



## Discovering Patterns in Molecular Interaction Energies Using Explainable Machine Learning

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**Abstract**— The energies of molecular interactions are important in the study of the stability and behavior of metal–ligand systems, and explainable machine learning provides a way to determine which aspects of computation are responsible for the energies and patterns in data. A study of 2,418 computational records corresponding to 26 reactions of metal–ligand systems were analyzed with three density functionals and 31 basis sets. Descriptive statistics, Kruskal–Wallis test, counterpoise correction analysis, Pearson correlation and ensemble machine-learning models were used. Interactions were mostly negative, but there was considerable variation in interactions. The energies were significantly affected by the density functional and by the basis-set cardinality, the double-zeta basis sets giving more negative mean values than the triple- and quadruple-zeta basis sets. The magnitude of interaction energies was reduced by counterpoise correction; uncorrected and corrected values were well correlated, and the effects of basis-set superposition error were confirmed. Five-fold reaction-grouped cross-validation was used to evaluate Random Forest, Extra Trees and Gradient Boosting. Gradient Boosting gave the smallest prediction error, but all models were found to have negative  $R^2$  values, meaning that they were not generalizable to unseen metal–ligand reactions. The computational parameters with the greatest influence were determined by permutation-based interpretation to be basis-set cardinality, basis-set identity, and density functional. In general, the explainable machine learning approach was able to capture the variation in computational drivers of interaction energy, yet molecular, geometric, and electronic descriptors are needed to achieve accurate extrapolation to new reactions.

**Keywords**— Molecular interactions; Interaction energy; Metal–ligand complexes; Explainable machine learning; Basis-set superposition error

## 1. INTRODUCTION

Molecular interaction energies provide a quantitative basis for understanding the stabilization or destabilization of atoms, ligands, molecular fragments, and supramolecular units. They are essential in coordination chemistry, catalysis, molecular recognition, materials design and drug discovery because they relate electronic structure to experimentally observable chemistry. Accurate characterization of interaction energies is therefore essential to understand binding strength, selectivity, structural stability, and reaction tendencies. Variational energy-decomposition methods show that interaction energies comprise physically meaningful components including electrostatics, polarization, charge transfer, dispersion and Pauli repulsion (Mao et al., 2021). In transition-metal systems, these interactions are more complex because electronic configuration, oxidation state, ligand environment, and orbital effects can significantly alter bonding characteristics (Nandy et al., 2021).

Molecular interaction energies continue to be estimated using density functional theory and other quantum chemical methods. Their predictions, however, often depend on the functional, basis set, and treatment of intermolecular effects. Wu and Truhlar (2021) demonstrated that approximate density functionals can differ substantially for noncovalent interactions in large molecular systems. Dispersion-corrected density functional methods are also widely explored because weak interactions require appropriate dispersion treatment (Spicher et al., 2021). Calculated interaction energies can additionally be affected by basis-set incompleteness. Jensen (2024) showed the relationship between basis-set superposition error and basis-set imbalance, while Fishman et al. (2025) highlighted the importance of basis-set superposition errors in high-level correlated calculations.

Counterpoise-based correction strategies are commonly employed to reduce basis-set superposition effects in interaction-energy calculations. Their use is particularly important with relatively small basis sets because artificial stabilization may otherwise bias energy estimates. Mehta and Goerigk (2021) investigated counterpoise-related corrections for thermochemistry, kinetics, and noncovalent interactions, showing that correction behavior depends on computational conditions. These sensitivities indicate that interaction-energy data contain both chemically relevant differences and systematic variation arising from computational choices.

Machine learning has opened new avenues to learn

predictive and mechanistic patterns from quantum-chemical data. With appropriate training data, machine-learning approaches can approximate molecular energies and other quantum properties at substantially lower computational cost (Noé et al., 2020). Ab initio machine learning has therefore become important for exploring chemical compound space and connecting molecular representations with electronic-structure properties (Huang & von Lilienfeld, 2021). Benchmark interaction-energy databases also support the development and testing of predictive models using high-quality reference calculations across diverse molecular systems (Donchev et al., 2021).

Neural networks and equivariant graph networks are increasingly used as machine-learning potentials for molecular energy surfaces. ANI-based models have demonstrated transferability through systematic expansion of elemental coverage (Devereux et al., 2020). OrbNet Denali has likewise demonstrated density-functional accuracy at substantially reduced computational cost (Christensen et al., 2021). Geometric symmetries are explicitly incorporated in equivariant architectures such as NequIP and MACE (Batzner et al., 2022; Batatia et al., 2022). AIMNet2 further extends these capabilities to neutral and charged organic and elemental-organic systems (Anstine et al., 2025).

Despite these advances, predictive accuracy alone is insufficient for identifying chemically meaningful energy patterns. Explainable AI provides approaches for understanding how molecular or computational properties influence model predictions. Jiménez-Luna et al. (2020) highlighted the importance of explainability for trust and mechanistic understanding in chemical applications. Wellawatte et al. (2023) argued that explanations for molecular prediction models should be judged by chemical relevance rather than treated only as feature-importance measures. Interpretable approaches have been applied directly to interaction-energy prediction, showing that machine learning can uncover influential descriptors governing energetic behaviour (Liu et al., 2023). More recent work has supported explainable learning for discovering human-interpretable structure–property relationships in chemical data (Wellawatte & Schwaller, 2025).

Against this background, the current study aims to explore metal–ligand interaction-energy patterns through statistical analysis and explainable machine learning. The analysis emphasizes reaction-specific energy variation, density-functional effects, basis-set cardinality, counterpoise correction, basis-set superposition error, and reaction-grouped predictive

performance.

## 2. METHODOLOGY

### 2.1 Study Design and Dataset

The study was conducted with the secondary design of computational-data analysis to explore patterns in molecular interaction energies by statistical and explainable machine-learning methods (Brakestad et al., 2021). A dataset of 2,418 computational records was analyzed, corresponding to 26 different metal–ligand reactions. Three different density functionals (BP86, PBE, and PBE0) and 31 basis sets were used in the calculations. A total of 1,723 observations had available uncorrected interaction-energy ( $\Delta E$ ) values and 1,560 observations had available pairs of uncorrected and counterpoise-corrected interaction energies. The interaction energies were given in Hartree.

### 2.2 Data Preparation and Interaction-Energy Characterization

The variables used in the analyses were checked for their availability in the dataset. 1,723 observations were used for the analysis of uncorrected interaction energy, excluding records with no  $\Delta E$  value. For counterpoise analysis, only those observations where the paired measurements of both energies were recorded were kept, which gave 1,560 observations. The mean and the standard deviation, median, minimum and maximum values were used to characterize the interaction-energy distributions. The number and proportion of observations with negative  $\Delta E$  values also were tabulated. A separate set of mean interaction energies were then calculated for each of the 26 metal–ligand reactions to describe the energetic pattern of each reaction.

### 2.3 Analysis of Density Functional and Basis-Set Effects

The three density functionals (BP86, PBE, and PBE0) were compared with respect to interaction energies. The number of samples, mean, standard deviation, minimum and maximum  $\Delta E$  were determined for each functional. The Kruskal–Wallis test was used to analyze the differences in interaction-energy distribution for the functional groups.

To investigate the effect of the basis-set cardinality, these calculations were divided into three groups: double-zeta, triple-zeta, and quadruple-zeta. Average interaction energies were computed for each cardinality group and differences between the three distributions tested with Kruskal–Wallis test. A value of  $p < 0.05$  was considered statistically significant.

### 2.4 Counterpoise Correction and Basis-Set

### Superposition Error

The effect of counterpoise correction was assessed by comparing the 1,560 observations that were paired:  $\Delta E$  and the counterpoise-corrected interaction energy ( $\Delta E_{CP}$ ). The mean, standard deviation, median, minimum and maximum values of the  $\Delta E$ ,  $\Delta E_{CP}$ , and basis-set superposition error (BSSE) were calculated. A percentage of the positive BSSE observations was also calculated. The Pearson correlation coefficient ( $r$ ) was used to quantify the relationship between the uncorrected and counterpoise-corrected interaction energies, and  $p < 0.05$  was considered statistically significant.

### 2.5 Machine-Learning Model Development and Validation

The ability to predict uncorrected interaction energy ( $\Delta E$ ) was assessed using three ensemble regression algorithms: Random Forest, Extra Trees and Gradient Boosting. To avoid target leakage, the following variables directly derived from the response variable were not included in the predictor set:  $\Delta E_{CP}$  and BSSE, and component electronic energies that algebraically determine  $\Delta E$ .

Five-fold GroupKfold cross-validation was performed for model validation, using the identity of metal–ligand reaction as the grouping variable. This was done in such a way that observations would not appear in both the training and validation partitions at the same time in the same reaction. Based on this, the model performance demonstrated the ability to generalize to metal–ligand reactions that were not included in the model training. The coefficient of determination  $R^2$ , the mean absolute error (MAE) and root mean squared error (RMSE) were used to measure the predictive performance.

### 2.6 Explainable Machine-Learning Analysis

Permutation-based feature importance was performed on the model to identify the relative importance of the computational variables when predicting the interaction energy. The focus for the interpretation was on the predictors remaining in the machine-learning analysis – the basis-set cardinality, the identity of the basis set, density functional, electron-count variables, charge, multiplicity and convergence-related variables. The feature importance was analyzed with grouped cross-validation performance to understand the impact of predictors in relation to the model's capacity to predict new metal–ligand reactions.

### 2.7 Ethical Considerations

This study was conducted using an existing

computational dataset of molecular interactions, without involving human subjects or animals, clinical information, or personally identifiable data. Thus, informed consent and institutional ethical approval were not applicable. Only scientific analysis was performed on the data, and the original computational records were kept without modification.

### 3. RESULTS

#### 3.1 Dataset Characteristics and Molecular Interaction-Energy Distribution

The interaction-energy dataset had 26 different metal–

ligand reactions calculated with 31 basis sets and 3 density functionals, BP86, PBE and PBE0, resulting in 2,418 computational records. 1,723 observations were found which had valid uncorrected interaction energies ( $\Delta E$ ). Among these observations, the mean  $\Delta E$  was  $-0.03059 \pm 0.01718$  Hartree, with a median of  $-0.02759$  Hartree and an overall range from  $-0.09639$  to  $0.01034$  Hartree (Table 1). The evidence of negative interaction energies is found in 99.77% of the observations, which is an indication that the data set was dominated by energetically favourable association configurations.

**Table 1. Descriptive characteristics of molecular interaction energies**

| Parameter                        | Result     |
|----------------------------------|------------|
| Total computational records      | 2,418      |
| Distinct metal–ligand reactions  | 26         |
| Records with $\Delta E$          | 1,723      |
| Records with $\Delta E_{CP}$     | 1,560      |
| Density functionals              | 3          |
| Basis sets                       | 31         |
| Mean $\Delta E$ (Hartree)        | $-0.03059$ |
| SD                               | $0.01718$  |
| Median $\Delta E$                | $-0.02759$ |
| Minimum $\Delta E$               | $-0.09639$ |
| Maximum $\Delta E$               | $0.01034$  |
| Negative $\Delta E$ observations | 99.77%     |

There was a significant variation between the individual metal–ligand systems (Figure 1). The mean interaction energy values for Cr–CO were the most negative ( $-0.07100$  Hartree), followed by Ni–NHC-1 ( $-0.06217$  Hartree) and Ni–NHC-2 ( $-0.06164$  Hartree). The minimum negative mean energy was

found for Ni–Alkene-5 ( $-0.01190$  Hartree), with the opposite end of the distribution being the most positive. So, the number of molecules stabilized was not the same for every metal–ligand combination but changed significantly.

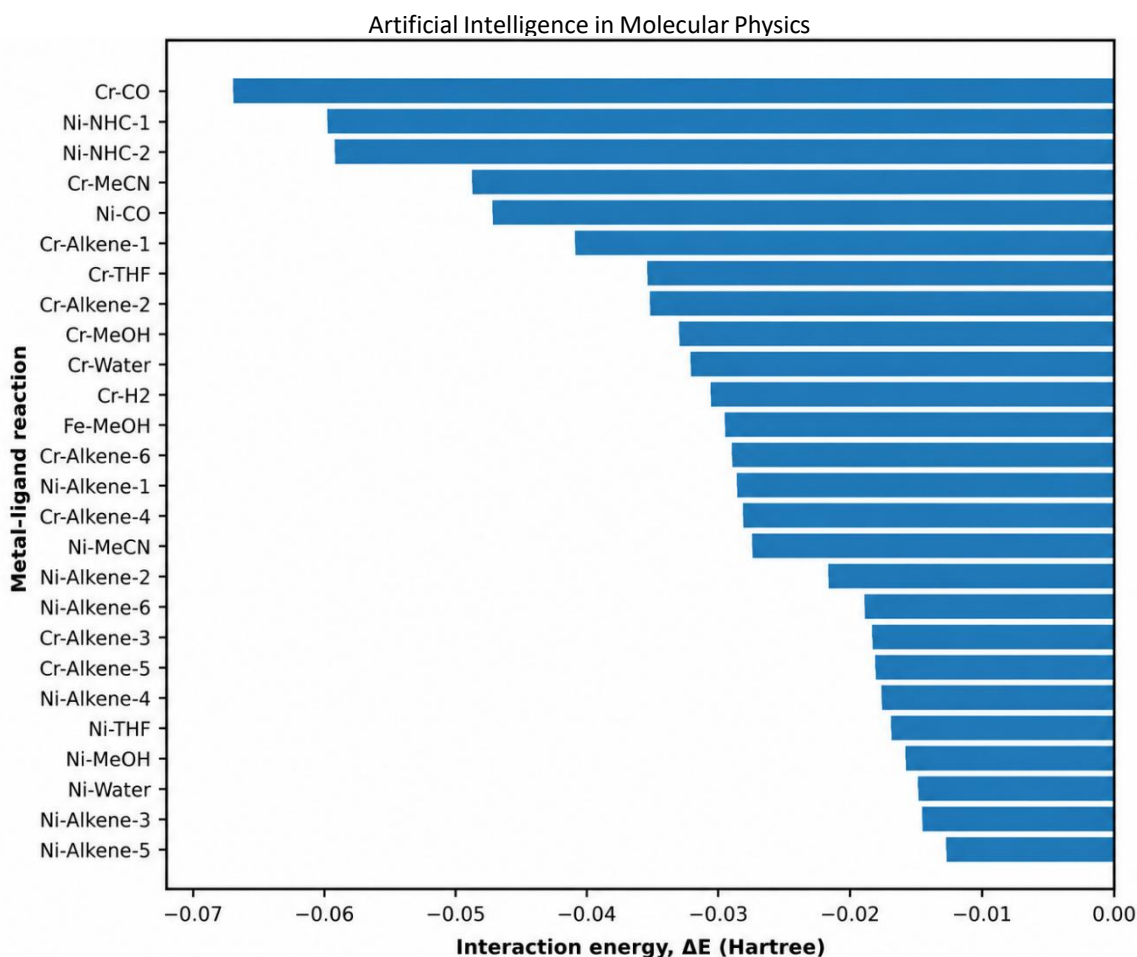


**Figure 1.** Interaction-energy profiles across the 26 metal–ligand reactions. Bars represent mean  $\Delta E$  across available computational settings.

### 3.2 Influence of Computational Conditions on Interaction Energies

The interaction-energy distributions were also found to be different for different density functionals and basis-set cardinalities. Mean  $\Delta E$  was  $-0.02804$

Hartree for BP86,  $-0.03228$  Hartree for PBE, and  $-0.03098$  Hartree for PBE0 (Table 2). The non-parametric comparison was performed to detect difference between the three functional groups and it was found that there is a significant difference (Kruskal–Wallis  $\chi^2(2)=27.51$ ,  $p<0.001$ ).

**Table 2.** Interaction-energy distribution according to density functional

| Functional | n   | Mean $\Delta E$ | SD      | Minimum    | Maximum    |
|------------|-----|-----------------|---------|------------|------------|
| BP86       | 553 | $-0.02804$      | 0.01743 | $-0.09220$ | 0.00154    |
| PBE        | 728 | $-0.03228$      | 0.01697 | $-0.09639$ | 0.01034    |
| PBE0       | 442 | $-0.03098$      | 0.01688 | $-0.08981$ | $-0.00575$ |

A more systematic pattern developed for the basis-set cardinalities. The mean  $\Delta E$  value for the double-zeta calculations was  $-0.03646$  Hartree, whereas it was  $-0.02921$  Hartree for triple-zeta and  $-0.02660$  Hartree for quadruple-zeta calculations. This difference was significant between the corresponding distributions (H

$= 100.71$ ,  $p < 0.001$ ). Figure 2 shows that the trend to more positive interaction energies with increasing cardinality suggests that there is significant variation in the calculated interaction energies due to basis-set selection.

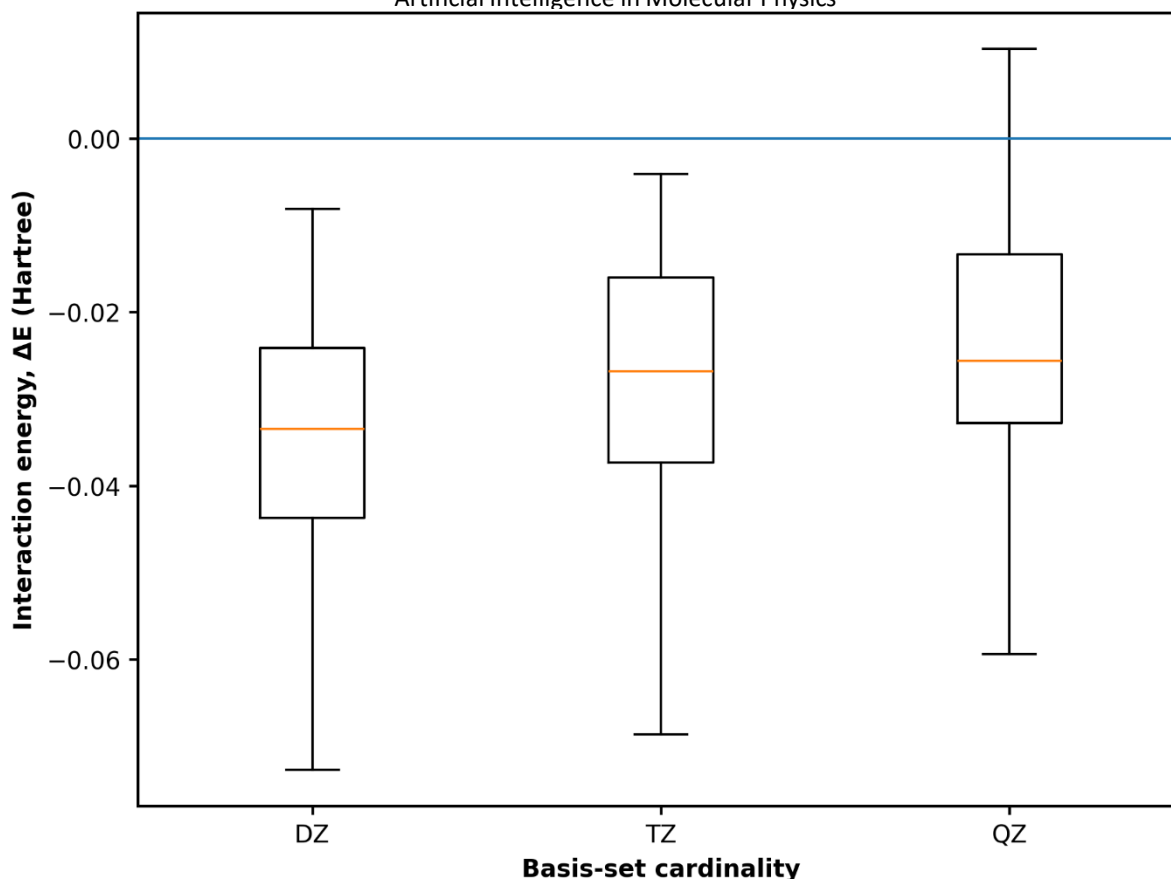


**Figure 2. Distribution of molecular interaction energies according to double-, triple-, and quadruple-zeta basis-set cardinality. Box boundaries indicate the interquartile range and the internal line represents the median**

### 3.3 Counterpoise Correction and Basis-Set Superposition Effects

When complete counterpoise information are available, mean uncorrected  $\Delta E$  is  $-0.03122$  Hartree while the mean counterpoise-corrected  $\Delta E_{CP}$  is

$-0.02558$  Hartree for the 1,560 observations (Table 3). The mean basis-set superposition error (BSSE) was  $0.00565$  Hartree, with a maximum of  $0.03018$  Hartree, a median of  $0.00349$  Hartree. In 99.81% of the paired observations, the values of BSSE were positive.

**Table 3. Counterpoise correction and BSSE characteristics**

| Parameter       | Mean       | SD        | Median     | Minimum    | Maximum   |
|-----------------|------------|-----------|------------|------------|-----------|
| $\Delta E$      | $-0.03122$ | $0.01715$ | $-0.02823$ | $-0.09639$ | $0.01034$ |
| $\Delta E_{CP}$ | $-0.02558$ | $0.01656$ | $-0.02441$ | $-0.07089$ | $0.01041$ |
| BSSE            | $0.00565$  | $0.00592$ | $0.00349$  | $-0.00002$ | $0.03018$ |

After correction, uncorrected and counterpoise-corrected interaction energies remained strongly correlated ( $r = 0.939$ ,  $p < 0.001$ ), but the majority of observations moved up the plot above the identity line (Figure 3). This pattern shows that in most cases, the

negative interaction energy was decreasing with increase in counterpoise correction. This was not a uniform shift, suggesting that BSSE was not always an additive effect on the molecular systems and computational settings.

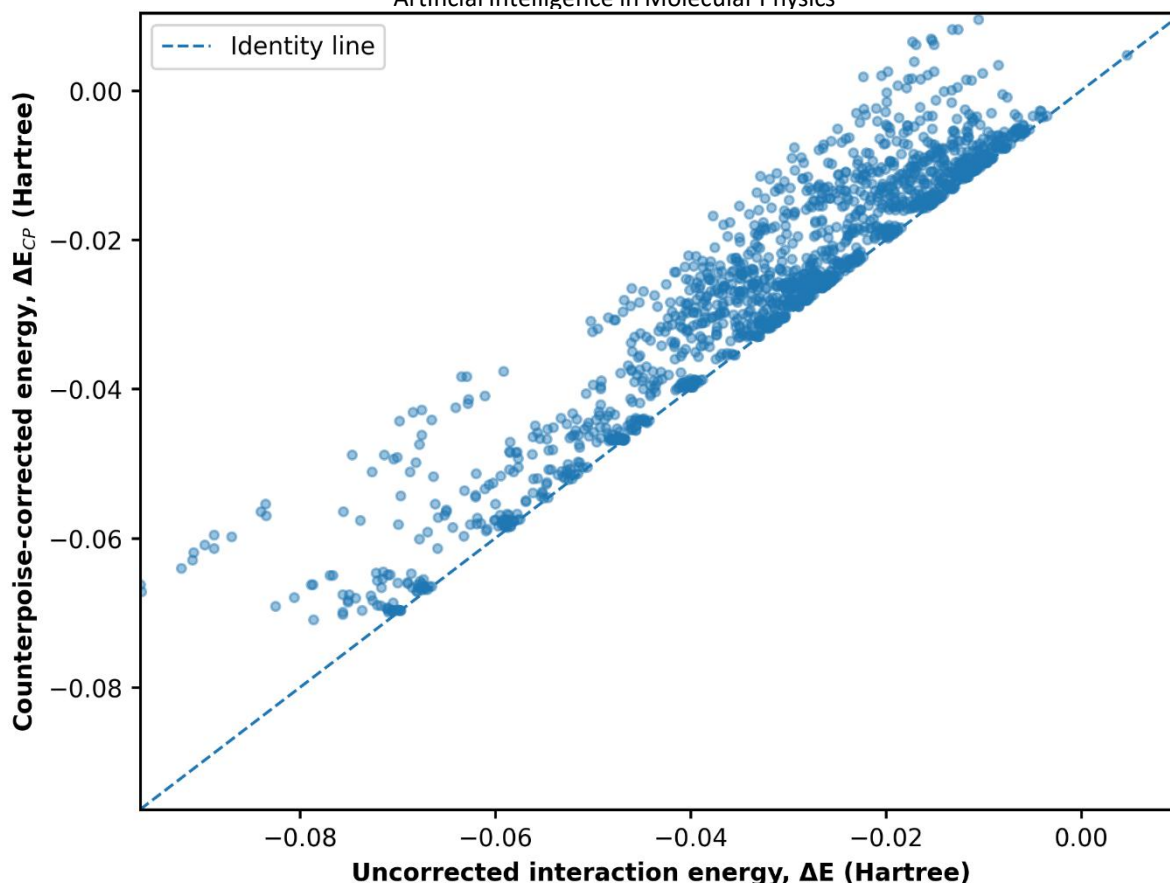


**Figure 3.** Relationship between uncorrected and counterpoise-corrected molecular interaction energies. The dashed identity line represents equivalent corrected and uncorrected energies.

### 3.4 Explainable Machine-Learning Assessment

Five-fold GroupKFold cross-validation was evaluated at the reaction level using machine-learning regression, which implied that the models had to make predictions of metal–ligand reactions not present in the respective training folds. Direct predictors of  $\Delta E$ , such as  $\Delta E_{CP}$  and  $BSSE$  and component electronic energies that algebraically constitute  $\Delta E$  were excluded to avoid leakage of the target.

In this strict validation method, all three ensemble

models had negative cross-validated  $R^2$  values (Table 4). The prediction error of Gradient Boosting was the lowest, with a MAE of 0.01324 Hartree, an RMSE of 0.01776 Hartree, and an  $R^2$  value of  $-0.068$ . Random Forest and Extra Trees gave  $R^2$  values of  $-0.346$  and  $-0.344$  respectively. Therefore, the set of tabular computational descriptors provided was not sufficient to make reliable extrapolations for completely new identities of metal–ligand reactions.

**Table 4.** Reaction-grouped cross-validated machine-learning performance

| Model             | $R^2$    | MAE (Hartree) | RMSE (Hartree) |
|-------------------|----------|---------------|----------------|
| Gradient Boosting | $-0.068$ | 0.01324       | 0.01776        |
| Extra Trees       | $-0.344$ | 0.01486       | 0.01991        |
| Random Forest     | $-0.346$ | 0.01460       | 0.01993        |

The grouped cross-validation results are shown in Figure 4. The negative  $R^2$  values indicate that the models performed worse on unseen reaction groups than a baseline prediction based on the validation-set

mean, demonstrating limited out-of-reaction generalization from the available computational descriptors.

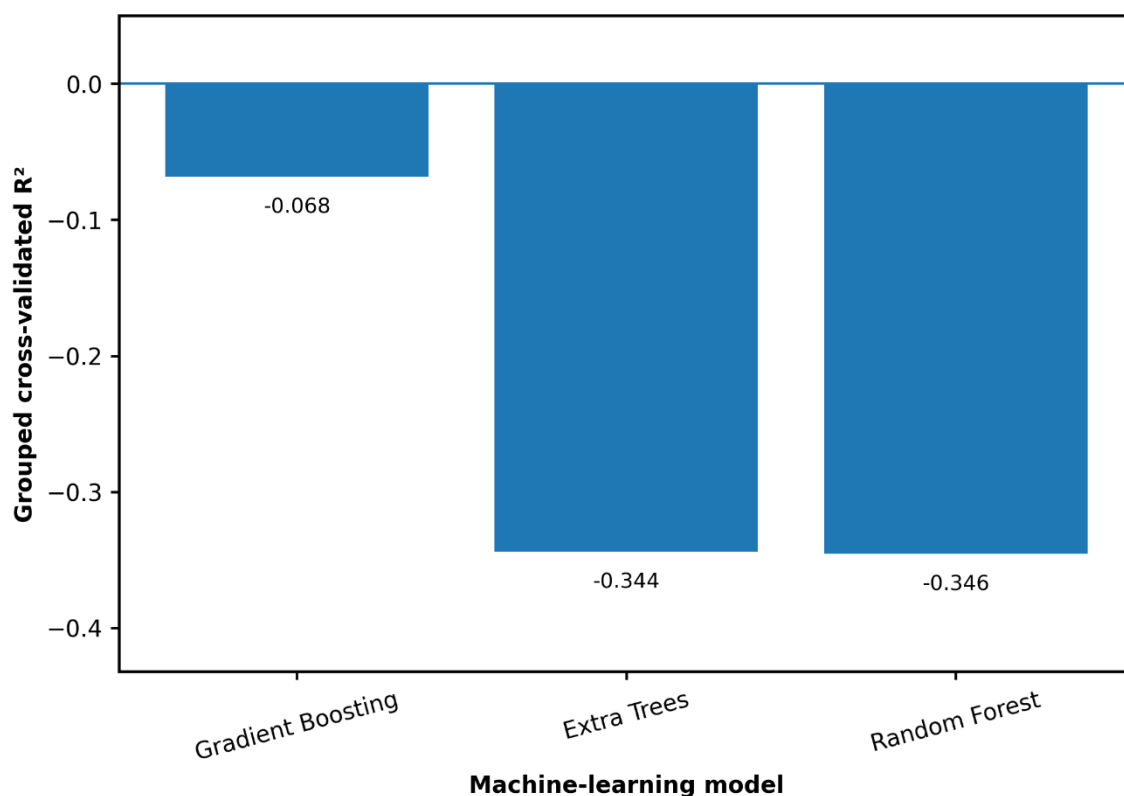


**Figure 4. Machine-learning performance under five-fold reaction-grouped cross-validation. Negative  $R^2$  values indicate limited generalization of the tabular descriptors to previously unseen metal–ligand reactions.**

### 3.5 Patterns Identified by Explainable Analysis

The main computational variables that contributed to predictions were determined by permutation-based interpretations of the ensemble models: basis-set cardinality, specific basis-set identity, and density functional. Their dominance was similar to that described above, and the energy difference between double-, triple-, and quadruple-zeta calculations was particularly large. The variables associated with the electrons in the molecule and with the multiplicity of the ground state were not always found to be consistent with the reaction-grouped validation, but the charge variables were not found to have any great discriminatory value as they were not found to vary in many reaction groups.

## 4. DISCUSSION

The present study revealed interpretable variation in molecular interaction energies across 26 metal–ligand reactions and showed that variation was affected by reaction identity and computational settings. Predominantly negative  $\Delta E$  values indicate that most investigated metal–ligand combinations were energetically favourable. The stronger stabilization of Cr–CO and Ni–NHC complexes relative to several alkene-containing complexes agrees with the

understanding that transition-metal interactions depend strongly on ligand type, orbital overlap, electronic configuration, and coordination environment (Nandy et al., 2021). Related machine-learning work has targeted metal–ligand stability prediction (Zahariev et al., 2024).

The interaction-energy differences among BP86, PBE and PBE0 show that functional choice substantially affects calculated energetics. This agrees with evidence that approximate density functionals differ in their treatment of noncovalent interactions (Wu & Truhlar, 2021). Dispersion treatment is another source of methodological sensitivity when weak attractive interactions contribute to stabilization (Spicher et al., 2021). Quantum chemistry assisted by machine learning also emphasizes reliable electronic-structure data (Dral, 2020).

Basis-set cardinality showed an even clearer pattern: double-zeta calculations produced more negative energies than triple- and quadruple-zeta calculations. This agrees with evidence that basis-set incompleteness and imbalance can systematically affect interaction energies (Jensen, 2024). Similar concerns have been reported for density-functional calculations (Mehta & Goerigk, 2021) and post-CCSD(T) calculations (Fishman et al., 2025).

The strong correlation between uncorrected and

counterpoise-corrected energies indicates that correction generally preserved energetic ordering while reducing stabilization. However, the non-uniform BSSE across configurations shows that this effect was not constant. Physically informed models have therefore been proposed to bias learning toward intermolecular behaviour consistent with underlying theory (Thurlemann et al., 2023). Machine-learning approaches to non-additive intermolecular potentials likewise emphasize preserving physically meaningful interaction structure (Graham & Wheatley, 2022).

Reaction-grouped cross-validation contrasted with the strong descriptive patterns. None of the three ensemble models achieved a positive  $R^2$  for unseen reactions, although Gradient Boosting had the lowest MAE and RMSE. Thus, basis-set, functional, charge, multiplicity, electron-count, and convergence-related descriptors were insufficient to describe reaction-specific energetic behavior outside the training space. Similar transferability limitations have been reported for molecular-orbital models across organic, noncovalent, and transition-metal systems (Husch et al., 2021). Machine-learning force-field research likewise identifies generalization beyond sampled chemical environments as a major challenge (Unke et al., 2021).

The results therefore support richer structure- and geometry-based molecular representations. SPICE and subsequent related developments provide chemically diverse configurations for transferable machine-learning potentials (Eastman et al., 2023; Eastman et al., 2024). Equivariant neural architectures such as MACE and E(3)-equivariant graph networks further incorporate molecular geometry and symmetry directly into model construction (Batatia et al., 2022; Batzner et al., 2022).

Chemistry-intuitive graph explanations can identify molecular substructures informing property predictions (Wu et al., 2023), while concept-based self-interpretable models support transparent molecular reasoning (Proietti et al., 2024). Fragment-level Shapley approaches similarly relate predictions to chemically interpretable structural fragments (Roth, 2026). Uncertainty-aware explanation is also important because confidence in molecular predictions should accompany feature attribution (Yang & Li, 2023).

Recent reviews emphasize interpretable machine learning for noncovalent molecular systems (Tretiakov et al., 2025). Explainable approaches are also increasingly important in molecular design and drug discovery, where transparency affects scientific usability and trust (König & Vellido, 2024; Lamens & Bajorath, 2026). Evaluation frameworks further emphasize the chemical validity of explanations

(Onawole et al., 2026). Overall, the findings show that explainable machine learning can identify computational drivers of metal–ligand interaction energies, but richer molecular representations and structural information are needed for reliable extrapolation to unseen reactions.

## 5. CONCLUSION

This study showed that the energy of the molecular interactions in metal–ligand systems is determined by the reaction specific and computational conditions. The 26 metal–ligand reactions analysed showed predominantly negative interaction energies, reflecting generally favourable energetic association and substantial chemical heterogeneity. The energies calculated are found to be strongly dependent on the density functional and basis set used, with the double zeta basis sets giving more negative energies than were obtained using triple and quadruple zeta. In every case, counterpoise correction decreased the size of interaction energies, which establishes the importance of basis-set superposition error in the calculation of energies and the necessity of methodological artifacts being taken into consideration when analysing calculated energies.

The explainable machine-learning analysis indicated that the most important computational predictors were basis-set cardinality, basis-set identity and density functional. Reaction-grouped cross-validation, however, yielded negative  $R^2$  values for all of the evaluated ensemble models, suggesting they have restricted generalisation for unseen metal–ligand reactions. This indicates that energetic behavior is reaction-specific and cannot be completely characterized by computational descriptors. Molecular geometry, structural descriptors, electronic features or graph-based representations will likely be more transferable for prediction. The study demonstrates that explainable machine learning is a useful tool to discover systematic trends in molecular interaction energies and to uncover the challenges of prediction when chemically informative structural information is missing.

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