

Double Hybrids and Noncovalent Interactions: How Far Can We Go?

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Abstract

The accurate evaluation of weak non-covalent interactions in large, that is containing up to thousand atoms, molecular systems represents a difficult challenge for any quantum chemical method. Indeed, some approximations are often introduced to render affordable these calculations. Here, we consider the PBE-QIDH/DH-SVPD protocol, combining a nonempirical double hybrid functional (PBE-QIDH) with a small basis set (DH-SVPD) tailored for noncovalent interactions with a double aim: i) explore the robustness and accuracy of this protocol with respect to other Density Functional Approximations; ii) illustrate how its performances are affected by the computational parameters underlying the calculation of the exact exchange and the Coulomb contribution, as well as the perturbative term. To this end, we consider three datasets, namely S66, L7 and CiM3, incorporating molecules of increasing size. On the bright side, our results suggest that the PBE-QIDH/DH-SVPD protocol is particularly accurate for large systems such as those contained in the CiM13 set (up to more than 1,000 atoms and 14,000 basis functions), for which the DLPNO approximation leads to a significant speed-up for the evaluation of the perturbative correlation term.

However, our analysis also points out the limit of this statistical exercise, when the quality of the reference data cannot be easily assessed, due to the size of the molecular complexes involved, and when the number of molecules is limited.

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1.Introduction

Double hybrid (DH) functionals are among the most sophisticated Density Functional Approximations (DFAs), lying on the highest rungs of the Perdew's quality ladder^{1,2}. These functionals can be considered as the consecutive extension of the global hybrids (GH), introduced by Becke about thirty years ago³. Suggested long time ago by Ernzerhof⁴, then proposed by Truhlar⁵, DHs have been definitely popularized by Grimme⁶. The inclusion of a second order perturbative (PT2) contribution into the functional leads to an increase accuracy for a wide range of molecular properties, ranging from structures to thermochemistry, reaction barriers, and electronic transitions energies^{2,7,8}. Still, some of these properties are not yet obtained with the looked-for accuracy, that is the one often defined as "chemical accuracy" in some fields like thermochemistry⁹. Indeed, these properties represent a practiced and challenging playground for any (new) DFAs.

Weak non-covalent interactions are a typical example of a field calling for an improvement of methods based on Density Functional Theory (DFT)^{10,11}. Here, DHs undoubtedly represent a step forward with respect to traditional DFAs, significantly reducing the errors in reference benchmarks¹²⁻¹⁶. Further improvements can be then obtained by adding empirical dispersion potentials¹⁷⁻¹⁹. Proposed by Yang²⁰ and then developed by Grimme²¹, these empirical potentials represent a fast and chemically sound correction to remedy the DFA flaws on such important class of chemical interactions. They are pairwise functions, parametrized on the atoms and exchange-correlation functional considered, derived from models used for classical force fields. Notably, these corrections have a smaller impact on DHs than on traditional functionals, such as GHs, since the formers already recover a part of the noncovalent interactions through the PT2 correlation contribution²².

Nonetheless, standard implementations of DHs are more computationally demanding than other DFAs, due to the numerical requirements of the PT2 contribution, thus limiting *de facto* the size of the systems that can be studied.

As usual the case in Quantum Chemistry, to overcome this problem two ways can be pursued: reducing the spanned atomic basis and/or approximating the PT2 term. In both cases, the strategy is to have a minor (negligible) degradation of the results with respect to the initial approaches. Concerning the first point, we have recently proposed a small split-valence basis set, named DH-SVPD²³, that, when coupled to DHs functionals, allows a good evaluation of noncovalent interactions. This basis set, derived from Def2-SVPD²⁴, was developed using an approach based on energy contributions of few reference monomers and related noncovalent dimers, computed at the same DH level of theory, and it does not require any tuning to external

reference values. When coupled to our non-empirical PBE-QIDH functional²⁵, this basis set avoids the introduction of empirical dispersion potential, thus restoring a full non-empirical DFA approach²⁶. At the same time, the small size of the basis set helps in containing the computational requirements, even for large systems, such as fullerene dimers²⁷. Previous works on standard benchmarks, such as S66 and S66x8 datasets^{28,29}, indicate that the PBE-QIDH/DH-SVPD model has an accuracy comparable (and sometime better) than that obtained when the same functional is coupled to larger quadruple- ζ or triple- ζ basis set and empirical dispersion corrections^{23,27}. This basis set is also transferable to other DHs, such as the popular B2PLYP⁶. A similar behavior has been found for the L7 set³⁰, that contains quite large molecules²³. Starting from this solid ground, we want to further push the limit of PBE-QIDH/DH-SVPD protocol, exploring larger systems, such as those included in the CiM13 dataset recently proposed by Neese³¹. This investigation gives us the opportunity to explore the speed-up obtained by computing the PT2 contribution with methods like Resolution of Identity (RI)³² or Domain-based Local Pair Natural Orbital (DLPNO)^{33,34}, and verify the accuracy of the obtained interaction energies for such very large noncovalent complexes. The quality of these approximations have been very recently discussed in the context of the CCSD(T) approach^{35,36}, but, at the best of our knowledge, never for DHs. However, their use is appropriate for accelerating the DH calculations and/or to enlarge the size of the investigated molecules. It could be argued that they are expected to have a significant positive impact also on the DHs, where the time limiting step is the evaluation of the PT2 contribution.

2. Computational details

All the calculations were carried out with the non-empirical PBE-QIDH²⁵ functionals and the Orca 5.0 program³⁷⁻³⁹. For each energy single point, a tight SCF convergence criteria together with the DefGrid3 integration grid are taken as default.

Contrary to our previous works, we considered only one DFA in order to have a straightforward evaluation of the effects of the computational parameters underpinning its evaluation on the large systems considered. Several approximations for speed-up the calculations of large systems have been considered. Unless when indicated with the NORI label, the RI approximation was always considered for Coulomb and exchange integrals together with the auxiliary basis set automatically generated by Orca for the DH-SVPD basis (keyword: AUTOAUX) and making use of the chain-of-spheres approximation (RIJCOSX)⁴⁰.

Few tests using different auxiliary basis⁴¹ did not lead to any significant variation of the obtained numerical results. The DLPNO approximation was also applied for the evaluation of

the PT2 correlation. Three parameter settings, indicated with the label *Loose*, *Normal* and *Tight*, were selected for the latter. As suggested by these labels, these three sets correspond to an increasing level of accuracy, assured by the cutoff thresholds of the domain (TCutDo), pair natural orbitals (TCutPNO) and orbital Mulliken population (TCutMKN), as reported in Table 1. Details on all these approximations can be found in the original papers^{33,34,40}, as well as in the Orca documentation. All the other parameters have been kept fixed to their default values. The DH-SVPD basis set was obtained from the original def2-SVPD basis set²⁴, upon a constrained optimization of one *s*- and one *p*-function for H atom and one *p*-f and one *d*-function for the C, N and O atoms. All other exponents are kept fixed to those of the original basis set. The optimized exponents are reported in Table S1, while an example of input for Orca is given in Table S2.

The good results obtained coupling the DH-SVPD basis and PBE-QIDH (or other DHs) stem from a compensation between Basis Set Superposition Error (BSSE) and Basis Set Incompleteness Error (BSIE), the former overestimating the interaction energies in weakly bonded systems, the latter underestimating them.²⁷ A similar compensation, leading to correct estimation of interaction energies, has been observed for CCSD(T) energies when double- ζ basis and, to a minor extent, triple- ζ basis are used.⁴²

Several molecular sets were considered in the present paper, namely S66, L7 and CiM13^{28,30,31}. While the first one can be clearly defined as a benchmark, in view of its significant number of systems and the general consensus on the reference energies, the other two are more a collections of large systems than real benchmark systems. Furthermore, the size of the molecules involved in these sets make difficult to have accurate reference energies, so that the reference values for their interaction energies are still matter of debate (see also *infra*). Here we use the DLPNO-CCSD(T) of Sancho-García and co-workers for the L7 set⁴³, and the CIM-DLPNO-CCSD(T)||RI-MP2 of Neese and co-workers for the CiM13 sets³¹.

The first data set, from reference 432, is obtained from DLPNO-CCSD(T) value, where the default threshold of Orca for DLPNO(*Tight*) model have been used, together with the def2-TZVPP basis set. Interaction energies were then extrapolated to the Complete Basis Set (CBS) limit using a two-point extrapolation⁴³.

The reference data for the CiM13 set were obtained using a more approximate model, based on the recently developed Cluster-in-Molecule (CIM) approach⁴⁴³. In particular, interaction energies were computed at the CIM-RI-MP2/CBS level and then corrected for the CCSD(T) correlation energy. The resulting model is denominated CIM-DLPNO-CCSD(T)||RI-MP2.³¹

The basis set was of double- ζ (aug-cc-pVDZ) or triple- ζ (aug-cc-pVTZ) quality depending on the system size. The interested reader can refer to the original reference 31 for more details on the computational procedure. Here we want to stress that even if these energy values could be not at convergence with respect to different computational parameters (such as basis set or CBS extrapolation scheme) they actually represent the current state-of-the-art for the large system investigated.

As usual in this kind of analysis, the original molecular structures were considered for the three sets, that are those reported in reference 45 for S66 and L7 and in reference 31 for CiM3. The molecules belonging to the L7 and CiM3 sets are also sketched in Figure 1 and 2, respectively.

3. Results and comments

3.1 Medium-sized sets: S66 and L7

The first two benchmarks, S66 and L7, are largely used in literature to assess the performance of modern (and less modern) functionals. Figure 3 gathers the Mean Average Errors (MAEs) computed for the PBE-QIDH/DH-SVPD model, using the 4 mentioned models (RIJCOSX and the three DLPNO settings) together with the conventional DFA calculations (NORI). These MAEs are obtained with respect to the reference values computed at the CCSD(T)/CBS level of theory, using density fitting for the MP2/CBS correlation energy²⁸. The numerical values are reported in Table S3. The S66 set is composed by relatively small molecules, containing between 6 and 24 atoms, whose weak interactions are classified as H-bonding, π -stacking, London or mixed interactions by the proposing authors²⁸.

First of all, it should be remarked that the computed MAEs on the whole set are equal for all the four approximations considered, all being around 0.37 kcal/mol, in agreement with our previous work²³. The negligible variations, on the third digit, found in going from the not-approximated DFA calculations to the approximated approaches (see Table S3) are not worth a detailed discussion. Looking at the different subsets, the only model showing a relatively large deviation is DLPNO(*Loose*) for the London subset, whose MAE increases of 0.1 kcal/mol with respect to the NORI value. Since this variation represents only 2% of the Mean Interaction Energy (MIE) of the S66 set (-5.5 kcal/mol), we can safely argue that our results indicate that all the 4 considered approximations can be applied on the S66 set, without any degradation of the results.

A similar exercise can be carried out for the L7 set, whose molecules have between 48 and 101 atoms. The computed deviations are collected in Figure 4, while the numerical values are given in Table S4. As expected, no significant variations are observed upon the introduction of

approximations of the Coulomb and exchange contributions (RIJCOX) whose MAE is very close to the reference NORI value (2.09 vs. 2.07 kcal/mol). A negligible decrease is found for the DLPNO approximation with the *Tight* setting (2.03 kcal/mol), while a significant increase is instead observed for the less severe thresholds: 2.31 kcal/mol for *Normal* and 3.10 kcal/mol for *Loose*. However, the variations with respect to NORI (+ 0.24 and + 1.03 kcal/mol, respectively) correspond to about 1% and 6% of the MIE for the L7 set (-17.4 kcal/mol). As a consequence, the DLPNO(*Loose*) setting begins to show its limits and cannot be recommended for L7.

The limited size of the benchmark set allows for a detailed analysis of the single molecules, thus revealing some interesting features. First of all, the single errors span a large energy interval, from -5.73 to +0.70 kcal/mol for the NORI model. This range is not peculiar to PBE-QIDH but other functionals, such as B3LYP-D3 and M06-2X³⁰, show similar behavior, thus underlining how this test can be considered difficult for any DFA. Then, it is interesting to remark that, while RIJCOSX and *Tight* and *Normal* settings are very close each others and show the trend already discussed for MAEs, an opposite behavior can be observed for the *Loose* model. Indeed, in this case the error is larger with respect to the other two settings for the molecules 1, 5, 6 and 7, while a lower error is predicted for molecules 2, 3 and 4. In other terms, the protocol DLPNO(*Loose*) has a behavior that cannot be easily predicted on the basis of the size of the system or the nature of the weak interactions involved.

Taken together, these results indicate that the DLPNO(*Loose*) protocol is not recommended for weak interactions also for PBE-QIDH (and other DHs), even if only a weight of 1/3 is introduced in the functional for the PT2 correlation.

3.2 Large set: CiM13

The CiM13 set, recently proposed by Neese³¹, contains among the largest systems (see Figure 2) used for analyzing the performance of DFT and post-Hartree-Fock (post-HF) methods. The number of atoms for the 13 molecules of the set, as well as the number of primitive and contracted basis functions for the DH-SVPD basis, are reported in Table 2. As it can be seen, the largest system is composed by about 1 thousand atoms and it already leads to 14 thousand basis functions with our small split valence basis set. Indeed, systems **1** to **8** are defined as components of the Extra-Large 8 (ExL8) set, just to stress their size³¹. It is therefore not surprising that these systems are too large for being processed without any approximation on the PT2 contribution, so that NORI results are not given and the RIJCOSX results will be considered as reference. In view of the negligible differences observed for these two models

(NORI and RIJCOSX) for the S66 and L7 sets, we are confident about this choice. A similar choice was also done in reference 31, where further approximations were introduced to compute the interaction energies of ExL8 set at CCSD(T) level. Furthermore, systems **6**, **7** and **8** are even too large to be computed with the RIJCOSX model without any further approximations, so that their values have been not considered in the corresponding RIJCOSX statistics.

Figure 5 reports our PBE-QIDH/DH-SVPD results, that clearly show an increase of the deviations in going from RIJCOSX to the DLPNO approximations. These variations are significant: + 22% of the MAE for *Tight*, + 36% for *Normal* and + 63% for *Loose* (see Table S5 for the numerical values). Indeed, the *Tight* setting correspond to a MAE of 4.13 kcal/mol, an error of 6% with respect to the MIE of the CiM13 set. Larger deviations are then found for the other settings: 4.59 kcal/mol for *Normal*, that is 7% of MIE and 5.49 kcal/mol for *Loose*, corresponding to 8% of the MIE. It should be also remarked that the difference between the MAE obtained with the RIJCOSX approximation and those computed for *Normal* and *Loose* is larger than the 1.0 kcal/mol threshold chased in thermochemistry (1.2 kcal/mol and 2.1 kcal/mol, respectively).

Looking more in details for the different systems, in several cases there are significant variations of the interactions energies that are smoothed in the statistical analysis. In fact, the RIJCOSX deviations range between -10.22 kcal/mol (molecule **2**) and +11.69 kcal/mol (molecule **c**), corresponding to 16% and 42% of the corresponding molecular interactions energies. Similar range can be observed for *Normal* and *Tight* settings, while the largest deviation is obtained with DLPNO(*Loose*) for molecule **7** (+23.11 kcal/mol, see Figure 5). It is also interesting to notice that in some cases (molecules **2**, **3**, **4**, **b** and **d**), the deviations decrease in going from *Tight* to *Loose*, thus suggesting some error compensations.

Before to comment the accuracy of the PBE-QIDH/DH-SVPD protocol with respect to other DFAs, a short summary on the above results is in order. This outline is reported in Figure 6 where all the MAEs for the three sets are collected. From these data, it is clear that the errors for the S66 are not affected by the different approximations. A negligible increase can be found for L7 set and the DLPNO(*Normal*) model, while the first signs of degradation appear with the *Loose* settings. This degradation is more evident with the last set, CiM13, whose MAEs systematically increase in going from RIJCOSX to the different settings for the DLPNO approximation. Despite such disappointing situation, it is still remarkable that such large systems can be computed at a reasonable computer effort and with errors that can be defined as acceptable even if far from the pursued chemical accuracy.

It is worth, at this point, a comment on the speed-up obtained with the different approximations. This point will not be discussed in details since (clock)time is strongly depending on the computer architecture, so that results are difficult to generalize and they can be easily misinterpreted. It is well known that RIJCOSX allows for a significant reduction of computer time and, indeed, the time for the L7 set is, in average, 40% of the standard one (NORI). More involved is the situation when the different DLPNO settings are considered. As reported in literature⁴⁶, DLPNO is not recommended for small- and medium-sized molecules. Indeed we found that it provides, for the L7 set, in average a comparable computational time with respect to RIJCOSX, but without any predictable tendency. Since the observed behavior is strongly system-dependent and the dataset is limited, these data will be not further discussed. Moving to CiM13 a more regular behavior is observed, as can be remarked from Figure 7, where the MAEs are reported as function of the fraction of time with respect to the RIJCOSX calculations. The speed-up is evident, the DLPNO model providing, in average, between 20% and 27% of the reference RIJCOSX time. This time reduction has a linear relationship with the MAEs: faster time corresponds to less-stringent thresholds and higher deviations. However, the gain in speed from *Tight* to *Loose* (+7%) is not enough to justify the high loss in accuracy (+ 40% on MAE, see Figure 7). As a consequence the *Tight* settings should be considered for all the calculations.

3.3 A comparison with literature data

As last step in this investigation, it is worth to compare the obtained results on the three data sets with those of other functionals. As above mentioned, the PBE-QIDH/DH-SVPD protocol has been already tested in literature on the S66 and L7 datasets, showing very good performances. In particular, it provides on the S66 set results that are close to those obtained with a dedicated protocol such as DSD-PBEP86/Def2-QZVP (0.78 kcal/mol) but better than standard B2-PLYP/Def2-QZVP (1.61 kcal/mol) or mPW2PLYP (1.71 kcal/mol)⁴³.

More complex is the situation for the L7 set where a consensus on the reference energies has not been reached. Indeed, at least two sets of reference energy values have been proposed, one based on QCISD(T)/CBS protocol by Hobza et co-worker³⁰ and another one by Sancho-García and co-workers, derived from DLPNO(*Tight*)-CCSD(T)/CBS calculations⁴³. More recent sophisticated Quantum Monte-Carlo calculations show a significant discrepancy with respect to a LNO-CCSD(T)/CBS model, as large as 29% of the interaction energy for the system **2** or 16% for system **3** of the L7⁴⁷. This point has been deeply discussed in a very recent article of Lao and co-workers⁴⁸, that also proposed revised values of the DLPNO(*Tight*)-CCSD(T)/CBS calculations. This uncertainty affects the error assessment for DFAs, variations in the reference

values leading to different statistics. For instance, the PBE-QIDH/DH-SVPD shows a MAE of 1.25 kcal/mol if the QCISD(T)/CBS values are considered, 1.18 kcal/mol for the Lao's CCSD(T) reference⁴⁷ and 2.3 kcal/mol with respect to the FN-DMC values of Tkatchenko and co-workers⁴⁶.

Concerning recent DFA approaches, it is worth to mention the ω B97M-V or the parent B97M-V functionals that give a MAE of 0.63 and 0.24 kcal/mol, respectively⁴⁸. Not far are PW6B95-D3(BJ) with a MAE of 0.79 kcal/mol and B2-PLYP-D3(BJ) with 0.95 kcal/mol. The best performance can be ascribed (at the moment) to the PBE0 functional, developed by Adamo and Barone⁴⁹, coupled with the D4 dispersion⁵⁰ (PBE0-D4), with an impressive MAD of 0.15 kcal/mol⁴⁸. Higher values are obtained with the more traditional B3LYP-D3(BJ) (1.76 kcal/mol) and M06-2X (3.39 kcal/mol)³¹. The MAE of about 2.0 kcal/mol obtained with PBE-QIDH/DH-SVPD is comparable to these latter values.

More involved is, instead, the situation for the CiM13 set, which was only considered in a single study before⁵¹. In this work, Truhlar and co-workers, considered 7 systems taken from the CiM13 (molecules *1* to *7* in Figure 2) in order to show that an accurate reproduction of noncovalent interactions in large systems is possible at DFT level. The MAEs, obtained for selected functionals for this subset are collected in Table 3. The lowest deviations are obtained for functionals casting empirical dispersions, such as B3LYP-D4 (4.81 kcal/mol) and ω B97X-D (5.06 kcal/mol). Higher deviations are obtained for the uncorrected models, such as M06-L (10.19 kcal/mol) and M06-2X (13.06 kcal/mol). It should be also remarked the (relatively) poor performance of the PW6B95-D3(BJ) functional (7.71 kcal/mol) that was among the best performers on the L7 set.

Our PBE-QIDH/DH-SVPD protocol provides the lowest error among the functionals listed in Table 3, with a MAE of 4.36 kcal/mol. Similar trends are obtained if the Root Mean Square Deviations (RMSD) are considered, even if B3LYP-D4 is now better than PBE-QIDH/DH-SVPD (5.53 vs. 5.99 kcal/mol, respectively). These results are even more noteworthy, considering the non-empirical nature of the PBE-QIDH functional and the absence of an empirical potential. Furthermore, this MAE is close to that provided by the CIM-RI-MP2 model, 4.26 kcal/mol³¹, that is almost as computing demanding as a DH (using RI). Interesting, the systems showing the largest errors (last column of table 3) are not the same for all the functionals and not even the largest, thus pointing out the heterogeneity of the molecular set.

It should be also noticed that the reference values are obtained with the CIM-DLPNO-CCSD(T)||RI-MP2 level of theory, a method that contains the Cluster-In-Molecule (CIM)

approximation on the top of the DLPNO model⁴⁴. The resulting approach is even faster than the DLPNO, but the quality of the reference data is weakened by the introduced approximation. Indeed, a MAE of 0.9 kcal/mol is found for the CIM-DLPNO-CCSD(T)||RI-MP2 model with respect to the parent DLPNO-CCSD(T) approach, if the energy of molecules *a* to *e* of Figure 2 are considered (taking all the data from Table 4 of reference 31). Conversely, the MAE of PBE-QIDH/DH-SVPD for these 5 molecules using the CIM-DLPNO-CCSD(T)||RI-MP2 references is 4.34 kcal/mol, a value to be compared to 3.80 kcal/mol obtained for the MAE with respect to the DLPNO-CCSD(T) values.

Extrapolating similar differences for the larger molecules *1* to *8* for which DLPNO-CCSD(T) reference are not available, a lower MAE than the actual one (4.36 kcal/mol) could be expected for PBE-QIDH/DH-SVPD. This example well illustrates the difficulty that can be encountered for not having well-assessed reference energies easily available.

More in general, it should also be noticed that for most of the functionals the MAE shows a steep increase with the size of the molecules. For instance, the MAEs for B3LYP-D3(BJ) are 0.38, 0.70 and 6.43 kcal/mol, for S66, L7 and CiM13 sets, respectively. A similar behaviour can be evidenced for M06-2X (0.26, 4.81, 13.06 kcal/mol) and PW6B95-D3(BJ) (0.19, 0.79, 7.71 kcal/mol) for the three sets (respectively). For DLPNO(Tight)-PBE-QIDH, these values are 0.38, 2.03 and 4.36 kcal/mol, in the same order. The different nature of the functionals, the inclusion (or not) of empirical dispersion and the limited number of molecules in the sets do not allow for a deeper analysis on the physics behind this behaviour. However, the closer range obtained for PBE-QIDH is reassuring and could be an indication of a lower dependence on the system size, due to a balanced treatment of the correlation effects on the weak interactions.

4. Discussion and Conclusions.

The above reported results well illustrate how efficient models and algorithms are pushing upward the computational limits in Density Functional Theory, but, at the same time, unveil underlying numerical problems.

From one side, these tests support the robustness of the PBE-QIDH/DH-SVPD protocol, based on a double hybrid functional and a basis set specifically developed for weak interactions. The very good results obtained for the CiM13 set, highly competitive with respect to others derived from empirical functionals, nicely illustrates this point. This protocol is fully nonempirical, since the functional does not contain parameters fitted on given properties and/or systems, and the basis set has been defined self-consistently without using external energy references.

These results have been obtained using different approximations for the evaluation of the exchange and Coulomb integrals, and second-order perturbative term (PT2) in the exchange-correlation functional, that allow the calculation of the large systems considered. In this case the DLPNO(*Tight*) model, on the top of the RI approximation, is that recommended also for double hybrids. Lower computational thresholds, like those present in the *Normal* and *Loose* settings, provide less accurate interactions energies, especially for (very) large systems.

Nonetheless, if the look-for chemical accuracy is easily reached by several DFAs for the S66 and L7 sets, apparently this is not the case for the large molecules of the CiM13 set. This unwelcome result depends however from different factors. The limited number of molecules in the two sets make difficult any robust statistical analysis, so that these sets can be considered more as a collection of (extra) large molecules than a real benchmark (like S66). Furthermore, the significantly deviations observed between computed and reference data point out a great inhomogeneity of the chemical interactions, that further weakens the statistics. In other terms, the sets are composed by few systems, ruled in a different manner by (subtle) chemical effects. For these reasons, not necessarily related to the quality of the tested functionals, the results obtained on small benchmark sets, like S66, cannot be safely extrapolated to larger systems.

This already complex situation is even worsened by the intrinsic difficulties arising from the post-HF calculations. Indeed, the approximations required to allow the evaluation of the interaction energies at a reliable level of theory, such as CCSD(T), affect the results for the large molecules of the CiM13 and, to a minor extent, of the L7 sets.

The picture emerging clearly shows the problems that can be encountered in the needed step of assessing the quality of any (new) DFT model, but, at the same time, it shows the significant progress made by quantum chemical models and algorithms in treating molecule of growing size and interaction chemical interest, so to fill one the last gap in Quantum Chemistry modeling.

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Supporting information

The Supporting Information is available free of charge on the ACS Publications website: optimized s , p and d exponents for C and H basis sets, Orca example input, row data of Figures 3 to 5.

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Table 1. Default parameter values for the DLPNO model.

setting	T_{cutPairs}	T_{cutPNO}	T_{cutMKN}
loose	$1.0 \cdot 10^{-3}$	$1.0 \cdot 10^{-6}$	$1.0 \cdot 10^{-3}$
normal	$1.0 \cdot 10^{-4}$	$3.33 \cdot 10^{-7}$	$1.0 \cdot 10^{-3}$
tight	$1.0 \cdot 10^{-5}$	$1.0 \cdot 10^{-7}$	$1.0 \cdot 10^{-4}$

Table 2. Number of atoms, contracted and primitive functions (f) for the CiM13 molecules and the DH-SVPD basis set.

molecule	atoms	primitive f	contracted f
1	200	3616	1472
2	296	4240	1808
3	328	6153	2539
4	381	6150	2558
5	552	7782	3330
6	750	11166	4722
7	910	14536	6076
8	1027	14810	6306
a	126	1800	768
b	137	2198	938
c	144	2034	870
d	160	2288	976
e	174	2634	1110

Table 3. Interaction energies (kcal/mol) for the molecules 1 to 7 of the CiM3 dataset, the corresponding Mean Average Errors (MAEs, kcal/mol), Root Mean Square Deviations (RMSDs, kcal/mol) and largest error (max, kcal/mol) with the concerned molecule indicated in parenthesis. Except for the PBE-QIDH/DH-SVPD values, all the data are from references 51 and 31.

functional	1	2	3	4	5	6	7	MAE	RMSD	max
B3LYP	-50.47	-18.14	-24.78	-0.03	-17.39	-4.90	-263.49	49.13	67.79	152.59 (7)
M06-2X	-72.38	-64.69	-36.02	-14.74	-36.16	-59.51	-354.88	13.06	24.35	61.2 (7)
M06-L	-70.38	-69.63	-36.54	-15.95	-37.39	-67.75	-366.72	10.19	19.29	49.36 (7)
B3LYP-D3(BJ)	-74.31	-76.69	-43.82	-21.74	-45.42	-82.81	-423.31	6.43	7.10	-8.64 (1)
B97-D3(BJ)	-63.09	-69.30	-43.55	-22.88	-40.22	-71.09	-405.15	6.21	6.92	10.93 (7)
M06-2X-D3(0)	-76.34	-79.42	-39.44	-20.12	-44.87	-84.06	-392.22	8.73	11.48	23.86 (7)
M06-L-D3(0)	-74.60	-85.39	-40.25	-21.76	-46.64	-93.84	-406.33	9.31	11.26	-15.76 (2)
PW6B95-D3(BJ)	-68.70	-71.51	-39.84	-20.52	-40.98	-75.93	-381.14	7.71	13.69	34.94 (7)
ω B97X-D	-69.33	-78.41	-41.18	-23.84	-44.03	-79.78	-411.78	5.06	6.67	-8.78 (2)
B3LYP-D4	-76.33	-72.99	-42.94	-20.41	-44.86	-76.25	-417.91	4.81	5.43	-10.66 (1)
M06-L-D4	-75.73	-84.99	-40.62	-21.93	-46.24	-90.84	-408.47	8.70	10.44	-15.36 (2)
PW6B95-D4	-72.10	-69.25	-37.86	-16.69	-40.60	-68.33	-377.18	8.56	15.41	10.47 (6)
B3LYP-D4-MBD	-76.65	-73.31	-43.05	-20.44	-45.02	-76.52	-419.00	5.06	5.65	-10.98 (1)
PBE-QIDH ^a	-69.66	-70.39	-43.86	-19.70	-41.35	-78.02	-404.00	4.36	5.99	12.08 (7)
CIM-RI-MP2/CBS ^b	-70.02	-71.25	-37.77	-19.53	-43.09	-88.50	-422.60	4.26	5.45	-9.70 (6)
Reference ^b	-70.11	-63.61	-36.55	-17.83	-40.13	-78.80	-416.08			

a) This work, using the DH-SVPD basis set and the DLPNO(*Tight*) approximation; b) from Table 5 of reference 31;

Figure captions

Figure 1. Molecular complexes in the L7 set.

Figure 2. Molecular complexes in the CiM13 set.

Figure 3. Mean Absolute Errors (MAE, kcal/mol) for the interaction energies of the S66 set, computed with the PBE-QIDH/SVPDH model and different approaches for the PT2 contribution. The terms *Loose*, *Normal* and *Tight* define the set of parameters used in the DLPNO approximation.

Figure 4. Errors (ΔE , kcal/mol) and Mean Absolute Errors (MAE, kcal/mol) for the interaction energies of the L7 set, computed with the PBE-QIDH/SVPDH model and different approaches for the PT2 contribution. The terms *Loose*, *Normal* and *Tight* define the set of parameters used in the DLPNO approximation.

Figure 5. Errors (ΔE , kcal/mol) and Mean Absolute Errors (MAE, kcal/mol) for the interaction energies of the CiM13 set, computed with the PBE-QIDH/SVPDH model and different approaches for the PT2 contribution. The terms *Loose*, *Normal* and *Tight* define the set of parameters used in the DLPNO approximation.

Figure 6. Mean Absolute Errors (MAE, kcal/mol) for the interaction energies of the S66, L7 and CiM13 sets, computed with the PBE-QIDH/SVPDH model and different approaches for the PT2 contribution. The terms *Loose*, *Normal* and *Tight* define the set of parameters used in the DLPNO approximation.

Figure 7. Scaling of the Mean Absolute Errors with the computer time relative to the RI calculations (%) computed for the CiM13 set and different DLPNO parameters.

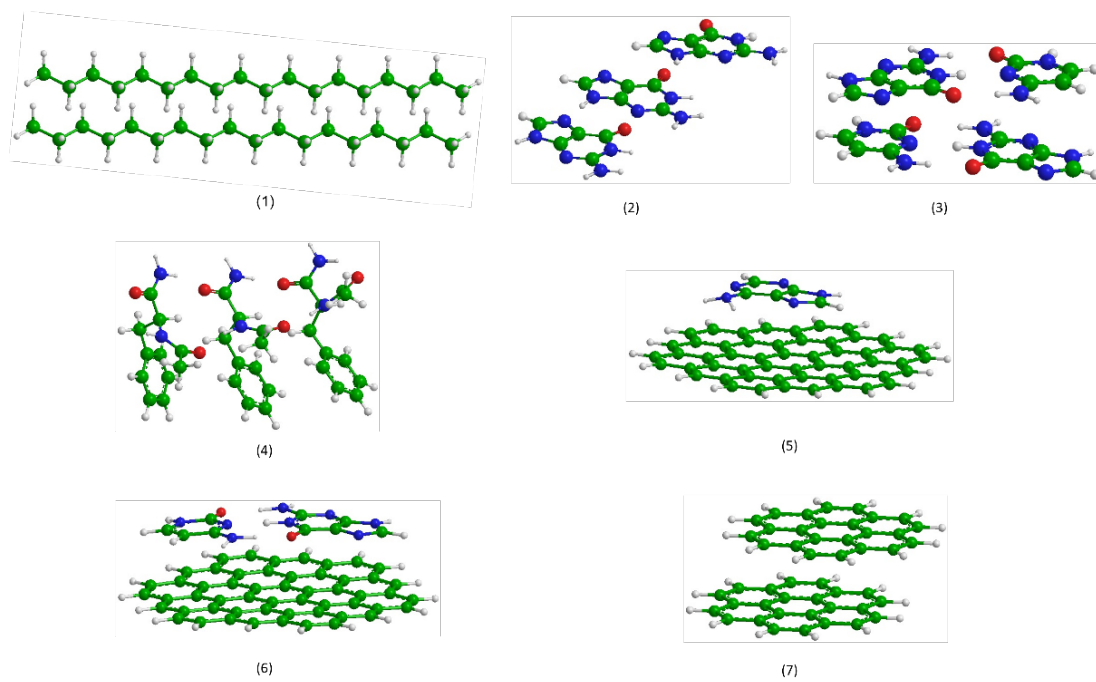


Figure 1

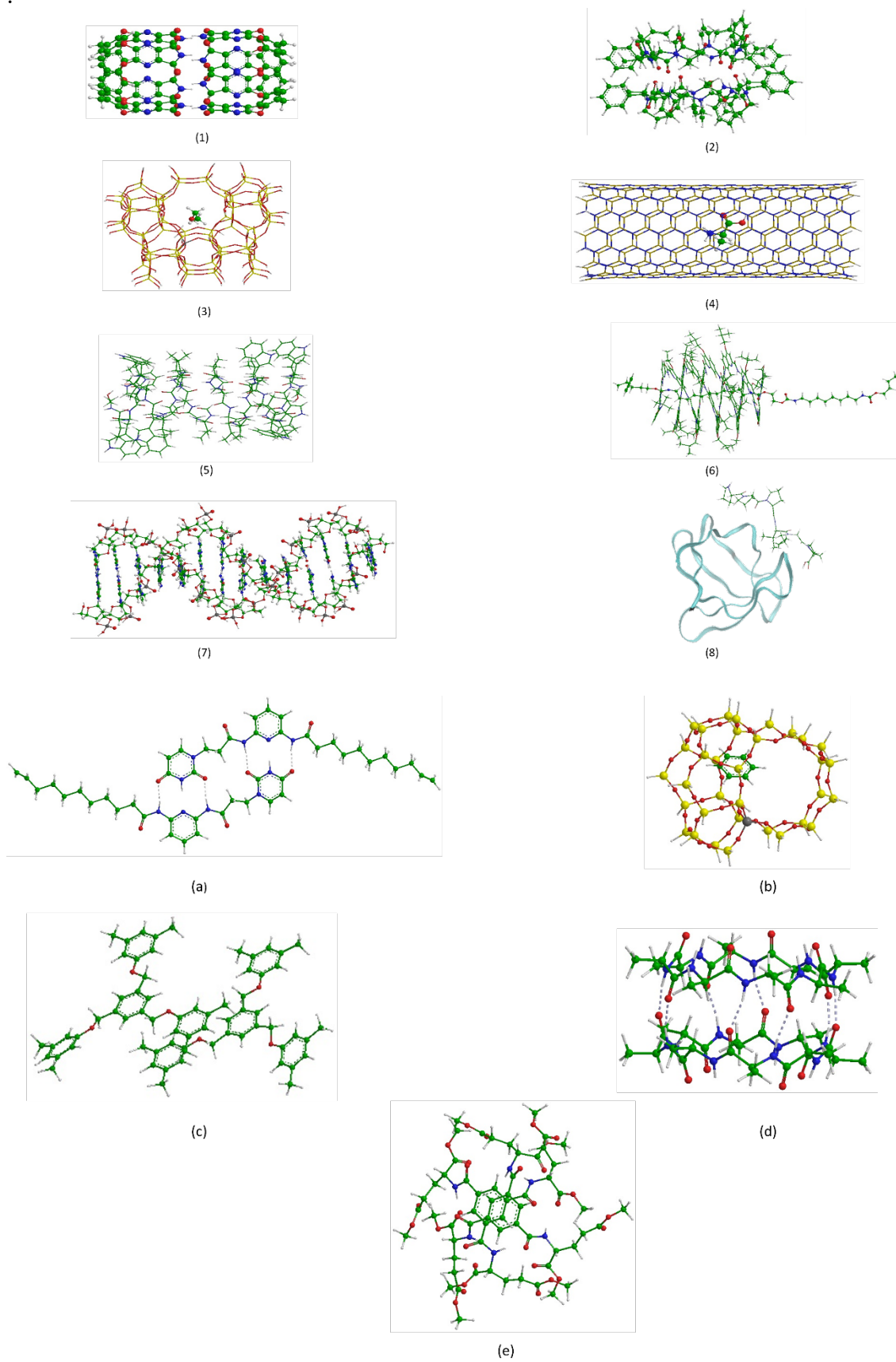


Figure 2

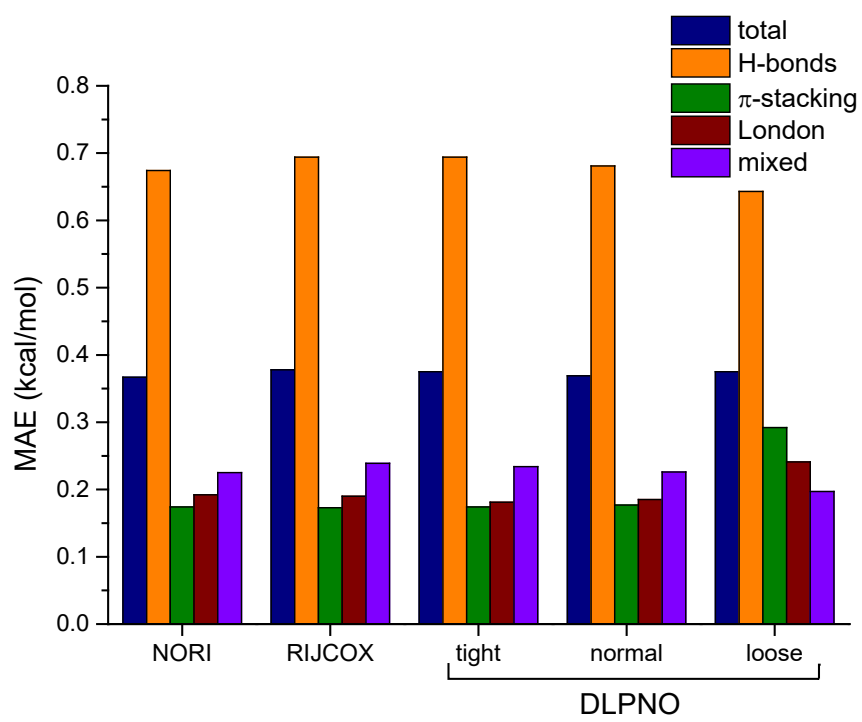


Figure 3

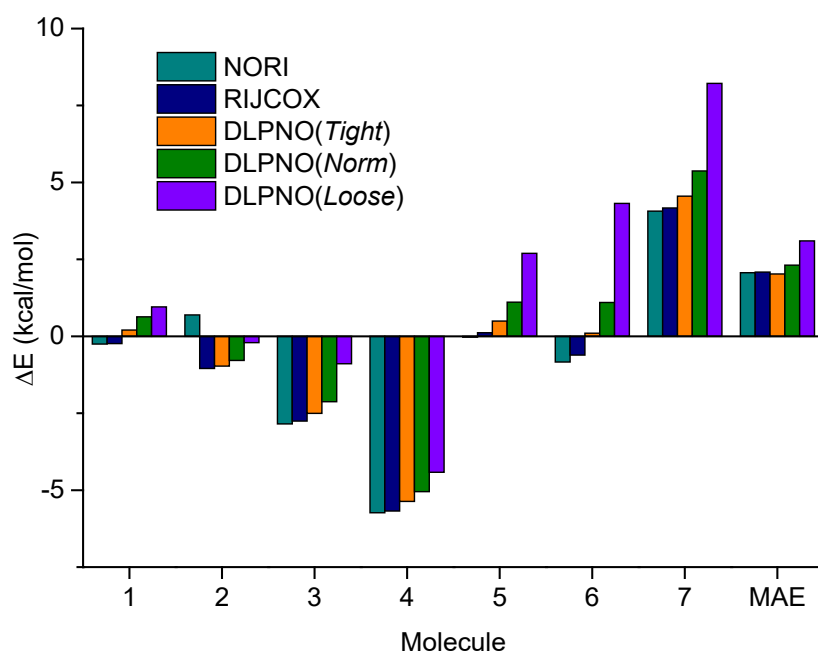


Figure 4

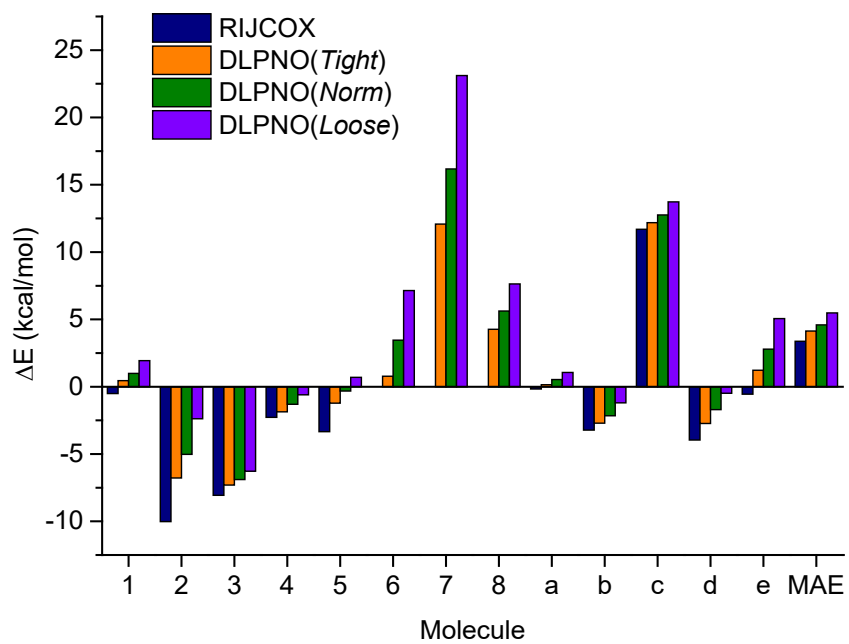


Figure 5

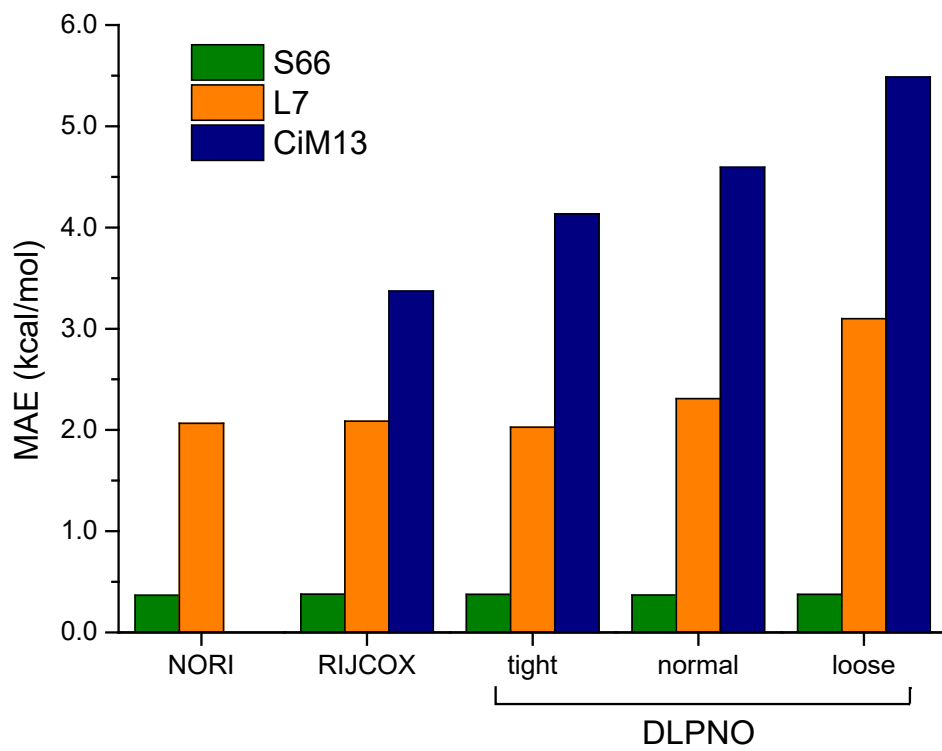


Figure 6

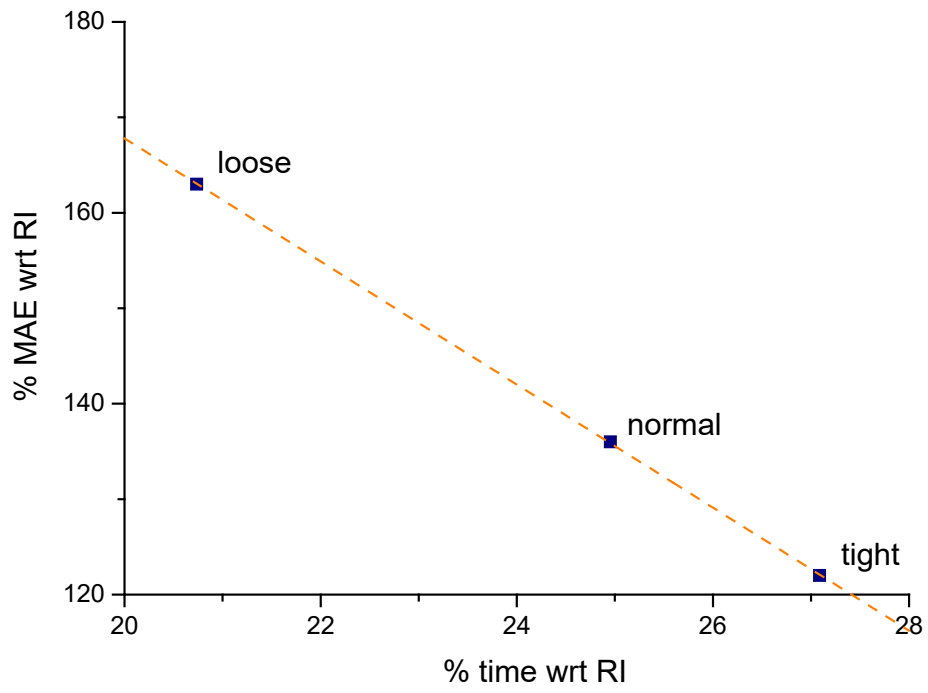


Figure 7

TOC Graphics

