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The Subtleties of Calculating Non-Covalent Interactions with Wavefunction Based Methods

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Non-covalent interactions are ubiquitous within the natural world, driving many biological, chemical and physical phenomena including protein folding, catalysis, gas storage, stacking of two-dimensional materials and molecular liquid properties. However, quantifying these interactions is highly complex from both a computational and experimental standpoint.

Calculations are problematic due to slowly convergent correlation energy with respect to basis set size, small magnitude of the interaction energies and the requirement for delicate error cancellation between approximations made within the component molecules and the whole. These issues were further exacerbated when two state of the art methods, coupled cluster with single, double and perturbative triple excitations (CCSD(T)) and fixed-node diffusion Monte Carlo (FN-DMC), were found to disagree in the quantification of interaction energies for many dimers.[1, 2] These issues have not only raised questions about the reliability of quantum chemistry for the calculation of non-covalent interactions, but also called into question the trustworthiness of the methods themselves.

While these state-of-the-art quantum chemical methods are exact in principle, a plethora of approximations are required to ensure computational tractability. While each approximation may, in and of itself, result in only a small introduction of error, the combination of these small errors could possibly lead to a significant discrepancy between the methodologies.

Establishing platinum standard non-covalent interaction benchmarks is imperative for understanding our calculations and their limitations. In this work, rigorous and systematic evaluation of the various approximations invoked in coupled cluster calculations is carried out. The effect of these approximations are quantified, critically assessed and compared to FN-DMC results.

[1] Al-Hamdani et al., Nat. Commun., 12, 3927 (2021).
[2] Shi et al., J. Chem. Phys., 162, 144107 (2025).