

Nielsen, Moore, and Ensing Reply: In the preceding Comment [1], the authors criticize the multiscale molecular dynamics study reported in our original Letter [2]. The authors of the Comment present results of a test simulation, with a one-to-one mapping so that the total number of particles is fixed, in the *NVE* ensemble (i.e., without any thermostats) based on an implementation of the total energy function as given by Eqs. (1)–(3) of our Letter [2]. Significant observed energy drifts lead the authors of the Comment to the conclusion that thermodynamic equilibrium cannot be maintained by the method in question.

This conclusion is based on a misunderstanding. The authors of the Comment assume that the method described in our Letter does not employ thermostats. However, our Letter, whose focus is a fine-graining technique for general macromolecular entities, is built upon our adaptive hybrid algorithm published over three years ago [3]. In this algorithm we explicitly state that “All particles are coupled to individual Nose-Hoover thermostat chains [...]” We simply could not include the full details of this algorithm in the Letter due to the severe space limitations. It is clear that the fine-graining process generates surplus energy. Since we consequently have to face a nonequilibrium process, thermostats are needed which take care of the generated surplus energy. It simply makes no sense to omit thermostats and conduct an *NVE* ensemble simulation.

In Ref. [3], we also point out why it is so important to add a bookkeeping term to the scaled potentials: The bookkeeping term cancels forces on particles due to the potential scaling in the healing region, however at the cost of being a space-dependent, nonconservative potential term (note that in Ref. [5] of their Comment, the authors have confused “conservative potential energy” with “nonconservative bookkeeping term”). This leads to heat exchange upon resolution switching which is illustrated in Fig. 2 of Ref. [3] for a two-atom molecule, which cools down when moving into the coarse-grain region and heats up in the other direction, in a symmetric way. When coupled to other degrees of freedom (i.e., interacting with other particles), the symmetry is broken and the net result is that the system heats up, which thus requires a thermostat to maintain a thermodynamic steady state.

The trivial exception is the case where the atomistic potential and the coarse-grain potential are exactly the same. It is interesting to note that by using our energy function of scaled potentials while omitting the bookkeeping term, a thermodynamically stable hybrid simulation of the one-to-one mapping system is possible without the use of thermostats. In that case, the forces include the extra

terms due to the derivative of the scaling factors (termed “spurious forces” in our first paper [3]), which, however, lead to a flux of particles over the healing region, resulting in unphysical density fluctuations (this is exactly what we set out to avoid in Ref. [3]). In Ref. [4], we illustrated this problem for a hybrid QM/MM simulation of water, which was simply remedied by including the bookkeeping energy term.

The authors of the Comment also criticize the total energy function as being unphysical and meaningless due to the presence of the bookkeeping terms. As we have shown several times [3–6], it is a helpful quantity, despite being unphysical, because it gives us a way to find conditions for performing stable and efficient simulations (note that the authors in their Comment at line 15 have confused “thermodynamic stability” with “stability of the integration of the equations of motion”).

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