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Quantifying the influence of conformational uncertainty in biomolecular solvation

Biomolecules exhibit conformational fluctuations near equilibrium states, inducing uncertainty in various biological properties in a dynamic way. We have developed a general method to quantify the uncertainty of target properties induced by conformational fluctuations. Using a generalized polynomial chaos (gPC) expansion, we construct a surrogate model of the target property with respect to varying conformational states. We also propose a method to increase the sparsity of the gPC expansion by defining a set of conformational "active space" random variables. With the increased sparsity, we employ the compressive sensing method to accurately construct the surrogate model. We demonstrate the performance of the surrogate model by evaluating fluctuation-induced uncertainty in solvent-accessible surface area for the bovine trypsin inhibitor protein system and show that the new approach offers more accurate statistical information than standard Monte Carlo approaches. Furthermore, the constructed surrogate model also enables us to directly evaluate the target property under various conformational states, yielding a more accurate response surface than standard sparse grid collocation methods. In particular, the new method provides higher accuracy in high-dimensional systems, such as biomolecules, where sparse grid performance is limited by the accuracy of the computed quantity of interest. Our new framework is generalizable and can be used to investigate the uncertainty of a wide variety of target properties in biomolecular systems.