Error Estimation in the Computational Modeling of Biomolecules: The End of End-point Methods?

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Physics-based energy functions used in computational models of biomolecular systems often make use of various approximations and parameterization to estimate thermodynamic quantities. We have shown how intrinsic modeling errors propagate with increasing system size, and we have suggested a chemical fragment-based method for estimating systematic and random errors in single-point energies for proteins and protein-ligand complexes. We have also investigated the propagation of these errors in statistical ensembles, leading to methods for error estimation for calculations of thermodynamic quantities such as free energy. Furthermore, we have observed how random errors in ensemble-based quantities are naturally reduced with increased “local sampling” of potential energy wells.