the thermodynamically correct coupling between the two large regions, the transition region does not have, *a priori*, any thermodynamic or physical meaning. An important characteristic of the adaptive approach is that while the overall number of molecules is conserved, this is not the case in the individual regions. Eventually, we aim for a flat density profile throughout the whole simulation box, including the transition region, so that we have a thermodynamic state point well defined without (kinetic) barriers for the exchange of molecules.

In the same spirit, the temperature has to be well defined and equal throughout the system. While this is simple to achieve in the "bulk" regions, the transition region requires some care since in this region a change in the number of degrees of freedom occurs. By switching from coarse grained to atomistic or vice versa, DOFs are reintroduced or removed and the related equilibration is accomplished by a "local" thermostating procedure (for details, see the supporting material [31]). The approach presented above, paves the way to an open system simulation scheme within a generalized, effectively grand canonical, framework.

A common method to derive coarse-grained interactions is based on matching the center of mass radial distribution functions between the molecules in the two systems. As a result, the compressibilities κ remain unchanged [32] by construction while the pressures in the fine and coarse-grained representation can be different [33]. In terms of the grand potential pV this reads (for identical volumes)

$$p_A(\mu_A, T)V \neq p_B(\mu_B, T)V; \qquad \kappa_A = \kappa_B, \tag{3}$$

where μ_A and μ_B are the respective chemical potentials. The inequality above will result in density variations in the system. Instead, we would like to have an average constant density ρ_0 throughout the whole simulation box, while keeping identical compressibilities. Different pressures at the boundaries of the transition region will produce a drift force on the molecules, leading to an unphysical inhomogeneous system. Different compressibilities would affect the molecule number fluctuations in the *still finite* regions. Thus, we keep $\kappa_A = \kappa_B$ and propose to exactly compensate this pressure generated drift force by a thermodynamic force $\mathbf{F}_{\text{th}}(x)$ acting on the molecules and Eq. (3) can then be rewritten as (see Fig. 1)

$$\left(p_A(\mu_A, T) + \frac{\rho_0}{M_\alpha}\int_a^b \mathbf{F}_{\text{th}}(x)dx\right)V = p_B(\mu_B, T)V, \tag{4}$$

with ρ_0 being the reference, uniform, molecular density. Equation (4) tells us that the subsystem A (B) is in equilibrium with a reservoir μ_B (μ_A), respectively, notwithstanding the fact that the pressures, p_A and p_B, and local chemical potentials, μ_A and μ_B, may be different. To overcome these variations, the related thermodynamic work, which exactly compensates any related drift force between the different regions, is provided or absorbed by $\mathbf{F}_{\mathrm{th}}$. Let the all-atom system, at a given density ρ_0, serve as a reference system, then the force on a molecule with mass M_α balancing $-\nabla p(x)$, reads

$$\mathbf{F}_{\mathrm{th}}(x) = \frac{M_\alpha}{\rho_0}\nabla p(x), \tag{5}$$

where $p(x)$ is the local pressure at the target density ρ_0. $\mathbf{F}_{\mathrm{th}}$ is applied for $a < x < b$, where a (b) is the left (right) boundary of the transition region. In Eq. (5), $p(x = a) = p_A$ and $p(x = b) = p_B$. Now the density will remain unchanged. With this generalization, the original equation for the coarse-grained forces in the transition region, Eq. (2) is changed so that the force $\hat{\mathcal{F}}^B_\alpha$ acting on the center of mass of molecule α reads

$$\hat{\mathcal{F}}^B_\alpha = \sum_\beta \mathcal{F}^B_{\alpha\beta} + \mathbf{F}_{\mathrm{th}}(X_\alpha). \tag{6}$$

The above line of arguments does not require the pressures in the two ("macroscopic") regions, p_A and p_B, to be the same, allowing us to couple rather different systems. Formally, this simply means that the thermodynamic force as well as the thermostat can perform work on the molecules to adjust the viral pressure and the thermal energy, respectively, while passing from one region to the other. This procedure allows one to couple almost arbitrary systems and keep them in equilibrium with respect to each other. For typical coarse-graining procedures like (iterative) Boltzmann inversion or reverse Monte Carlo calculations, which are mostly based on radial distribution functions and reproduce structural rather than thermodynamic aspects very well, this is of special advantage.

The optimized pressure profile $p(x)$ is not directly accessible as it has to be measured under the constraint of enforcing the equilibrium density ρ_0 in the system. Thus, we developed an iterative approach based on the density profile. Within a linear approximation, a first estimate of the local pressure $p(x, \rho(x))$ for an enforced overall constant density ρ_0 is

$$p(x, \rho(x)) \approx p_A + \frac{1}{\rho_0 \kappa_T}(\rho_0 - \rho(x)), \tag{7}$$

where κ_T is the (constant) isothermal compressibility, and $\rho(x)$ is the (nonuniform) density to which the system would adjust itself to without applying an external force. In order to enforce the uniform density ρ_0, Eqs. (7) and (5) allow us to obtain an initial thermodynamic force, that can be refined iteratively through

$$\mathbf{F}^{i+1}_{\mathrm{th}}(x) = \mathbf{F}^{i}_{\mathrm{th}}(x) - \frac{M_\alpha}{\rho_0^2 \kappa_T}\nabla \rho^i(x), \tag{8}$$

until the system evolves to the target uniform density. Here, for $i = 1$, we have $\rho^1(x) = \rho(x)$ and $\mathbf{F}^1_{\mathrm{th}}(x) = 0$. The prefactor $1/\rho_0^2\kappa_T$ can be interpreted as a variation of local chemical potential, by the identity [32]

$$\left(\frac{\partial \mu}{\partial \rho}\right)_{V,T} = \frac{1}{\rho^2 \kappa_T}, \tag{9}$$

a fact explored already before in this context [23]. In the following, we will demonstrate the power of this concept for the illustrative case of liquid water, where the compressibility of the SPC/E water and a structure based coarse-grained model are the same, while the pressure in the coarse-grained system is 6000 bar [34].

Coarse-graining liquid water with a focus on the liquid structure usually leads to models for which the pressure is significantly higher while the compressibility remains essentially unchanged. Thus, pressure correction terms are often used, which add linear terms to the coarse-grained potential. The compressibility is then affected as $\kappa_T \propto \int r^2(g(r) - 1)dr$ and small deviations at high r values can have dramatic effects [34]. However, for adaptive resolution methods, but also solvent-solute systems, it is important that the compressibility in the coarse-grained and all-atom regions is the same. This minimizes finite size effects for our (in most cases on purpose as small as possible) atomistic region, imposed by the *still finite* coarse-grained region. For many applications in computational biology, but also for studies of water itself, the SPC/E model is employed [35]. A standard structure based coarse-grained model perfectly fits the radial distribution function, but does not comply with the tetrahedral packing [34,36]. It has, within the error bars, the same compressibility but a very high pressure of about 6000 bar, making it an ideal test case for the thermodynamic force principle described above. If not properly accounted for, this pressure difference between the different models would lead to density distortions throughout the simulation box and create a transient flow of molecules from the coarse-grained to the atomistic region. Using κ_T^A at the outset of the iteration scheme of Eq. (8) as described before, after only four iterations for the thermodynamic force we arrive at a flat density profile, as illustrated in Fig. 2.

The thermodynamic force creates a stationary state with the correct target density, removing both the effect of the pressure difference of the models on the distribution of molecules in either region and the artifacts from the change of resolution in the transition region. The advantages are also clearly displayed, when looking at local density fluctuations. While in the thermodynamic limit, the molecule number fluctuations are related to the compressibility through $\rho k_B T \kappa_T = \frac{\langle N^2\rangle - \langle N\rangle^2}{\langle N\rangle}$. Here we analyze an effective compressibility in terms of molecule number fluctuations in slabs along the axis of resolution change. The increased

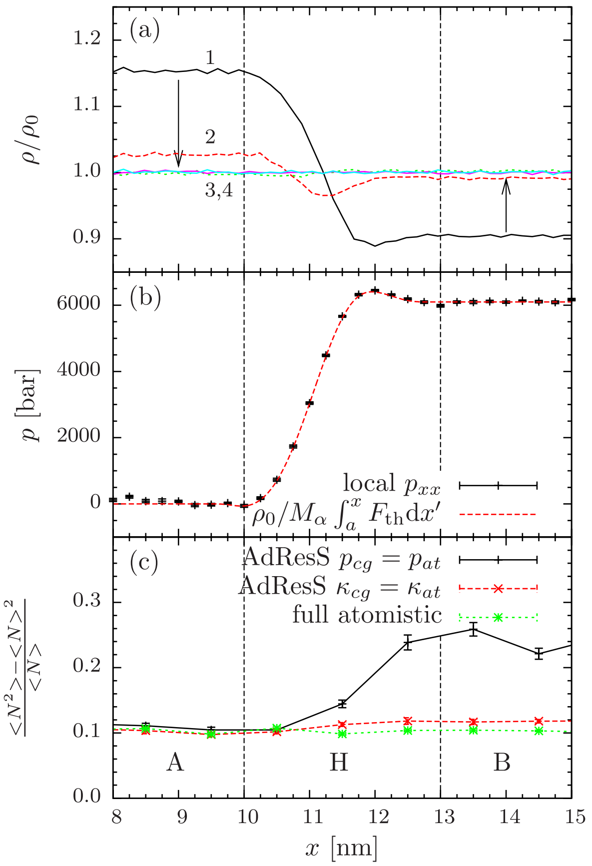

FIG. 2 (color online). (a) Density profile for the water simulation for the uncorrected AdResS simulation of water and several iterations of the thermodynamic force with A being the all-atom SPC/E region and B the coarse-grained region. The final density profile shows deviation of less than 0.4%. (The arrow indicates the development of the density with the iteration.) (b) Compensation of the local pressure change between regions by the thermodynamic force. (c) Molecule number fluctuations in slabs (width $\Delta x = 1$ nm) along the x axis for pressure corrected and uncorrected coarse-grained models.

compressibility for a pressure corrected coarse-grained SPC/E water model leads to an increase in the local density fluctuations. Within our setup, we do not alter the effective compressibility anywhere in the system as shown in Fig. 2(c). Actually, the molecule number fluctuations in subvolumes of region A are the same as in similar subvolumes of a full all-atom simulation. Hence, the particle distribution in region A shows the expected Gaussian distribution as it is the case in the full all-atom simulation, shown in Fig. 3. Leveling out any pressure undulations in the transition region, while keeping the compressibilities, the same also means that there is no barrier for molecule exchange between regions (see the supporting information [31]). Coupling two systems with different pressures means that the thermodynamic force performs work on the molecules, when they cross from one region to the other. In practice, the integral over the thermodynamic force over the transition region does not have to be zero, which would be the case if the pressures on either side were the same. Thus, for the present setup, the thermodynamic force has to exactly compensate the local pressure variation due to the constant density. The comparison of the final local pressure (see supporting information for details) and the thermodynamic force as derived in form of an external local pressure field is shown in Fig. 2(b). They perfectly match, illustrating the overall consistency of the approach. Thus, by applying the thermodynamic force, we arrive at a robust and efficient simulation setup, which enables us within a single molecular-dynamic simulation to keep rather different systems with quite different intrinsic pressures but identical compressibilities in equilibrium with each other.

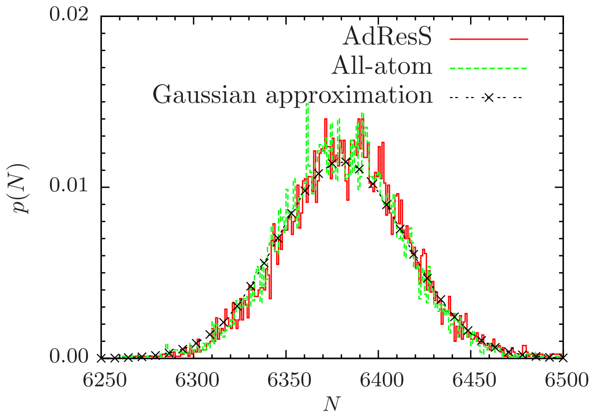

FIG. 3 (color online). Particle number distribution in a slab of width $l = 4$ nm and for an atomistic zone in adaptive resolution with the same width. Both distributions match the expected Gaussian behavior with the same $\langle N\rangle$ and variance $\sigma^2 = \rho k_B T \kappa_T \langle N\rangle$.

The fact that the number of particles at a given resolution fluctuates suggests for one to view each subsystem as a reservoir of particles for the other, i.e., effectively a grand canonical setup. We have shown that the average and the fluctuating number of molecules or particles in each subsystem are the same as analyzed in a full atomistic system. The extreme example of liquid SPC/E water at temperature 300 K and pressure 1 bar, where the coarse-grained model at the same temperature and density has a pressure of more than 6000 bar, shows the power of the present approach. This opens new pathways to study systems, where a rather high level of detail is only required within a rather restricted area, while at the same time the exchange with the surrounding area is essential. Examples are (small) organic molecules in mixed solvents, e.g., water and urea, or growth and structure formation phenomena in soft matter where locally the assembly process needs details of the molecular structure (templated crystal growth, biomineralization, etc.).

In conclusion, a new method has been proposed that enables an adaptive resolution description of atomistic systems within a single simulation setup. The computational procedure couples a high resolution system to a low resolution system on a particle based level. The molecules freely move between the regions and adapt their molecular resolution automatically. The (large) lower resolution region can be viewed as a reservoir of molecules for the high resolution region, which preserves the basic thermodynamical and structural conditions of the equivalent subsystem in a full high resolution simulation. Moreover, the coupling scheme is determined in a self-consistent way via the iterative determination of a thermodynamic force in the transition region, which acts as an active membrane facilitating the change of resolution of the molecules. More generally, the coupling of an all-atom with a coarse-grained system at the same average density requires a simulation setup where the work performed by the thermodynamic force can account for the difference in the excess chemical potential μ between the regions (the temperature part due to the internal degrees of freedom is taken care of by the thermostat). The iterative procedure is general and successfully applied to a rather delicate system, namely, liquid water at ambient conditions, where for the same density and temperature, the coarse-grained model has a pressure that is almost four orders of magnitudes larger than that of the atomistic model. Its computational efficiency and applicability to an extended class of systems renders the method useful for the study of problems in condensed matter, chemical physics, and material science where the coupling of different levels of resolution in a particle based scheme is very desirable.

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