Adaptive Resolution Molecular Dynamics Technique

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Abstract

Soft matter systems display properties that span different time and length scales. In addition, scales' interplay is often the key to understand fundamental mechanisms to the aim of controlling and/or designing materials with properties on demand. On the other hand, computational soft matter is limited by computational power for both, size and time of simulation and analysis of large sets of

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data. In this perspective, computational efficiency to treat large systems on long time scales becomes one of the main goals in constructing modern algorithms, together with the capability of designing theoretical schemes for data analysis capable of extracting the relevant information of interest above all the effects of scales' interplay. One common and recurrent feature, in such studies, is the need to include relevant chemical details in a specific region where an event of interest is taking place, while the environment plays simply the role of a macroscopic thermodynamic bath that can be treatable at a coarse-grained level. Thus, an efficient computational strategy consists in employing multiple resolution methods, which simultaneously consider models with different resolution in different regions. This chapter provides a basic introduction to the adaptive resolution simulation (AdResS) method and its recent extensions. This methodology is designed with the idea of efficient computation and analysis of multiple scales as envisaged above. We will report its basic principles and technical aspects for the various directions along which the original idea was developed. As it will emerge in the next sections, the basic idea of adaptive resolution, already highly efficient in its first implementation, has now reached a high level of theoretical solidity, being framed in different but complementary ways in physically rigorous principles. Finally, selected applications, relevant in the field of materials science, chemical physics, and biochemistry, are illustrated in order to show the advanced possibilities of application of the method.

1 Adaptive Resolution Simulations

AdResS (Praprotnik et al. 2005, 2008) is a multi-resolution simulation method that links two regions of a simulation box having different resolutions: region 1, atomistic (AT), and region 2, coarse-grained (CG). The innovative aspect of such a setup is that the boundary between such regions is open; thus, it allows the free exchange of particles/molecules between the two regions. This free exchange occurs through a coupling transition region (HY) where molecules have space-dependent hybrid atomistic/coarse-grained resolution or intermolecular interactions. In the original version (Praprotnik et al. 2005, 2008), the guiding principle employed was that the coupling between two regions must be smooth enough so that the dynamics of the atomistic and the dynamics of the coarse-grained region, through a hybrid resolution region, would not be perturbed in a sizable way, i.e., Newton's 3rd law should be fulfilled. This empirical principle corresponds to a straightforward molecular dynamics (MD) algorithm based on the interpolation of the atomistic and coarse-grained forces. The above requirement prevents the use of an interpolation based on a Hamiltonian (Delle Site 2007). While for most typical applications not of a serious concern and for some even advantageous, e.g., hydrodynamics, the desire to base such an interpolation scheme on a Hamiltonian description led to the development of H-AdResS (Potestio et al. 2013a,b). At the cost of a weak violation of Newton's 3rd law, the Hamiltonian description offers some advantages, including the option to perform adaptive Monte Carlo (MC) simulations. Recently,

AdResS has been also extended to simulate open molecular systems within the grand canonical ensemble by grand canonical AdResS (GC-AdResS) (Wang et al. 2012, 2013) and open boundary molecular dynamics (OBMD) (Delgado-Buscalioni et al. 2015; Sablić et al. 2016, 2017a,b). In the following, the different adaptive resolution approaches will be introduced, and some typical applications will be presented.

2   Adaptive Resolution Simulations: AdResS

The original concept is based on the idea that forces between particles/molecules should change upon variation of the molecular resolution and that this should, in principle, not affect the intermolecular dynamics. Thus, the explicit coupling is such that the force between two molecules α and β is computed via a space-dependent interpolation formula and is written as

$$F_{\alpha\beta} = w(X_\alpha)w(X_\alpha)F_{\alpha\beta}^{AT} + [1 - w(X_\alpha)w(X_\alpha)]F_{\alpha\beta}^{CG} \tag{1}$$

here, $F_{\alpha\beta}^{AT}$ is the atomistic force between the particles and $F_{\alpha\beta}^{CG}$ is the coarse-grained force; $w(x)$ is the interpolating function and is defined as

$$\left\{ \begin{array}{ll} 1 & x < d_{AT} \\ cos^2[\pi/(2d_\Delta)(x - d_{AT})] & d_{AT} < x < d_{AT} + d_\Delta \\ 0 & d_{AT} + d_\Delta < x \end{array} \right\}$$

where d_{AT} and d_Δ are the linear dimension of the atomistic region and hybrid regions, respectively (see Fig. 1). The weighting function smoothly goes from 0 to 1 in the hybrid region and allows the coarse-grained particles to change their resolution into an atomistic molecule and vice versa. A local thermostat takes care of adsorbing and releasing the excess of heat produced by the change of resolution (see e.g., Poblete et al. 2010). This minimal ansatz has been shown to be already sufficient for performing accurate simulations in both the atomistic and coarse-grained regions (see e.g., Praprotnik et al. 2007b). Other more natural choices of coupling, e.g., through an energy, were not considered at this point. Provided that the dynamics should be governed by intermolecular forces only, it was shown that a spatial interpolation of any energy functional, instead of forces, leads to the mathematical nonexistence of a global physically consistent energy in the adaptive sense. As a consequence, any energy functional constructed on the basis of spatial interpolation would be artificial from the physical point of view (see Eqs. 14 and 15 in Delle Site 2007). Nevertheless, relaxing the constraint on the exact conservation of Newton's 3rd law, energy-based algorithms, which have the technical capability of conserving energy (a familiar concept for practitioners of MD and needed for MC) and enable more flexibility in the choice of the standard technical setups, can be devised. In both types of approach one needs to carefully consider the
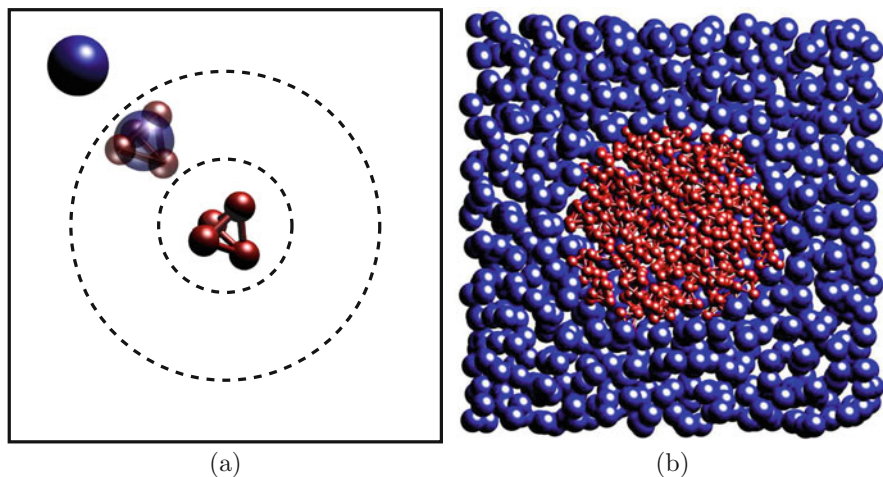
Fig. 1 (**a**) Cartoon of the AdResS setup with spherical regions modeled with different levels of resolution. In the center, there is the AT domain with the molecules surrounded by the HY and CG domains, respectively. (**b**) Multiscale system of a liquid composed of tetrahedral molecules. (Reprinted from Praprotnik et al. 2006)

meaning of global ensemble averages in order to identify realistic and artificial results. In the next sections, we will consider these two different options. From the basic technical point of view, they are actually more or less equivalent (Delle Site and Praprotnik 2017). As a final general remark, it must be underlined that AdResS, in any of its variations, turned out to be conceptually and computationally far more robust than other similar methods (Ensing et al. 2007; Heyden et al. 2007; Mones et al. 2015). In fact, beyond the basic coupling structure, several additional technical aspects were also implemented and tested; relevant examples are the design of a diffusing high-resolution region where the high resolution follows a solvated molecule in space (Praprotnik et al. 2007a) or the design of high-resolution regions of adjustable size (Kreis et al. 2016b), the use of the method for the calculation of potential of mean force for the solvation of relevant biomolecules (Fiorentini et al. 2017) or for the calculation of the chemical potential of liquids and mixtures (Agarwal et al. 2014).

3   Grand Canonical AdResS: GC-AdResS

Further methodological developments of the initial idea based on force interpolation led to the definition of a space-dependent thermodynamic force acting on to the centers of mass of molecules in the hybrid region. Such a force imposes a priori a proper thermodynamic equilibrium and a correct exchange of particles between the AT and CG region (Poblete et al. 2010; Fritsch et al. 2012a). Later on, it has been shown that the thermodynamic force and the work of the thermostat exactly

give the proper chemical potential of coupling even when coarse-grained models reproduce only density and temperature that is only macroscopic thermodynamics. Thus, AdResS was reframed within a grand canonical-like approach (Wang et al. 2012, 2013). Finally, the coupling of the atomistic region to the rest of the system has been rationalized in such a way that a rigorous formalization of a control error is employed to check whether or not the textbook definition of grand canonical system (see, e.g., the procedure in Huang 1987) is satisfied (GC-AdResS). The corresponding formula for the control of the error opened the gate to the conceptual embedding of GC-AdResS into the so-called Bergman-Lebowitz model of open systems (Lebowitz and Bergmann 1957; Bergmann and Lebowitz 1955) and hence to the definition of a Liouville equation for a system that exchanges particles with a reservoir. This led to the physically correct definition of ensemble average time correlation functions for open systems (Agarwal et al. 2015; Agarwal and Delle Site 2015, 2016). In this context, a surprising result of an unexpected locality in the IR spectra of water was found (Agarwal and Delle Site 2016), which is due to the interplay between local quantum effect and global structural properties for the solvation of hydrophobic molecules (Agarwal et al. 2017). Another success of GC-AdResS is its application to ionic liquids, due to the highly challenging role of electrostatics (Krekeler and Delle Site 2017). We could show that independently from the fact whether the coarse-grained model is charged or not, the AT region reproduces always the results of an equivalent subregion of a large full atomistic simulation. The absence of any atomistic degree of freedom outside the atomistic region allowed us to confirm and quantify the structure of the cage within which an ion rattles (Jabes et al. 2018). Here, it should be underlined that the fact that the method applied is force-based plays no more a role for the conceptual justification of the method, since the embedding of the algorithm into the grand canonical frame, and its correspondence to the Bergman-Lebowitz model of open system applies to any possible form of coupling between the AT region and the reservoir. Along such lines, recent theoretical progress has led to the construction of a numerical protocol for allowing the adaptive resolution simulation of molecules with electrons where physical consistency at statistical mechanics level is strictly assured by exact formulas of control of the approximations (Delle Site 2018). In general, AdResS can handle systems in equilibrium and beyond, and, in the next sections, the idea of system with open boundaries is moved even forward to a truly open systems such as coupling to continuum or an ideal gas.

4   AdResS and Its Coupling to Continuum: Open Boundary MD (OBMD)

Another extension of the force-based AdResS that allows for simulations of open molecular systems that exchange mass, momentum, and energy with their surroundings has been coined open boundary MD (OBMD) (Delgado-Buscalioni et al. 2015; Sablić et al. 2016, 2017a,b). The OBMD methodology, which is an offspring of two linear-momentum-preserving methods, i.e., open MD (Flekkoy et al. 2005;

Delgado-Buscalioni 2012) and AdResS, enables us to perform equilibrium MD simulations in the grand canonical ensemble as well as non-equilibrium fluid flow simulations. The flow is introduced via an external boundary condition, while the equations of motion for the bulk remain unaltered.

In the OBMD simulations, the MD domain is typically sandwiched in between two (auxiliary) buffer domains. The latter two act as mass reservoirs and hence enable the former to exchange particles, momentum, and energy with its surrounding. Thus, the OBMD system is opened, i.e., not periodic, in the coupling direction. Molecules freely move between the MD and buffer domains. Moreover, in the buffers, the molecules change their resolution from the fine- (close to the MD domain) to the coarse-grained resolution (at the outer boundaries of the simulation box). The underlying idea of the resolution change is that AdResS allows for the insertion of molecules of arbitrary size into the system. In the coarse-grained parts of the buffers, relatively large molecules can thus be easily inserted due to soft effective interactions among coarse-grained beads (Delgado-Buscalioni and Coveney 2003; De Fabritiis et al. 2004). Then, as the molecules move toward the MD domain, they gain the fine-grained details owing to AdResS used in the buffers. Molecules are deleted once they leave the outer boundary of a given buffer, and new molecules are inserted to achieve the mass balance, i.e., to have a desired average density in the system.

The OBMD setup can be further extended to computational fluid dynamics (CFD) description of a liquid, i.e., Navier-Stokes (NS) are used to describe the dynamics of the liquid on the continuum scale (going beyond the particle-based modeling of the liquid) (Delgado-Buscalioni et al. 2008, 2009). Such hybrid MD/CFD approaches are especially useful for simulations of the transport of nanoparticles through fluids. Simulations using MD can capture the atomistic details of the nanoparticle-liquid interface, but due to their computational cost, they cannot be extended, in the foreseeable future, to the macroscale regime of the full flow field. In turn, continuum descriptions, using the NS equations may capture the macroscale behavior of the flow, but they fail to represent accurately the flow field at the nanoparticle surface. The hybrid approaches, on the other hand, combine the powerful features of both descriptions, i.e., the ability to describe the macroscale behavior of the flow as well as accurate boundary conditions around nanoparticles (Walther et al. 2012).

While technically and (when considering the AT region as a grand ensemble) conceptually equivalent to the force-based approach, the energy-based approach (H-AdResS), presented in the next section, becomes particularly relevant if one wants to perform MC adaptive resolution simulations.

5   Hamiltonian-Based AdResS: H-AdResS

The AdResS method ensures that Newton's 3rd law is exactly satisfied everywhere within the simulation box. As a consequence, it is impossible to interpolate the potential energy using a position-dependent switching function and simultaneously

preserve Newton's 3rd Law. This, as shown in previous sections, proves not to be a major practical problem (Wang et al. 2013). However, without a global Hamiltonian, it is unfeasible to technically carry out NVE or MC simulations in a straightforward way. In the Hamiltonian AdResS (H-AdResS) method (Potestio et al. 2013a,b; Español et al. 2015), the constraint of global momentum conservation of momentum is relaxed in order to overcome the limitations of AdResS reported above. In H-AdResS, total energy of each molecule is expressed in terms of a position-dependent function:

$$H = \mathcal{K} + V^{int} + \sum_{\alpha} \left\{ \lambda_\alpha V_\alpha^{AT} + (1 - \lambda_\alpha) V_\alpha^{CG} \right\} \tag{2}$$

where $\mathcal{K}$ is the (all-atom) kinetic energy of the molecules, V^{int} is the interaction internal to the molecules, and

$$\begin{cases} V_\alpha^{AT} \equiv \dfrac{1}{2} \displaystyle\sum_{\beta,\beta \neq \alpha}^{N} \sum_{ij} V^{AT}(|\mathbf{r}_{\alpha i} - \mathbf{r}_{\beta j}|) \\ V_\alpha^{CG} \equiv \dfrac{1}{2} \displaystyle\sum_{\beta,\beta \neq \alpha}^{N} V^{CG}(|\mathbf{R}_\alpha - \mathbf{R}_\beta|) \\ \lambda_\alpha = \lambda(\mathbf{R}_\alpha) \end{cases}$$

As in the AdResS scheme, the switching function λ goes from 0 (purely CG) to 1 (purely AT). The force acting on atom i in molecule α is obtained through differentiation of the Hamiltonian in Eq. 2. In particular, differently from standard AdResS in this case, one has a further term: $\left[V_\alpha^{AT} - V_\alpha^{CG} \right] \nabla_{\alpha i} \lambda_\alpha$. This term is asymmetric and locally breaks Newton's 3rd law. This force, which is nonzero only in the hybrid region, is proportional to the difference between the potential energies of a molecule in the AT and the CG representation. The effect of this term is to push molecules into one of the two bulk regions, similar to AdResS, where the thermodynamic force has been introduced. Formally, the solution to this is to introduce a compensation term in such a way that

$$\left. \frac{d\Delta H(\lambda)}{d\lambda} \right|_{\lambda = \lambda_\alpha} = \left\langle \left[V_\alpha^{AT} - V_\alpha^{CG} \right] \right\rangle_{\mathbf{R}_\alpha} \tag{3}$$

The subscript in the average indicates that the latter has to be performed constraining the CG site of molecule α in the position $\mathbf{R}_\alpha$. This correction leads to a position-dependent correction term in the hybrid zone:

$$\left\langle \left[V_\alpha^{AT} - V_\alpha^{CG} \right] \right\rangle_{\mathbf{R}_\alpha} \simeq \frac{1}{N} \left\langle \left[V^{AT} - V^{CG} \right] \right\rangle_{\lambda'} \tag{4}$$

where $\lambda' \equiv \lambda(\mathbf{R}_\alpha)$ is the same for all molecules.

Formally, this can be seen as a position-dependent compensation term to the change in the *Helmholtz free energy* difference between the AT and the CG system (Kirkwood 1935). Therefore, it is possible to calculate the compensating function needed to restore, on average, Newton's 3rd law by performing a Kirkwood thermodynamic integration and add it to the Hamiltonian, so that an effective global Hamiltonian for MD (Potestio et al. 2013a) and MC (Potestio et al. 2013b) approaches, resulting in

$$\Delta H(\lambda) \equiv \Delta \mu(\lambda) = \frac{\Delta F(\lambda)}{N} + \frac{\Delta p(\lambda)}{\rho^{\star}} \tag{5}$$

Practically, while the free energy difference between the AT and the CG description is correctly reproduced, details of the local shape of the compensations force are determined by a few iterations. This ensures perfectly flat density profiles. In general, for such methods global ensemble averages must be carefully considered, since the transition region always represents an artificial filter. Like for AdResS this has been done in very detail for H-AdResS in a recent publication (Español et al. 2015). The general Bergman and Lebowitz framework allows to include H-AdResS within an overall adaptive resolution framework. As for (GC-)AdResS (Poma and Delle Site 2010, 2011; Potestio and Delle Site 2012; Agarwal and Delle Site 2015, 2016; Agarwal et al. 2017) also H-AdResS can be employed to put the coarse-grained resolution in connection with a quantum path integral description of molecules (Kreis et al. 2016a, 2017). The technical advantage in this case is that the presence of a global Hamiltonian allows for a straightforward quantization of the Hamiltonian in the high-resolution region. Other examples are the appropriate treatment of electrostatic interactions in the AT and CG region (Heidari et al. 2016) or the connection to relative entropy coarse-graining methodologies (Kreis and Potestio 2016).

6 AdResS, GC-AdResS, and H-AdResS: Examples of Complementary Approaches in a Unified Framework

All AdResS versions are equivalent when considering the AT region as an open system embedded in a reservoir (Agarwal et al. 2015) and that they are equivalent regarding the technical efficiency. Moreover, recent works (Kreis et al. 2014; Zhu et al. 2016) show that a formal connection can be drawn between force-based methods for dual-resolution simulations, such as AdResS, and energy-based methods, such as H-AdResS. Specifically, in Kreis et al. (2014), it was shown that the force-based version of the H-AdResS scheme, i.e., without the drift force, has the same statistical properties of a H-AdResS simulation with a colored noise. Furthermore, mathematical analysis of the asymptotic properties of the force-based and Hamiltonian-based versions (Zhu et al. 2016) reveals that they are equivalent under the condition of large coarse-grained region compared to the atomistic region and (at the same time) large atomistic region compared to the hybrid region. Such

connections prove the mathematical and physical solidity of the AdResS idea in general, which accompanied to its computational efficiency makes the method a powerful tool of simulation and analysis to address the modern challenges in different fields of applied molecular science, as illustrated in the next section.

The AdResS development has meanwhile reached a mature stage at which we can readily apply the methodology to tackle interesting problems in life and material sciences. For instance, AdResS has been applied to study biomolecular systems such as solvated proteins (Fogarty et al. 2015; Kreis et al. 2016b; Fogarty et al. 2016; Tarenzi et al. 2017) and DNA molecules (Zavadlav et al. 2015a, 2017a; Netz et al. 2016). In those examples, we have used a 1-to-1 molecular mapping, in which one coarse-grained bead corresponds to one atomistic water molecule. The next stage of development has involved coupling of atomistic to supramolecular water models such as the widely used MARTINI force-field (Marrink et al. 2004; Marrink et al. 2007; Marrink and Tieleman 2013), where four water molecules are represented with one coarse-grained bead (4-to-1 molecular mapping). Here, water changes its resolution from four molecules to one coarse-grained particle and vice versa adaptively on-the-fly (Zavadlav et al. 2014a,b, 2015b, 2016a; Nagarajan et al. 2013); see Fig. 2. To this end, we have developed a dynamic clustering algorithm SWINGER that can concurrently assemble, disassemble, and reassemble water bundles, consisting of several water molecules (Zavadlav et al. 2016b). Thus, it allows for a seamless coupling between any standard atomistic and supramolecular water models, e.g., dissipative particle dynamics (DPD) (Hoogerbrugge and Koelman 1992; Español and Warren 1995), in adaptive resolution simulations (Zavadlav and Praprotnik 2017). This multiscale approach paves the way for efficient multiscale simulations of biomolecular systems without compromising the accuracy of atomistic water models (Zavadlav et al. 2017b).
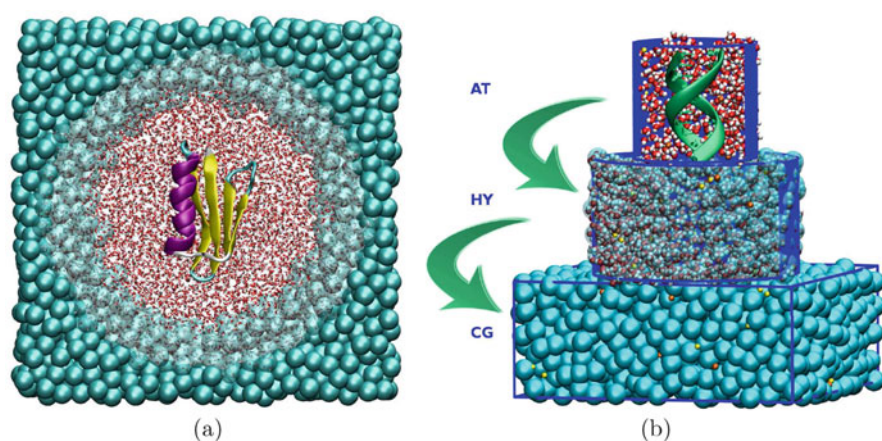

Fig. 2 (**a**) AdResS simulation of an atomistic protein in MARTINI water. (**b**) AdResS simulation of an atomistic DNA molecule in MARTINI water. (Reprinted from Zavadlav et al. 2014a, 2016a)

A recent use of AdResS, in its GC-AdResS version, as a tool to investigate the structural locality of ionic liquids, has allowed to unambiguously conclude that specific atom-atom electrostatic interactions do not play a role in the formation of structures on spatial scales beyond the ion-ion distance. Such a conclusion is rather surprising because in current literature, it is actually postulated the opposite, although purely coarse-grained simulations (without explicit charges) had already put the postulate in discussion (Krekeler and Delle Site 2017; Jabes et al. 2018). The study allowed to draw a picture of the essential feature of the liquid structure for a relevant class of ionic liquids (see Fig. 3). Further on, a particularly promising direction to take full advantage of the coupling between models at different resolution is to employ in the CG region the most computationally inexpensive model available, relying on the fact that the compensating external field (thermodynamic force in AdResS, free energy compensation (FEC) in H-AdResS) guarantees that the AT region will reproduce the correct thermodynamics. The extreme case of a model with few, simple interactions is the ideal gas, to be interpreted as a collection of thermostatted noninteracting particles. In Kreis et al. (2015), this possibility was explored by simulating a water system where 6526 water molecules were modeled at the atomistic level in the high-resolution region, while in the CG region, they were subject to no interaction other than the Langevin thermostat. The results show that neither the structure nor the dynamics of the fluid in the AT region of the water-ideal gas hybrid system are compromised. This can be seen from the fully atomistic pair correlation functions and diffusion profiles of the H-AdResS simulation as reported in Fig. 4. These RDFs and diffusion profiles are fully consistent with those measured in completely atomistic reference simulations. Another application which goes beyond the previous examples is the triple-scale simulation of an enzyme in solution with a binding ligand (Fogarty et al. 2016). There the center part of the enzyme, the ligand, and the surrounding water are treated on an all-atom level, while
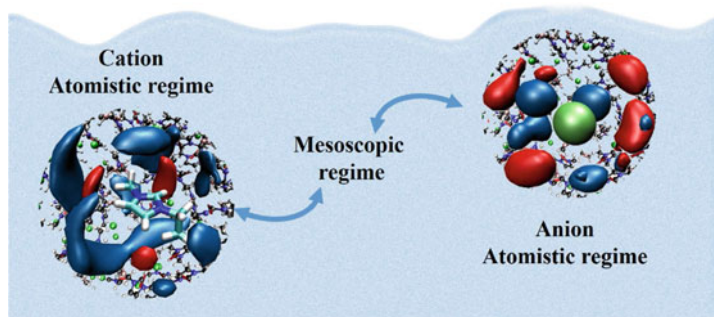

Fig. 3 Cations and anions in imidazolium-based ionic liquids need only a first shell of neighboring ions to build typical structures of the liquid. Such atomistic islands are embedded in a thermodynamic bath without the need of explicit electrostatic interactions. This picture deviates from the intuitive argument put forward in many papers in the field that explicit electrostatic interactions play a key role in the formation of typical liquid structures, even at local level. (This figure is an adaptation from Jabes et al. 2018)
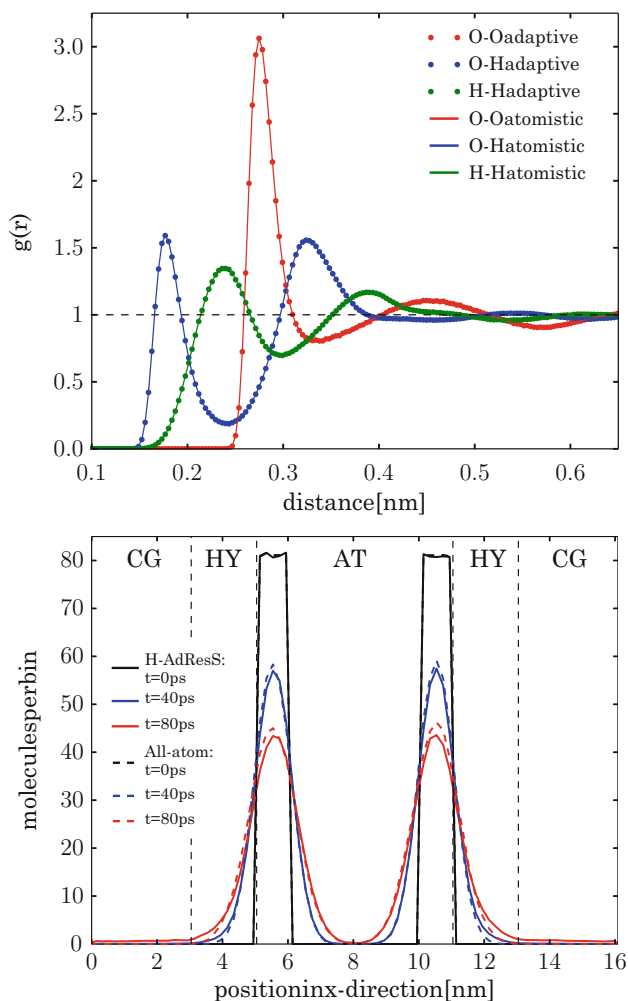
Fig. 4 Top: RDFs for pure water and for the atomistic region of the H-AdResS water-ideal gas with Kirkwood TI-based Gibbs FEC. Since a rigid water model is employed, all RDFs consider only intermolecular atom pairs. Bottom: diffusion profiles in H-AdResS simulations of the water-ideal gas system and in fully atomistic reference simulations of SPC/E water: time evolution of the position of molecules initially located in a 1-nm-wide slab in the atomistic region, immediately adjacent to the HY region. The y-axis is the absolute number of these molecules whose center of mass X coordinate is in a given bin at the given time. (Figures from Kreis et al. 2015)

the water molecules further away are treated on a coarse-grained level and the rest of the residues of the enzyme is considered on an elastic network level. Finally, on the practical side, it must be reported that all the various method start to be included in some of the most popular simulation codes used within the community. In particular, AdResS, H-AdResS, and OBMD are implemented in ESPResSo++

(Halverson et al. 2013; Guzman et al. 2017), AdResS, H-AdResS, and GC-AdResS are implemented in GROMACS (Abraham et al. 2015; Fritsch et al. 2012a), and H-AdResS is implemented also in LAMMPS (Plimpton 1995; Heidari et al. 2016).

7   Perspectives

By now, the general AdResS concept with its variants is well established and has been shown to be robustly applicable to a variety of important problems. Beyond that new developments, which require more or less effort of method development or code adjustment open the path to new applications and opportunities. In fact, the possibility of treating molecules with electrons would allow AdResS to become a tool that can span all the relevant scales of molecular science up to the fluid dynamics. In this perspective, H-AdResS has been connected to QM/MM approaches in which a small sub-domain of the system of interest is treated at the ab initio level, while the rest is described with a classical potential (Boereboom et al. 2016). Furthermore, as anticipated in the section dedicated to GC-AdResS, it has been proposed to go even beyond that and use AdResS (in any form GC-AdResS or H-AdResS) as a physical rigorous platform for a truly grand canonical method for molecules with electrons (Delle Site 2018). A resulting electronic quantum mechanical AdResS approach (el-QM-AdResS) would allow to treat local quantum events, such as conformational deformations of atomistic structures, chemical reactions, specific solvation, and atom-atom bonding effects, to name a few, while assuring the correct statistical mechanics electronic structure and macroscopic thermodynamics. The coupling of any region of resolution to an ideal gas allows the easy treatment of systems, which are driven by an external supply of matter, such as controlled growth or structure formation.

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