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# Hamiltonian adaptive resolution simulation for molecular liquids

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Adaptive resolution schemes allow the simulation of a molecular fluid treating simultaneously different subregions of the system at different levels of resolution. In this work we present a new scheme formulated in terms of a global Hamiltonian. Within this approach equilibrium states corresponding to well defined statistical ensembles can be generated making use of all standard Molecular Dynamics or Monte Carlo methods. Models at different resolutions can thus be coupled, and thermodynamic equilibrium can be modulated keeping each region at desired pressure or density without disrupting the Hamiltonian framework.

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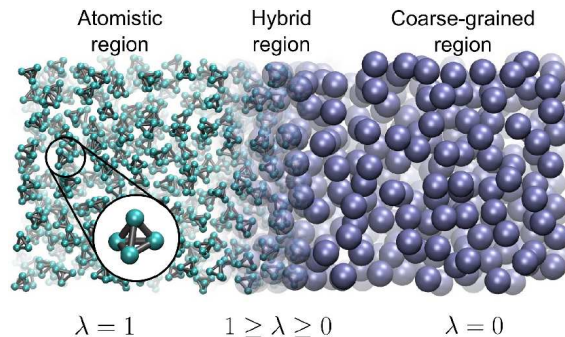


FIG. 1. (color online) Illustration of the simulation setup for adaptive resolution simulations. Molecules freely move from an atomistic region, AA,  $\lambda = 1$ , through a transition zone H to the coarse-grained region, CG,  $\lambda = 0$ .  $\lambda(\mathbf{R})$ ,  $\mathbf{R}$  being the position of the center of mass of the molecules, is a smooth transition function that interpolates between the AA and the CG region.

Complex molecular fluids and soft matter typically display inherently multiscale phenomena and properties. To handle this problem general strategies have been developed, which can be classified as either *sequential* or *simultaneous*. In the former class of methods, coarse-grained models are (usually) developed from microscopic input [1–3]; systems are then simulated separately at different levels of resolution. In the latter class, which we pursue here, systems are treated within a single simulation on different levels of resolution. A small, well defined region of space is kept at a higher level of detail, while the surrounding can be treated on a coarser, computationally more efficient level.

This idea has been successfully employed, for example, to investigate crack propagation in hard matter [4–8] and in mixed quantum mechanics/molecular mechanics (QM/MM) simulations, where particles are assigned statically to either the QM or the MM region [9–13]. For soft matter and liquids, inherent fluctuations and particle diffusion require a setup where molecules, or parts of them, can cross boundaries between areas at different resolution, while maintaining the overall thermodynamic equilibrium. Scale-bridging methods have been developed in various fashions to couple all atom (AA) and coarse-grained (CG) models [14], and even particle-based models to the continuum [15–17]. To our knowledge, to date the only energy-conserving mixed-resolution approach is the ‘Adaptive Partitioning of the Lagrangian’ method by Heyden and Truhlar [18, 19]. In this method, a combinatoric sum of all possible AA and CG interactions between molecules in different resolution regions is taken into account. The practical viability of this approach is limited by its intrinsic combinatoric complexity, and by the fact that the resulting equations of motion are not amenable to a standard symplectic integrator (e.g. velocity Verlet or leap frog), so that an *ad hoc*, more complicated one had to be developed.

With this idea of mixed resolution in mind the AdResS (Adaptive Resolution Scheme) method was developed, in which one can dynamically couple specific regions of a simulation box at different levels of resolution, while maintaining the correct thermodynamic equilibrium between them [14, 20–26]. The particles move from one region to the other through a hybrid resolution zone (Fig. 1): in this region the resolution switch is defined by a transition function  $\lambda(x)$ , smoothly changing the interactions from an atomistic description,  $\lambda = 1$ , to a coarser one,  $\lambda = 0$ , which typically contains a considerably smaller number of degrees of freedom (DOF’s) per molecule. AdResS is based on the requirement that molecules interact through pairwise forces, and Newton’s third law is strictly satisfied in the whole simulation box by construction. These requirements lead to a force interpolation scheme between molecules,  $\mathbf{F}_{\alpha\beta} = \lambda(\mathbf{R}_\alpha)\lambda(\mathbf{R}_\beta)\mathbf{F}_{\alpha\beta}^{AA} + [1 - \lambda(\mathbf{R}_\alpha)\lambda(\mathbf{R}_\beta)]\mathbf{F}_{\alpha\beta}^{CG}$ , where the force  $\mathbf{F}_{\alpha\beta}$  between centers of mass of molecule  $\alpha$  and  $\beta$  consists of an atomistic,  $\lambda(\mathbf{R}_\alpha)\lambda(\mathbf{R}_\beta)\mathbf{F}_{\alpha\beta}^{at}$ , and a coarse-grained part,  $[1 - \lambda(\mathbf{R}_\alpha)\lambda(\mathbf{R}_\beta)]\mathbf{F}_{\alpha\beta}^{cg}$ . Yet, it was formally demonstrated [27] that a Hamiltonian compatible with this force interpolation scheme can not exist.

The method is nonetheless robust, since it allows us to define temperature, pressure and density everywhere, and the introduction of a thermodynamic force [28] in the transition zone paved the way to open system MD simulations [20, 29]. Despite the success of the force-interpolation based AdResS method, though, the lack of a Hamiltonian description in the transition region is a drawback: it hampers a general statistical theory for the whole setup, limits the choice of the simulation ensemble and prevents Monte Carlo simulations. Moreover, in the transition region the system has to be stabilized by a local thermostat that removes excess heat thus keeping the system in a state of dynamical equilibrium [14, 20–22, 24–26, 30, 31]. In this Letter we propose a new resolution-interpolation and coupling concept, *H*-AdResS, which is formulated in terms of a general Hamiltonian *H* for the whole system. Furthermore, we develop an analogy to the Kirkwood [32] coupling parameter scheme where we relate the variation of the thermodynamic properties through the transition zone in *H*-AdResS to the integration over  $\lambda$  in homogeneous

systems. We demonstrate our approach on a prototypical mixed AA/CG system, showing that the existence of a global Hamiltonian makes it possible to perform microcanonical (NVE) adaptive resolution simulations.

Let us consider a system composed of  $N$  molecules. [33] (labeled by greek indices), each having  $n$  atoms (labeled by latin indices) The resulting  $M = nN$  atoms interact *via* general intramolecular potentials, and pairwise intermolecular potentials. The Hamiltonian of this system can be written as:

$$H^{AA} = \sum_{\alpha=1}^N \sum_{i=1}^n \frac{p_{\alpha i}^2}{2m_{\alpha i}} + \sum_{\alpha=1}^N V_{\alpha}^{AA} + V^{int} \quad (1)$$

$$V_{\alpha}^{AA} \equiv \frac{1}{2} \sum_{\beta \neq \alpha}^N \sum_{ij}^n V^{AA}(|\mathbf{r}_{\alpha i} - \mathbf{r}_{\beta j}|)$$

$V^{int}$  indicates the intramolecular interaction, for which we do not need to make any assumption.  $p_{\alpha i}$ ,  $m_{\alpha i}$ , and  $\mathbf{r}_{\alpha i}$  are the momentum, mass, and position, respectively, of atom  $i$  of molecule  $\alpha$ . We now consider a CG pair potential  $V_{\alpha\beta}^{CG} \equiv V^{CG}(\mathbf{R}_{\alpha} - \mathbf{R}_{\beta})$  that depends on the center of mass (CoM) positions  $\mathbf{R}$  of the molecules  $\alpha$  and  $\beta$ ; the total CG potential energy of molecule  $\alpha$  is given by  $V_{\alpha}^{CG} \equiv \sum_{\beta \neq \alpha} V_{\alpha\beta}^{CG}/2$ . In analogy to Kirkwood's thermodynamic integration (TI) method to compute free energy differences [32], we define a 'mixed resolution' Hamiltonian  $H$ :

$$H = \sum_{\alpha i} \frac{p_{\alpha i}^2}{2m_{\alpha i}} + \sum_{\alpha} \{ \lambda_{\alpha} V_{\alpha}^{AA} + (1 - \lambda_{\alpha}) V_{\alpha}^{CG} \} + V^{int} \quad (2)$$

where coupling parameters  $\lambda_{\alpha} = \lambda(\mathbf{R}_{\alpha})$  were introduced, which depend on the position of the molecules' centers of mass. The local resolution  $\lambda(\mathbf{R})$  varies between 1 (completely AA system) and 0 (completely CG system); intermediate  $\lambda$  values define a hybrid region, interfacing the atomistic and the coarse-grained ones (as in Fig. 1). According to the Hamiltonian in Eq. 2, for molecules interacting with a mixed-resolution (having  $\lambda \in (0, 1)$ ) both AA and CG *total* potential energies are calculated and weighted according to their own resolution  $\lambda$ . The atomistic DOF's are retained everywhere [20] and their dynamics is seamlessly evolved, allowing coarse-grained molecules close to the hybrid region to interact also at the atomistic level. Being defined in terms of a Hamiltonian, this hybrid-resolution scheme conserves the total energy in a microcanonical simulation, as it is numerically verified [34]. Furthermore, as different regions exchange particles and energy the resulting stationary state is an *equilibrium state*.

The force derived from  $H$  (Eq. 2) has the form:

$$\mathbf{F}_{\alpha i} = \sum_{\beta, \beta \neq \alpha} \left\{ \frac{\lambda_{\alpha} + \lambda_{\beta}}{2} \sum_{j=1}^n \mathbf{F}_{\alpha i|\beta j}^{AA} + \left( 1 - \frac{\lambda_{\alpha} + \lambda_{\beta}}{2} \right) \mathbf{F}_{\alpha i|\beta}^{CG} \right\} + \mathbf{F}_{\alpha i}^{int} - [V_{\alpha}^{AA} - V_{\alpha}^{CG}] \nabla_{\alpha i} \lambda_{\alpha} \quad (3)$$

where  $\mathbf{F}_{\alpha i|\beta j}^{AA}$  (resp.  $\mathbf{F}_{\alpha i|\beta}^{CG}$ ) is the AA (resp. CG) force acting on atom  $i$  of molecule  $\alpha$  due to the interaction with molecule  $\beta$ . The distribution of CoM forces onto the atoms is described in Ref. [29]. The first term of Eq. 3 contains a weighted sum of pairwise forces and is antisymmetric by exchange of the molecules' labels; this term therefore complies with Newton's 3rd law everywhere, and is analogous to the AdResS force interpolation. The second term,  $\mathbf{F}_{\alpha i}^{int}$ , is the force exerted on atom  $\alpha i$  by the other atoms *in the same molecule* and does not contribute to the force balance between molecules. The third term,  $\mathbf{F}_{\alpha i}^{dr} \equiv -[V_{\alpha}^{AA} - V_{\alpha}^{CG}] \nabla_{\alpha i} \lambda(\mathbf{R}_{\alpha})$ , introduces in the hybrid region a drift force which violates Newton's 3rd law and momentum conservation.  $\mathbf{F}_{\alpha i}^{dr}$  plays the role of an external force inducing, in general, pressure and density inhomogeneities in the system as it reaches equilibrium (no temperature gradients are present because energy is conserved and freely flows between the two subdomains). In particular, the drift force is balanced by a hydrostatic pressure gradient across the hybrid region given by  $\nabla p = \rho \langle \mathbf{F}^{dr} \rangle$  [35].

We validated our approach on the same model system as in [20] and illustrated in Fig. 1. A detailed description of these simulations is given in the supplementary information [34]. The AA system consists of tetrahedral molecules, each composed by four atoms of unit mass connected by anharmonic springs. The atomistic interaction between molecules is given by a purely repulsive Weeks Chandler Andersen (WCA) potential, while the CG potential was obtained via Iterative Boltzmann Inversion (IBI) [36]. In contrast to the original AdResS scheme, we could perform these adaptive resolution simulations in the microcanonical ensemble, achieving conservation of the total energy (Fig. S1). The resulting density profiles are flat in both the AA and the CG regions, and within 1% of the reference values

(Fig. S2). In addition, the structure of the fluid in the AA region is unchanged compared to a purely AA simulation (Fig. S2).

Such seamless coupling stems from the good matching between the thermodynamic properties of the AA potential and the CG potential. In general, however, the employed CG potentials are only approximations to the exact many-body CG potential [37, 38]. As a consequence, there is usually a thermodynamic mismatch between the AA and the CG systems, which can have different chemical potentials and equations of state [3]. If compensations are introduced as time-independent functions of the position of the molecules, then the modified Hamiltonian  $\hat{H}$  is expressed as

$$\hat{H} = H - \sum_{\alpha=1}^N \Delta H(\lambda(\mathbf{R}_\alpha)), \quad (4)$$

and conserves the energy. The compensation terms change the drift force to

$$\hat{\mathbf{F}}_\alpha^{dr} \equiv - \left[ V_\alpha^{AA} - V_\alpha^{CG} - \frac{d \Delta H(\lambda)}{d\lambda} \Big|_{\lambda=\lambda(\mathbf{R}_\alpha)} \right] \nabla_\alpha \lambda(\mathbf{R}_\alpha) \quad (5)$$

In the following, we relate suitable compensations to the Kirkwood's TI scheme for the free energy difference  $\Delta F(\lambda)$  between a hybrid system with a position-independent coupling parameter  $\lambda \leq 1$  and a coarse-grained system ( $\lambda = 0$ ) at the reference concentration  $\rho^*$ :

$$\begin{aligned} \frac{\Delta F(\lambda)}{N} &= \frac{1}{N} \int_0^\lambda d\lambda' \frac{d \Delta F(\lambda')}{d\lambda'} \\ &= \frac{1}{N} \int_0^\lambda d\lambda' \left\langle \frac{d H(\lambda')}{d\lambda'} \right\rangle_{\lambda'} \\ &= \frac{1}{N} \int_0^\lambda d\lambda' \langle [V^{AA} - V^{CG}] \rangle_{\lambda'} \end{aligned} \quad (6)$$

Consider first a situation, where we wish to embed the AA region in a CG region with identical molecular (Virial plus kinetic) pressure. [39] To avoid the buildup of a hydrostatic pressure gradient [35] across the hybrid region, we need to assure that  $\nabla p = \rho \langle \hat{\mathbf{F}}^{dr} \rangle \equiv 0$  or

$$\frac{d \Delta H(\lambda)}{d\lambda} \Big|_{\lambda=\lambda(\mathbf{R}_\alpha)} \equiv \langle [V_\alpha^{AA} - V_\alpha^{CG}] \rangle_{\mathbf{R}_\alpha} \quad (7)$$

If we replace the local average at each given  $\lambda = \lambda(\mathbf{R}_\alpha)$  by the corresponding value in the 'bulk' of a pure- $\lambda$  fluid,  $\langle [V_\alpha^{AA} - V_\alpha^{CG}] \rangle_{\mathbf{R}_\alpha} \simeq \frac{1}{N} \langle [V^{AA} - V^{CG}] \rangle_{\lambda=\lambda(\mathbf{R}_\alpha)}$ , then the compensation will take the form

$$\Delta H(\lambda_\alpha) = \frac{\Delta F(\lambda_\alpha)}{N}. \quad (8)$$

Since atomistic and coarse-grained systems usually follow different equations of state [37, 38], as depicted in Fig. 2, the densities of the two regions will generally differ. It is worth noting, though, that by adjusting the number of particles in the system one can easily tune the particle density in the AA region to the reference value  $\rho^*$ . In this case the pressure *in the entire system* would adjust to the reference value of the atomistic system.

A different compensation route has to be taken if, instead of the same pressure, one wants to ensure that both subsystems coexist at the same reference density  $\rho^*$ . In particular, the chemical potential gradient, which is generally established across the transition region, would have to be counterbalanced [29]. This idea leads to the following form of the compensation term in Eq. (4),

$$\Delta H(\lambda(\mathbf{R}_\alpha)) \equiv \Delta \mu(\lambda) = \frac{\Delta F(\lambda)}{N} + \frac{\Delta p(\lambda)}{\rho^*}, \quad (9)$$

where  $\Delta \mu$  is the difference in chemical potential across the transition layer and is related to the (molar) Gibbs free energy difference by  $\Delta \mu = \Delta G/N = \Delta F/N + \Delta p/\rho^*$ . Again, Kirkwood TI provides a way to predict  $\Delta \mu$  by simultaneously evaluating the Helmholtz free energy difference  $\Delta F(\lambda)$  and the pressure difference  $\Delta p(\lambda)$  in independent simulations of pure- $\lambda$  fluids at the reference state ( $\rho^*, T$ ) and varying  $\lambda$ .

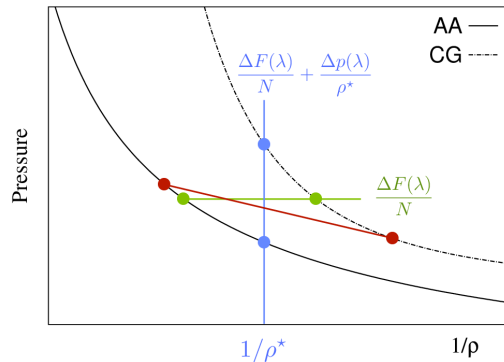


FIG. 2. (color online) Cartoon illustrating the thermodynamics of H-AdResS. The isothermals of AA and CG models (black solid and dashed lines) are shown. When no compensation term is added to the H-AdResS Hamiltonian in Eq. (4) density and pressure in the two regions are different from their reference values (red). Applying compensation terms it is possible to maintain the coupled systems either at the same density (“constant density route”, blue) or at the same molecular pressure (“constant pressure route”, green).

Fig. 2 graphically summarizes the possible routes allowed by these two forms of the free energy compensation. The “pressure route”, with  $\Delta H(\lambda) = \Delta F(\lambda)/N$ , cancels the extra interface “pressure” and guarantees that mechanical equilibrium is uniquely established by inter-molecular forces (however, in general, the AA and CG subregions will attain different densities). On the other hand, in the “density route”, the addition of  $\Delta H(\lambda) = \Delta\mu(\lambda)$  compensates the difference in chemical potential across the transition region leading to an equilibrium state where both subsystems coexist at the same density, but different molecular pressure.

To test and validate the proposed compensation schemes we considered the above mentioned tetrahedral system, but we substituted the CG IBI potential with a WCA potential, which was deliberately parametrized to give a higher molecular pressure and  $\Delta F(\lambda) < 0$  than the atomistic system at the same state point. For sake of simplicity, the same number of molecules, total volume of the system and relative volumes of the different subregions were used in all simulations (see also [34]).

The red curves in Fig. 3 show the pressure and density profiles for the uncorrected H-AdResS Hamiltonian, Eq. 2. Both quantities exhibit jumps in the transition regions, and in the AA region neither pressure nor density attain the reference values. Making use of Eqs. 8 and 9 we can compensate for the free energy imbalance between the AA and CG regions. The “constant pressure route” balances on average the drift force  $\langle \mathbf{F}^{dr} \rangle$ , thus producing a flat molecular pressure profile and leading to an average momentum conservation in the whole system; the density is nonetheless different in the two regions. In contrast, the “constant density route” levels out the density to the reference value  $\rho^* = N/V$  by taking the pressure in the bulky AA and CG regions to the values they have in the corresponding homogeneous simulation. The compensation term of Eq. (9) does not take into account density-density correlations over the transition layer and, as observed in Fig. 3, this produces small density fluctuations (of about  $\sim 3\%$ ) in the transition region. We are currently working on a generalization of the present framework to include such correlations. In any case, if required, the small density fluctuations can be removed by an iterative refinement scheme (see e.g. [28]).

To summarize, we have presented a method, H-AdResS, to simulate molecular liquids with position-dependent interpolation between two different levels of resolution. Whereas in the original AdResS scheme the exact enforcement of Newton’s 3rd law impedes a general Hamiltonian formulation [20, 27], in H-AdResS this requirement is relaxed to formulate the problem in terms of a global Hamiltonian function. This method allows us to generate equilibrium states in any well defined statistical ensemble, which therefore can be sampled by either Monte Carlo or Molecular Dynamics. In H-AdResS, the potential energies of the molecules are weighted according to their ‘local nature’ (atomistic, coarse-grained or hybrid). Based on the analogy with standard Kirkwood thermodynamic integration we have proposed two schemes to correct for the drift force appearing in the hybrid region. Also these compensation terms are not time- or path-dependent, so that no bookkeeping is required to enforce energy conservation; in particular, thermodynamical equilibrium is achieved without the help of a local thermostat to remove the excess heat produced in the hybrid region. The pressure and density routes for free energy compensation offer a simple way to optimize the embedding of the system as well as to modulate the thermodynamic balance between AA and CG regions. This new approach thus significantly widens the options to couple within a single simulation setup representations at rather different

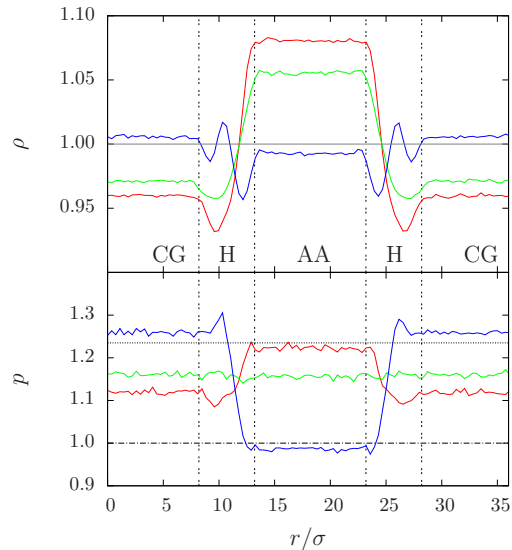


FIG. 3. (color online) Plots showing the effect of the free energy compensations on the density profile (upper panel) and pressure profile (lower panel) in a H-AdResS simulation with CG potential having larger molecular pressure than the fully atomistic. Density and pressure profiles were obtained using the H-AdResS Hamiltonian in Eq. 2 (red lines), the “constant-pressure” compensation route (Eq. 8, green lines) and the “constant-density” compensation route (Eq. 9, blue lines). All pressures are normalized to the value of the all atom simulation (dash-dot line); the dotted line indicates the pressure of the coarse-grained system at the reference atomistic density.

resolution, making for a valuable tool for many problems in soft matter science.

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