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# Adaptive molecular resolution via a continuous change of the phase space dimensionality

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For the study of complex synthetic and biological molecular systems by computer simulations one is still restricted to simple model systems or by far too small time scales. To overcome this problem multiscale techniques are being developed. However, in almost all cases, the regions and molecules of different resolution are kept fixed and are not in equilibrium with each other. We here give a basic theoretical framework for an efficient and flexible coupling of the different regimes. The approach leads to a concept, which can be seen as a geometry-induced phase transition, and to a counterpart of the equipartition theorem for fractional degrees of freedom. This represents the initial step in developing a general theoretical framework for computer simulation methods applying simultaneously different levels of resolution.

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A long-standing and often most challenging problem in condensed matter physics is to understand the microscopic origin of macroscopic properties. While in certain cases a microscopic scale can be clearly separated from a macroscopic one, this is not the case for many experimental systems, where details of the local interaction and generic universal aspects are closely related. Already the proper determination of the fracture energy and crack propagation in crystalline materials requires a hierarchical and interrelated description, which links the breaking of the interatomic bonding in the fracture region to the response of the rest of the system on a micron scale [1]. The presence of microscopic chemical impurities in many metals and alloys changes their macroscopic mechanical behavior [2,3]. Even more complicated are synthetic and biological soft matter systems. Whether one is dealing with the morphology, the glass transition of a polymeric system, the function of a molecular assembly—e.g., for electronic applications or studies ligand-protein recognition or protein-protein interaction—in all cases the generic soft matter properties, such as matrix or chain conformation fluctuations, and details of the local chemistry apply to roughly the same length scales. For all these problems, which due to their complexity are heavily studied by computer simulations, there is a common underlying physical scenario: the number of degrees of freedom (DOF) involved is very large and exhaustive exploration of the related phase space is prohibitive. For many questions, however, such a deep level of detail in the description is only required locally.

Theoretical methods employed to study these systems span from quantum-mechanical to macroscopic statistical approaches. Their efficiency and scope increase significantly if two or more such different approaches are combined into hybrid multiscale schemes. This is the case for dual-scale resolution techniques [4–17] aiming at bridging the atomistic and mesoscale length scales as well as for the quantum-based quantum-mechanical/molecular-mechanical (QM/MM) approach [18]. However, the common feature and limitation of all these methods is the fact that the regions or parts of the system treated at different level of resolution are fixed and do *not* allow for free exchange. It is exactly this constraint one has to overcome in order to study typical complex, fluctuating molecular systems with a higher computational efficiency. What is needed is an approach that allows one to zoom into a specific area which, even though the number of DOF treated is different, stays in equilibrium with the more coarse-grained surrounding. In computational terms such a simulation translates into a scheme of changing the number of DOF on demand and on the fly in a selected region. Technically the requirement above has been fulfilled for first test cases by the recently introduced classical AdResS scheme [19,20] and somewhat different in a related Monte Carlo scheme [21]. The underlying concept, however, still requires this to be put into a solid, rigorous theoretical framework, making it applicable also for the other schemes mentioned before. In the present communication we report the first step to do this for classical systems. The continuous transition from a less to a more coarse-grained description (and vice versa) is illustrated in terms of a "geometry-induced first-order phase transition," where the similarity with a standard phase transition is further put into the context of noninteger dimensions of the phase space as DOF are slowly switched off and on. In this way the present approach is based on a generalization the equipartition theorem to noninteger dimensions. This shows how to obtain relevant thermodynamic quantities within a continuous variable resolution of the phase space. In this sense, the original problem of high-dimensional systems, multiscale in nature, can be considerably simplified on the basis of a general and rigorous statistical mechanics framework.

Without loss of generality let us assume a system of molecules in a volume $V$, modeled on a rather coarse-grained level. Now let us further assume that in a certain subvolume $V'$ a higher resolution is needed—i.e., to study some function. This is a typical situation, which one encounters— e.g., in proteins or functional molecular assemblies. In statistical terms this translates into saying that the resolution employed in one region is lower (or higher) than in the rest. Thus the

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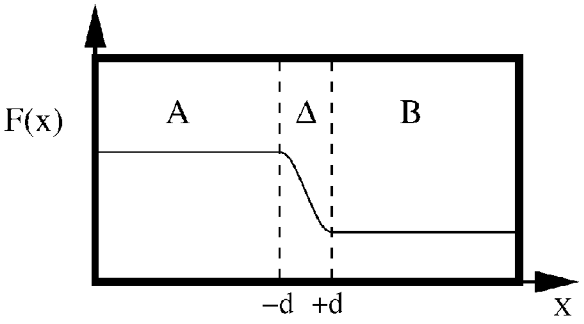

FIG. 1. The free energy $F$ as a function of $x$. $A$ and $B$ are the regions with high and low levels of detail, respectively, while $\Delta$ is a transition regime. The constant values of $F_A$ and $F_B$ are arbitrary and do not play any role in the following treatment.

number of DOF of the molecular model in such a region is lower (or higher). For simplicity, we divide the volume $V$ into two parts $A$ and $B$. In region $A$, each molecule is characterized by $n_A$ DOF and in region $B$ by $n_B$. For example, in region $A$ one has higher resolution and a molecule can be considered as a collection of atoms linked by springs while in $B$ the molecule consists only of its center of mass and a spherical excluded volume as in our previous numerical example [19,20]. The natural question now is how to reach true thermodynamic equilibrium between the two regions with the same overall structure of the system on both sides. At this point we assume, tested numerically in previous work [19–28], that for a state point $(\rho, T)$ it is in general possible to reduce the many-body potential of the higher-resolution representation into a dimensionally reduced effective potential. The latter, when applied to a system composed exclusively of molecules with lower resolution, reproduces the statistical properties of a system composed exclusively of highly resolved molecules, when analyzed accordingly. However, treating one overall system with regions of different resolution requires special attention. The problem of the changing DOF must be addressed in a way that $A$ and $B$ are in equilibrium with each other and, additionally, the general overall structure is the same, even though the free energy per molecule will be different. To address this we visualize the free energy $F$ as a function of the position $x$. [In order to do so we can divide the system into "large enough" equal slabs, so that $F(x)$ is a truly extensive quantity of the slab; cf. Fig. 1.] The free energy is a thermodynamic potential and hence in thermodynamic equilibrium $F(x)=F_A$, constant in region $A$, and $F(x)=F_B$, constant in region $B$. In general, $F_A \neq F_B$, since $F$ is extensive and $n_A \neq n_B$ [29]. Note, however, that despite this free energy difference, which stems exclusively from the different levels of a molecular representation in regions $A$ and $B$, the chemical potentials must be equal in both regions. This guarantees that the molecules experience no spurious driving force which would pull them from one region into the other due to the choice of the level of resolution. Figure 1 sketches a "typical" free energy profile across the system.

Let us now focus on the transition regime $\Delta$ between the two subsystems—i.e., $-d \leqslant x \leqslant +d$, where the points $-d$ and $+d$ denote the boundaries of $\Delta$ with regions $A$ and $B$, respectively; see Fig. 1. In $\Delta$ we gradually change the level of resolution and consequently the value of $F(x)$. The width of $\Delta$ is set by the range of the effective pair potential between molecules [19]. Our system is in equilibrium, which implies that at the boundaries

$$\lim_{x\to d^-} \frac{\partial F_A(x)}{\partial x} = \lim_{x\to d^+} \frac{\partial F_B(x)}{\partial x} = 0. \tag{1}$$

If this condition did not hold, a molecule would "see" a free energy gradient along $x$ within the same level of resolution, leading to a drift along the $x$ axis. Next, let us write $\frac{\partial F_A}{\partial x} = \frac{\partial F_A}{\partial N_A}\frac{\partial N_A}{\partial n_A}\frac{\partial n_A}{\partial x}$ and the same for $B$, $\frac{\partial F_B}{\partial x} = \frac{\partial F_B}{\partial N_B}\frac{\partial N_B}{\partial n_B}\frac{\partial n_B}{\partial x}$. Here $N_A$ and $N_B$ are the numbers of molecules in $A$ and $B$, respectively. $\partial N_A/\partial n_A$ and $\partial N_B/\partial n_B$ are two nonzero constants, while $\partial F_A/\partial N_A = \mu_A$ and $\partial F_B/\partial N_B = \mu_B$, where $\mu$ is the chemical potential. Note that due to equilibrium, $\mu_A = \mu_B \neq 0$. The condition of Eq. (1) is hence reduced to

$$\lim_{x\to d^-} \frac{\partial n_A(x)}{\partial x} = \lim_{x\to d^+} \frac{\partial n_B(x)}{\partial x} = 0. \tag{2}$$

Thus, the switching on and off of a given DOF via a weighting function $w(x)$ requires that $w(x)=1$, $\forall x \in A$ and $w(x)=0$, $\forall x \in B$, with zero slope at the boundaries of $\Delta$. In accordance with Eq. (2), this requires $w(x)$ to be continuous up to the first derivative. The additional requirement of $w(x)$ to monotonically vary between 1 and 0 reflects the fact that we want to switch gradually on the fly without extra equilibration from more to less (or vice versa) DOF [30]. The switching procedure implies that in the transition regime, where $0 \leqslant w(x) \leqslant 1$, we deal with fractional DOF; i.e., by switching on and off a DOF we continously change the dimensionality of the phase space. To rigorously describe this we resort here to fractional calculus [31–35]. According to Refs. [33–35] and to the formula for dimensional regularization [36], the infinitesimal volume element of the fractional configurational space is defined as $dV_\alpha = d^\alpha x\,\Gamma(\alpha/2)/[\pi^{\alpha/2}\Gamma(\alpha)] = |x|^{\alpha-1}dx/\Gamma(\alpha) = dx^\alpha/[\alpha\Gamma(\alpha)]$ where the positive real parameter $\alpha$ denotes the order of the fractional coordinate differential and $\Gamma$ is the gamma function. To make the connection with the switching on and off of DOF we consider in our case each $\alpha$ as a value that $w(x)$ can take and apply the formalism to each DOF separately. Hence, we have to go beyond Refs. [34,35] so that each DOF can take its own value of parameter $\alpha$ according to the level to which the particular DOF is switched on. Such a formulation leads to an interpretation of the switching as a "geometrically induced phase transition." Here, we deal with a representation-driven geometrical transition, which has formal similarities to the concept of a first-order phase transition [29,37]. In this context the switching function $w(x)$ can be viewed as an order parameter. In fact, while in a standard first-order phase transition we have a latent heat—e.g., of solidification—in this case we have a latent heat due to the fact that the free energy depends on the position of the slab and we need to furnish or remove "latent" heat from an external bath to compensate the free energy gradient due to changing the number of DOF in $\Delta$.

To explain this concept in more detail we define the temperature in $A$ in the usual way as $T_A=2\langle K_A\rangle/n_A$ and in $B$, $T_B=2\langle K_B\rangle/n_B$, where $\langle K_A\rangle$ and $\langle K_B\rangle$ are the average kinetic energies of a molecule in regions $A$ and $B$, respectively; since we have equilibrium, $T_A=T_B$. In a similar way we would also like to define the temperature in the interface region $\Delta$ as $T_\Delta=2\langle K_\Delta\rangle/n_\Delta$ with $\langle K_\Delta\rangle$ and $n_\Delta$ being the average kinetic energy and the number of DOF of a molecule in a given slab $x$ in $\Delta$, respectively. However, for such a definition we first need to determine how $K_\Delta$ and $n_\Delta$ scale with $w(x)$. Let us demonstrate this with a simple example. In Fig. 2 we show a disk representing a two-dimensional molecule with three DOF in the high-resolution region $A$—i.e., two translational DOF of the center of mass $\mathbf{R}=(R_x,R_y)$ and one rotational DOF around the center of mass characterized by angle $\Theta$, the transition representation of the molecule in the region $\Delta$, and the coarse-grained molecule in region $B$ with only two translational DOF. The kinetic energy in region $A$, setting the mass, the molecule's radius, and the Boltzmann constant $m=r=k_B=1$, is $K_A=[\dot{\mathbf{R}}^2+p_\Theta^2]/2=[\dot{R}_x^2+\dot{R}_y^2+\dot{\Theta}^2]/2$ and, in region $B$, $K_B=\dot{\mathbf{R}}^2/2=[\dot{R}_x^2+\dot{R}_y^2]/2$. Here $p_\Theta$ denotes the angular momentum. According to the equipartition theorem each full quadratic DOF—i.e., $R_x$, $R_y$, and $\Theta$—contributes to the kinetic energy with an amount of $T/2$. Hence, $T_A=2\langle K_A\rangle/3$, $T_B=2\langle K_B\rangle/2$. In the region $\Delta$, however, $\Theta$ is not a full DOF, because its weight varies between 0 and 1. This has to be considered when calculating the local temperature. To determine such a contribution one should account for the following: Let us consider a given value $w(x)=\alpha$ and use $\alpha$ as a variable parameter. The instantaneous kinetic energy of a fractional DOF should gradually vanish as the DOF is slowly switched off (or vice versa); thus, in the region $\Delta$, our ansatz for the kinetic energy associated with $\Theta$ is $f(\alpha)p_\Theta^2/2$, where $f(\alpha)$ is a monotonic function in $\Delta$ with $f(1)=1$ and $f(0)=0$. Apart from these requirements we do not need to specify the exact form of $f(\alpha)$ at this point. Accordingly, the kinetic energy in the position with coordinate $x$ in region $\Delta$ is $K_\Delta=[\dot{R}_x^2+\dot{R}_y^2+f(\alpha)p_\Theta^2]/2$. For the fractional quadratic DOF $\Theta$ we can then write the partition function as

$$\begin{aligned}\exp(-\beta F_\alpha) &= C\int \exp[-\beta f(\alpha)p_\Theta^2/2]dV_\alpha \\ &= 2C\int_0^\infty \exp[-\beta f(\alpha)p_\Theta^2/2]|p_\Theta|^{\alpha-1}\frac{dp_\Theta}{\Gamma(\alpha)} \\ &= \frac{2^{\alpha/2}C\Gamma(\alpha/2)}{\Gamma(\alpha)}f(\alpha)^{-\alpha/2}\beta^{-\alpha/2} \sim \beta^{-\alpha/2},\end{aligned} \tag{3}$$

where $C$ is a normalization constant, $\beta=1/T$, and $F_\alpha$ the free energy associated with the fractional DOF $\Theta$, respectively [38]. The consequence of Eq. (3) is the fractional analog of the equipartition theorem:

$$\langle K_\alpha\rangle = \frac{d(\beta F_\alpha)}{d\beta} = \frac{\alpha}{2\beta} = \frac{\alpha T}{2}, \tag{4}$$

where $\langle K_\alpha\rangle$ is the average kinetic energy per fractional quadratic DOF with the weight $\alpha$. Thus, for $\alpha=0,1$ we obtain the correct limits in the coarse-grained and fully resolved regimes, respectively, with the correct contributions to the kinetic energy. Furthermore, we have $T_\Delta=2\langle K_\Delta\rangle/n_\Delta=(2+\alpha)T/n_\Delta$. To satisfy the equilibrium condition $T_A=T_B=T_\Delta=T$ we must set $n_\Delta=2+\alpha$, which is in accordance with the "intuitive" definition in Ref. [19]. The number of quadratic DOF and the average kinetic energy thus scale linearly with $w(x)$. Equation (4) also tells us that, although the equipartition is independent of the specific choice of $f(\alpha)$, since the average kinetic energy scales as $\alpha$, also the instantaneous one should scale in the same way. This means that $f(\alpha)=\alpha$ and it is determined by the fractional character of the phase space. Note that for nonquadratic DOF the functional form of $f(\alpha)$ is generally more complicated [39]; however, it is not needed for the present purpose.

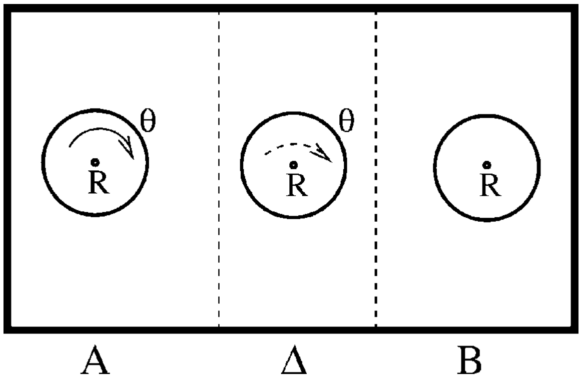

FIG. 2. The molecular resolution of a simple two-dimensional circular molecule in the high- and low-resolution regions $A$ and $B$ and the transition region $\Delta$, respectively.

Recently we have developed an efficient particle-based molecular dynamics simulation scheme [19,20], which is in accordance with the above considerations. For intermolecular force calculations we use an interpolation formula for the force acting between centers of mass of given molecules $\alpha$ and $\beta$:

$$\mathbf{F}_{\alpha\beta} = w(x_\alpha)w(x_\beta)\mathbf{F}_{\alpha\beta}^{atom} + [1-w(x_\alpha)w(x_\beta)]\mathbf{F}_{\alpha\beta}^{cg}, \tag{5}$$

where $x_\alpha$ and $x_\beta$ are the center-of-mass coordinates of the molecules $\alpha$ and $\beta$, respectively, $\mathbf{F}_{\alpha\beta}^{atom}$ is the sum of all pair atom interactions between explicit atoms of molecule $\alpha$ and explicit atoms of molecule $\beta$, and $\mathbf{F}_{\alpha\beta}^{cg}$ is the total force between the centers of mass of the respective two molecules [19,20]. This ansatz satisfies Newton's third law and takes into account the transfer of the turned-off explicit DOF onto the molecular center of mass [40]. Each time a given molecule crosses a boundary between different regimes it gains or loses (depending on whether it leaves or enters the region $B$) its equilibrated rotational DOF while retaining its linear momentum. By extension of the equipartition theorem to fractional DOF we are able to define the means to supply the latent heat, which is required or removed for the transition from coarse grained to high resolution or vice versa. Since this generalized equipartition theorem also applies to the fractional quadratic DOF, standard thermostats based on the fluctuation-dissipation theorem are applicable.

In conclusion, we provided a formal basis for an efficient computational scheme that concurrently couples different length scales via different levels of resolution—i.e., atomistic and mesoscopic length scales—by adapting the resolution on demand. The transition region is well defined by the here-introduced generalization of the equipartition theorem for fractional dimension of phase space. While it directly applies to a scheme recently tested [19,20], it in the same way should also serve as the first step towards a general theoretical framework to extend other commonly used schemes [11,15,16] into a truly adaptive multiscale simulation method.

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