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DOI

[10.1103/PhysRevLett.105.237802](https://doi.org/10.1103/PhysRevLett.105.237802)

Publication date

2010

Document Version

Final published version

Published in

Physical Review Letters

[Link to publication](#)

Citation for published version (APA):

Nielsen, S. O., Moore, P. B., & Ensing, B. (2010). Adaptive multiscale molecular dynamics of macromolecular fluids. *Physical Review Letters*, 105(23), 237802.
<https://doi.org/10.1103/PhysRevLett.105.237802>

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Adaptive Multiscale Molecular Dynamics of Macromolecular Fluids

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(Received 18 May 2010; published 3 December 2010)

Until now, adaptive atomistic-coarse-grain (A/CG) molecular dynamics simulations have had very limited applicability because the on-the-fly CG $\rightarrow$ A transformation is problematic for all but those molecules whose CG representation consists of a single particle. Here, we solve this problem by combining a transitional healing region with a rotational dynamics of rigid atomistic fragments in the CG region. Error control is obtained by analysis of the A $\leftrightarrow$ CG energy flow. We illustrate the method with adaptive multiscale simulations of liquid hexane and of a dilute polymer solution in a theta solvent.

DOI: [10.1103/PhysRevLett.105.237802](https://doi.org/10.1103/PhysRevLett.105.237802)

PACS numbers: 36.20.Ey, 02.70.Ns, 36.20.Hb, 61.20.Ja

Multiscale molecular dynamics (MMD) holds great promise for the modeling of the wide variety of newly discovered phenomena that display an inherent multiscale character [1–5]. Examples include membrane fusion, ion diffusion in polymer electrolytes, signal transduction between proteins, nanostructure formation on surfaces, flexible protein-ligand docking, and phase transitions in organic crystals. MMD would complement experiments by interpreting and linking the mesoscale phenomena to the underlying fundamental atomic motions and is thus expected to have an important impact on research fields ranging from polymer physics and surface science to biophysics and drug discovery.

Apart from the expected physical insight from its applications, MMD also raises various statistical mechanics issues by itself that are very exciting to address. For example, what does it mean to simulate a system partly in atomistic detail and partly at a CG level; how should particles adapt their resolution when they diffuse between an atomistic region (AR) and a coarse-grain region (CGR), and what ensemble does such a hybrid simulation sample? These and many other questions have been addressed by us and others with detailed MMD studies of toy models during the last five years [6–12].

Although these efforts have led to several MMD approaches as well as a wealth of understanding, until now none of these hybrid methods have been shown to work for realistic soft matter systems, due to a fundamental difficulty related to the reverse mapping of a CG model to its atomistic representation. That is, the current approach of using an intermediate healing region (HR) to smoothly (re-) insert the chemical details into CG particles that leave the CGR and enter the AR unfortunately only works in practice for simple systems with spherical CG molecules, such as methane [7] and water [13]. MMD of molecules that are represented by several bonded CG particles requires an unworkably large HR or additional reverse

mapping techniques. Clearly this reverse mapping problem has held back MMD of soft matter systems but also further study of the statistical mechanics implications of MMD at higher levels of coarse graining.

In this Letter, we present a hybrid molecular dynamics method that implements the adaptive A/CG coupling for general molecular systems in an efficient manner. We solve the reverse mapping problem by combining the healing region approach with an auxiliary rotational dynamics of atomistic fragments in the HR and CGR. The rotational dynamics maintains near-optimal orientations of the fragments with respect to their CG molecular frame which preconditions reverse mapping taking place in the HR. This dynamical preconditioning is distinct from other recent reverse mapping methods in which restrained optimization or simulated annealing calculations reoptimize the atomistic degrees of freedom [14–16]. This would be too computationally demanding here. Rather, the rotational dynamics is analogous to the rotamer library approach used in the protein community to restore atomistic structure [17]. Hereafter we show that our novel MMD algorithm has some appealing properties, such as conservation of momentum and error control through conservation of a total energy function despite the continuously fluctuating number of degrees of freedom and the nonequilibrium dynamics in the HR.

Prerequisites for a MMD simulation include an atomistic and a CG model of the system, a mapping between groups of atoms and the CG particles, and a choice for the spatial partitioning of the system into high- and low-resolution regions. The atomistic and CG models should be parametrized to represent the same thermodynamic state (e.g., temperature and pressure), such that the molecules have the same average chemical potential in either representation [18]. In the AR and HR, the inactive CG positions are updated from the center of mass positions of the corresponding atom groups. In the CGR, the inactive

atom groups are frozen and treated as rigid bodies that follow the CG particles and rotate according to an auxiliary rotational dynamics.

For the rotation of the frozen fragments in the CGR, we make use of an SO(3) integrator which is the velocity Verlet algorithm for rotational dynamics [19]. Given an initial angular velocity ω_0 and angular acceleration α_0 , the dynamics occurs in a 4-step loop with a time step τ :

$$\text{step 1 } \omega'_n = \omega_{n-1} + \frac{\tau}{2} \alpha_{n-1},$$

$$\text{step 2 } R_n = \exp[\tau J(\omega'_n)],$$

$$\text{step 3 } I_n \alpha_n - t_n + \left(\omega'_n + \frac{\tau}{2} \alpha_n \right) \times I_n \left(\omega'_n + \frac{\tau}{2} \alpha_n \right) = 0,$$

$$\text{step 4 } \omega_n = \omega'_n + \frac{\tau}{2} \alpha_n.$$

Steps 1 and 4 are the velocity half-steps. In step 2 the operator J is used to transform the angular velocity into a skew symmetric matrix which is then scaled by the time step τ . This scaled matrix [which is technically an element of the Lie algebra $\mathfrak{so}(3)$ corresponding to the Lie group SO(3)] represents the vector in the tangent space of SO(3) along which we should step. However, since SO(3) is a curved manifold, we must apply the exponential map to this vector to obtain a rotation matrix R_n which is used to update the atom positions relative to their centers of mass. In step 3, first the moment of inertia tensor I_n is updated and then the forces are evaluated to obtain the torque t_n . With the new moment of inertia tensor and the new torque the angular acceleration is computed using Newton's root finding method to be consistent with the angular velocity.

The rotational dynamics is governed by a potential energy function V^{rot} that consists of a subset of the atomistic force field, such as the bond and bend and dispersion potentials between atoms that span neighboring CG particles [20]. These interactions produce the torques t_n on the frozen atomistic fragments causing them to rotate and follow the orientation of the moving (CG) molecules. The total energy function of the mixed A/CG dynamics plus rotational dynamics is

$$E = T^A + T^{\text{CG}} + T^{\text{rot}} + V_{\text{intra}}^{\text{A/CG}} + V_{\text{inter}}^{\text{A/CG}} + V^{\text{rot}} + \Delta T^{\text{A/CG}} + \Delta U_{\text{intra}}^{\text{A/CG}} + \Delta U_{\text{inter}}^{\text{A/CG}}. \quad (1)$$

Here, the first three terms are the atomistic kinetic energy (from the AR and HR), the CG kinetic energy (from the CGR), and the kinetic energy of the rotating fragments (in the CGR). The A/CG potential energy is separated into $V_{\text{intra}}^{\text{A/CG}}$ due to the intra-CG bead atomistic interactions, and $V_{\text{inter}}^{\text{A/CG}}$ due to the A and CG interactions that span different CG beads. The latter interactions between each pair of beads α and β are composed of the CG pair potentials $\Phi_{\alpha\beta}^{\text{CG}}$ mixed with the pair potentials between atoms i (belonging to bead α) and atoms j (belonging to bead β):

$$V_{\text{inter}}^{\text{A/CG}} = \sum_{\alpha\beta} \left(\lambda_{\alpha\beta} \Phi_{\alpha\beta}^{\text{CG}} + (1 - \lambda_{\alpha\beta}) \sum_{i \in \alpha} \sum_{j \in \beta} \Phi_{ij}^A \right). \quad (2)$$

Here, λ is a scaling function that switches smoothly from zero to one for particles in the HR [7]. The intra-CG bead atomistic interactions are not scaled, which would otherwise require introduction of fractional degrees of freedom and complicated thermostats to avoid the molecules from disintegrating in the HR [10,21]. The last three terms are bookkeeping terms that allow us to recover the total energy as a conserved quantity. A derivation of the adaptive coupling is found in the supplementary information [22].

The bookkeeping terms for the kinetic energy and the intra-CG bead potential energy collect the surplus energy of the atomistic degrees of freedom that is removed from the system when the atoms are frozen and replaced by a CG bead upon leaving the HR. Vice versa, when a CG bead enters the HR and the atomistic dynamics takes over, the surplus energy is released from $\Delta T^{\text{A/CG}}$ and $\Delta U_{\text{intra}}^{\text{A/CG}}$. The inter-CG bead interactions are gradually replaced in the HR, so that the bookkeeping of the instantaneous surplus energy takes the form

$$\Delta U_{\text{inter}}^{\text{A/CG}} = \sum_{\alpha} \int dr \sum_{\beta > \alpha} \frac{\partial \lambda_{\alpha\beta}}{\partial r} \left(\Phi_{\alpha\beta}^{\text{CG}} - \sum_{i \in \alpha} \sum_{j \in \beta} \Phi_{ij}^A \right), \quad (3)$$

with r the position of the CG particle [23]. It is important to note that Eq. (3) not only provides an efficient means to recover the total energy as a conserved quantity, but also that its derivatives $-\nabla \Delta U_{\text{inter}}^{\text{A/CG}}$ exactly cancel the $\partial \lambda / \partial r$ terms included in the thermodynamic forces, $-\nabla V$, which would otherwise cause a particle flux across the HR and impair total momentum conservation. Note also that this total energy does not resemble a physical observable because the bookkeeping terms continuously reset the reference for the energy scale. This is in a sense analogous to the Nose-Hoover "potential energy" of the thermostat, which is added to book-keep the energy flow between the system and the thermostat and to recover the energy as conserved quantity [24].

To complete the implementation of the rotational dynamics within the hybrid A/CG MD, two technical aspects require special attention. First, the CG dynamics must be back-coupled to the rotational dynamics to maintain stability and energy conservation. CG bond vibration (see panel B in Fig. 1), which would pump energy into the rotational dynamics in the absence of backcoupling, is removed from the torque evaluation by renormalizing the CG bond to its equilibrium distance; in this manner the CG dynamics is not perturbed by the stiff atomistic bonds. On the other hand, a rotational CG motion, for example, due to intramolecular bending (panel C in Fig. 1), cannot be removed from the torque evaluation as this would defeat the purpose of orienting the fragments. Here the proper backcoupling is added which causes torque on the CG particles (see panel C in Fig. 1) [25]. Second, the rotational dynamics

FIG. 1 (color online). Rotational dynamics of rigid atomistic fragments on top of the dynamics of CG molecules. A bond interaction between atoms induces a torque t_1 and a rotation of the atoms (A). CG bond stretching is removed from the rotational dynamics (B). CG bending couples to the rotational dynamics (C).

is gradually replaced by the atomistic interactions in the HR, simply by adding the forces from torques to the atomistic MD forces, after scaling by λ and removing the fragment center of mass translational component.

We illustrate our novel adaptive MMD algorithm with two examples. Our first example is liquid hexane in which the different resolution regions are 2D slabs. The system was initialized from a CG isothermal-isobaric simulation (303 K and 1 atm) to obtain 1900 equilibrated hexane molecules in a rectangular box with initial dimensions $60 \times 60 \times 120$ Å subject to periodic boundary conditions. At the CG level hexane molecules consist of two beads connected with a harmonic spring; dispersion is modeled using a 9-6 Lennard-Jones pair potential [26]. Atomistic (frozen) C_3H_7 fragments were positioned over each CG bead, after which the rotational dynamics energy function was minimized. To drive the rotational dynamics, a subset of the atomistic force field was employed consisting of the atomistic bond between CG beads and the WCA repulsive

FIG. 2 (color online). Total energies (offset) of MMD simulations of liquid hexane, using different widths of the HR, ranging from $d_{HR} = 1$ to 6 Å. Without the rotational dynamics, the total energy is not conserved (see irregular line using the right axis).

potential between the hydrogen atoms attached to the carbon atoms involved in this bond [27]. The AR is selected to be a 2D slab with a thickness of 24 Å centered on an immobilized dummy atom. The atomistic molecules are fully flexible using the CHARMM force field without electrostatics [28]. Short, 50 ps, NVT MMD simulations were performed to further equilibrate the atomistic degrees of freedom in the AR and HR, followed by several MMD simulations in which we varied the HR width between 1 and 6 Å. Figure 2 shows the total energy of Eq. (1) (offset for comparison) during the first 100 ps of each simulation. Excellent stability of E is observed with a 3 Å HR width or greater. The irregular curve shows the erratic result obtained from MMD without the rotational dynamics.

Our second example is the swelling of a $C_{450}H_{902}$ (150 CG beads) polyethylene chain in a theta solvent of liquid hexane. The system was prepared by immersing a densely coiled polymer chain, taken from a 10 ns CG simulation of the chain in vacuum, in a cubic box containing 1900 hexane molecules. The CG force field is identical to the hexane slab system. The solvent was equilibrated with the chain fixed, after which atomistic fragments were introduced as above. To study swelling (due to the penetration of solvent molecules) at different resolutions, a spherical AR with a radius of 10 Å was centered at the 75th CG bead of the polymer and a 5 Å HR was used. The MMD

FIG. 3 (color online). Snapshots from the MMD simulation of the swelling of a polyethylene chain in a theta solvent (hexane), taken at $t = 0$, $t = 100$, and $t = 1000$ ps. Solvent molecules completely outside the AR are omitted for clarity. The large transparent sphere indicates the AR, which is centered at the middle of the chain (small bright sphere).

FIG. 4 (color online). Top panel: Increasing radius of gyration of the polymer during the first ns. Bottom panel: number of carbon atoms of polyethylene (lower gray line) and hexane solvent (upper gray line) within the AR plus HR. Linear fits to the first and second 500 ps are shown with dashed lines. The slight decrease in the total number of carbon atoms (black line) is due to the lower carbon atom density of the solvent.

simulation shows that segment fluctuations allow hexane molecules to penetrate the polymer on a subnanosecond time scale. In Fig. 3, the initial configuration of the system is shown in the left panel. Because the center of the AR is located at the polymer globule surface, hexane molecules are found only in the lower part of the AR. After 100 ps already several segment contacts have separated allowing solvent to enter (middle panel). After 1000 ps almost all segment contacts have been released (right panel) and swelling continues as shown by the increasing radius of gyration (top panel in Fig. 4). The lower panel in Fig. 4 shows how the number of solvent carbon atoms within the AR + HR spherical region increases over the first 500 ps, after which it stabilizes.

In conclusion, we have developed a hybrid atomistic—coarse-grain molecular dynamics method which treats the adaptive coupling between the different resolutions using a healing region and a rotational dynamics to precondition the frozen atomistic structure in the coarse-grain region in anticipation of a resolution change. Starting from an energy function, we obtained a conserved quantity to assess the quality of the integration of the equations of motion. This allows us to choose an optimal time step and HR width. Two examples illustrated that the method is a robust algorithm applicable to general soft matter systems.

B. E. acknowledges financial support through an NWO-CW VIDI grant.

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