Tests for Physical Validity of Thermodynamical Observables in Molecular Mechanics Simulations

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Advances in recent years have made molecular dynamics (MD) and Monte Carlo (MC) simulations powerful tools in molecular-level research, allowing the prediction of experimental observables in the study of systems such as proteins, membranes, and polymeric materials. The quality of any prediction based on molecular dynamics results will strongly depend on the validity of underlying physical assumptions. Based on a number of examples, in which (sometimes hard-to-spot) unphysical behavior of simulations had statistically important influence on their results, we propose a series of physical validation tests of different complexity, ranging from simple post-processing analysis to more involved tests requiring additional simulations. These tests are shown to significantly increase the reliability of molecular simulations by catching a number of common simulation errors violating physical assumptions, such as non-conservative integrators, deviating from the Boltzmann ensemble, or lack of ergodicity between degrees of freedom. These errors are then shown to have significant influence on thermodynamical observables calculated from simulations, as routinely used in force-field parametrization, structure predictions, or binding-energy calculations. To render the usage as easy as possible, an open-source and platform-independent Python library containing the presented tests is available.