# Improving Efficiency in Symmetry-Adapted Perturbation Theory via Empirical Dispersion

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From understanding reaction stereoselectivity in the catalysis of organic reactions to the increased {\em in vivo} toxicity of chloro- versus methyl-substituted therapeutic agents for the prevention of stroke and other vascular diseases, symmetry adapted perturbation theory (SAPT) has become an indispensable computational tool offering physical insight into the fundamental nature of non-covalent interactions (NCI) in diverse chemical systems. Further application of SAPT to novel problems is limited primarily by its computational expense, which scales as the fifth power of system size [$O(N^5)$] for even its most affordable variant, SAPT0. In order to reduce the expense of SAPT0 such that it may be applied more widely, we present here SAPT0-D, whereby the exact dispersion from SAPT0 has been replaced with an empirical dispersion correction inspired by the popular dispersion-corrected density functional theory (DFT-D3) family of methods. In this way, we simultaneously reduce the algorithmic scaling of SAPT0 from $O(N^5)$ -> $O(N^4)$ while retaining the physically meaningful interpretation of IE components characteristic of all SAPT methods. This order of magnitude reduction in scaling for SAPT0-D translates into a nearly 5x speedup over conventional SAPT0 when computing the interaction energy (IE) for a truncated subsystem of the HIV-II protease--indinavir complex with 195 atoms, while offering nearly equivalent accuracy to SAPT0 when compared against gold-standard reference IEs for a diverse set of nearly 5,000 bimolecular complexes. Thanks to its unique combination of accuracy, reduced expense, and physical insight, SAPT0-D can be reliably applied to interrogate NCI in large, chemically diverse systems which were previously inaccessible, thereby serving a vital role in the advancement of numerous fields in the computational molecular sciences.