# Stacking Interactions in Nucleobases

Thesis submitted in partial fulfilment
of the requirements for the degree of

*Master of Science in **Computational Natural Sciences** by Research*

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# CERTIFICATE

It is certified that the work contained in this thesis, titled “Stacking Interactions in Nucleobases” by Sagar Gaur, has been carried out under my supervision and is not submitted elsewhere for a degree.

_____

Date

Adviser: Dr. U. Deva Priyakumar

Dedicated to making mistakes and to
the grace of second chances

# Acknowledgments

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Above all, I owe an immense debt of gratitude to my family—my parents and my wife—for their unconditional love, motivation, and unwavering support.

Additionally, I deeply appreciate my friends for their companionship and for making my college life and the time beyond fun. Sadly, one of our dear friends, and batchmate is no longer with us, and his absence is deeply felt. We miss him dearly and hold his memory close as we continue our journeys.

# Abstract

Vertical stacking interactions are essential for stabilizing the DNA double helix. This study investigates the interactions among all four nucleobases—adenine, guanine, cytosine, and thymine—using ab-initio quantum mechanical calculations at the RI-MP2 level with the aug-cc-pVDZ basis set.

Our findings reveal that intermolecular interaction energies within the modelled dimers are predominantly influenced by dispersion effects. However, these energies do not correlate directly with dispersion alone. Instead, a significant correlation is observed with the electrostatic component of the Hartree-Fock (HF) interaction energy, underscoring the complex interplay of forces that govern stacking interactions. Additionally, analyses of modified nucleobase systems demonstrate the additivity of effects from heteroatom groups, suggesting their independent operation.

The study classifies the relative impacts of different groups of heteroatoms, providing insights into how substituent modifications affect the molecular stability and interaction dynamics of all nucleobases.

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*Chapter 1*

# Introduction

Noncovalent pi-stacking interactions are known to play an important role in a wide range of chemical and biological phenomena [1], [2], [3], [4]. These interactions are not as strong as compared to covalent or ionic interactions, but they can be found to play critical role in stabilizing the DNA, explaining denaturation of RNA in presence of urea [5], determining protein structure and functions [6], [7], [8], [9], enzyme design [10], several important chemical reactions[11], molecular recognition [12] and supramolecular chemistry [2]. Stacking is affected by some geometrical factors, and it is known that parallel displaced and T-shaped configurations are much more favourable than sandwich configuration. Substituent groups present on rings play a very important role in modulating the interaction energies of stacked complexes. [13], [14]

A number of studies have been done to understand the mechanism by which substituent groups affect stacking interactions. An early model was given by Hunters and Sanders [15], [16], according to which electron donating groups increase the electron density in the pi-cloud resulting in decreasing the overall stability of the system due to increased electrostatic repulsion. Through a similar mechanism, electron withdrawing substituents would enhance the interactions between two rings. However numerous other studies have found results contradictory to the Hunters-Sanders model and have suggested that stacking interactions are not primarily governed by electrostatic effects. [17], [18], [19], [20]
Another important model was proposed by Wheeler and Houk, known as the direct interaction model [21]. Their analysis of substituted benzene dimers in face-to-face sandwich configuration, showed that interactions between Ph-X and benzene were similar to interactions between H-X and benzene as the energies in the two systems had an almost one-to-one correlation. Further it was shown that aromaticity is not required for pi-stacking interactions [22]. Direct evidence of the Wheeler-Houk picture was given by Sherrill and coworkers [23]. They separated the contributions of the ring and substituent using F-SAPT and showed that Wheeler-Houk picture is dominant and found that Hunter-Sanders picture also does contribute to interaction. Noncovalent stacking interactions are known to be primarily dispersive [24] in nature with small but important contributions due to electrostatic interactions [25].

Previously the role of dispersion energy and electrostatic energy on the geometry and stability of B-DNA has been studied by Černý et al [3]. They showed that both the forces are important in maintaining the overall stability of DNA strands.

In the present study we expand upon these foundational models by examining the stacking interactions among all four nucleobases—adenine, guanine, cytosine, and thymine—utilizing quantum chemical methods to assess both dispersion and electrostatic effects on the stability of stacked nucleobase dimers. This research aims to substantiate and expand upon previous findings in pi-stacking interactions, and tries to provide a comprehensive understanding of the forces that influence the structure and stability of DNA.

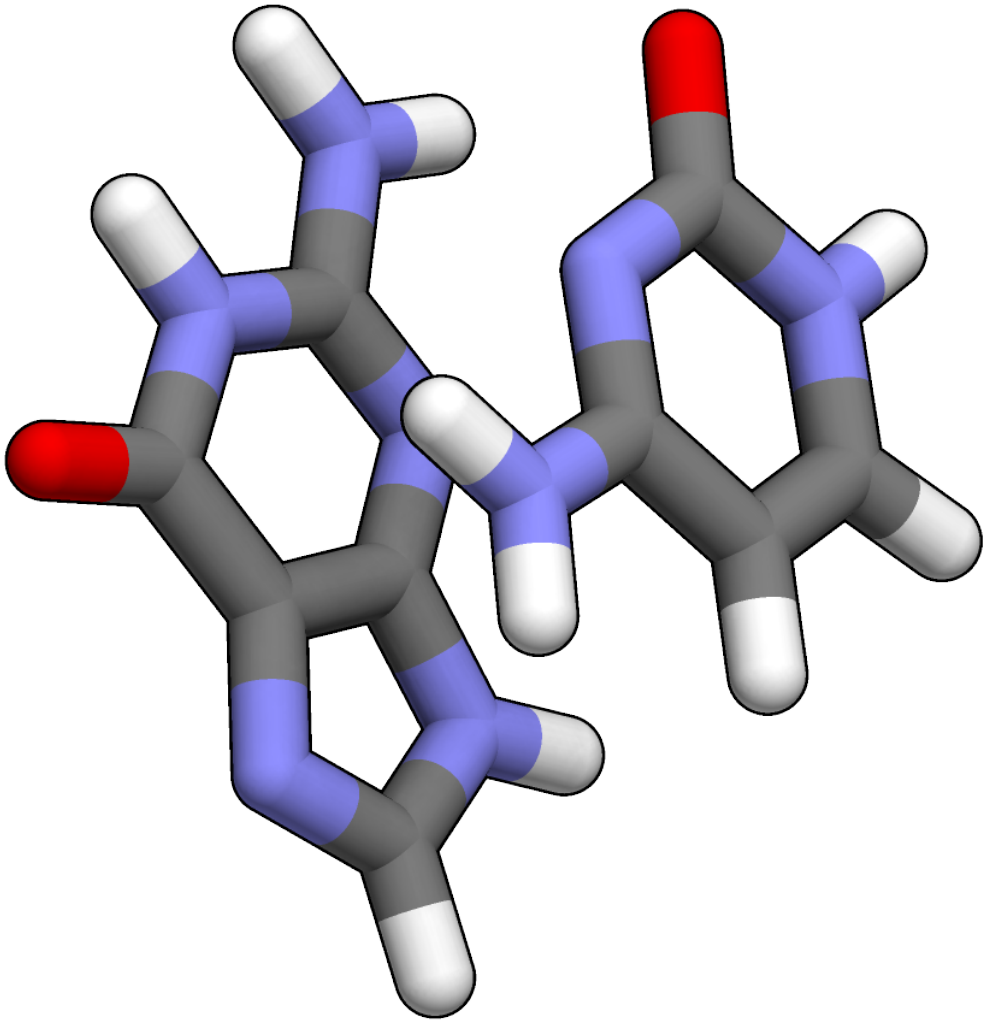

Figure 1 Stacking In Guanine and Cytosine

# *Chapter 2*

# Computation Details

## 2.1 Nucleobase Representation

Guanine is a fused pyrimidine-imidazole ring system, and cytosine is a pyrimidine system with nitrogen and oxygen heteroatoms as substituents. Similarly, adenine is a purine base with an amino group at position 6, and thymine, a pyrimidine similar to cytosine, features a methyl group at position 5. In this paper, substituents and heteroatom groups on these nucleobases are referred to as functional groups (see Chart 1), named Gu1 - Gu4 for guanine, Cy1 - Cy3 for cytosine, Ad1 - Ad4 for adenine, and Th1 - Th3 for thymine.

To examine stacking interactions among all nucleobases, the molecules were conceptualized as aromatic rings (indole for guanine, benzene for cytosine, and similarly suitable analogues for adenine and thymine) with various functional groups attached. This treatment makes studying stacking in nucleobases analogous to studying stacking in aromatic rings with multiple substituent groups.

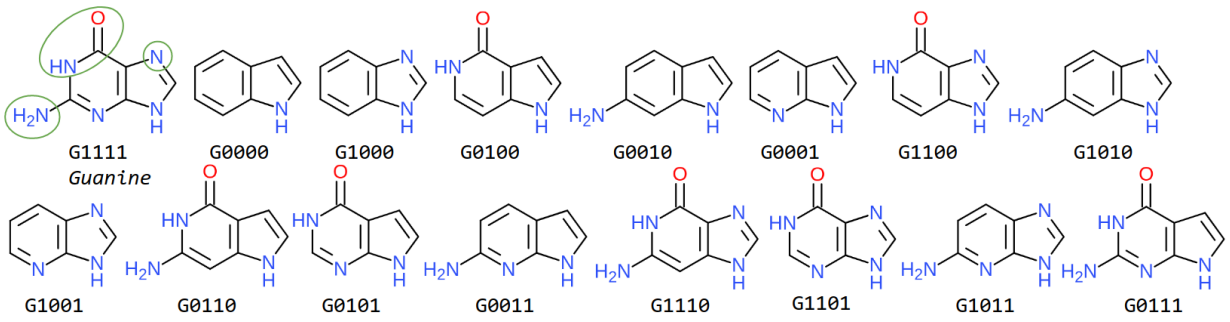


Chart 1 Structures of Representative Guanine Models

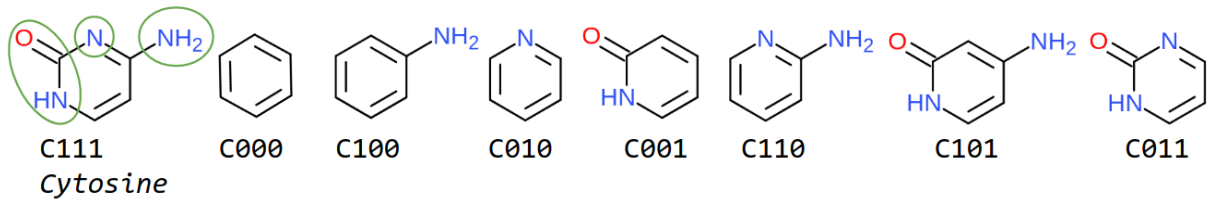


Chart 2 Structures of Representative Cytosine Models

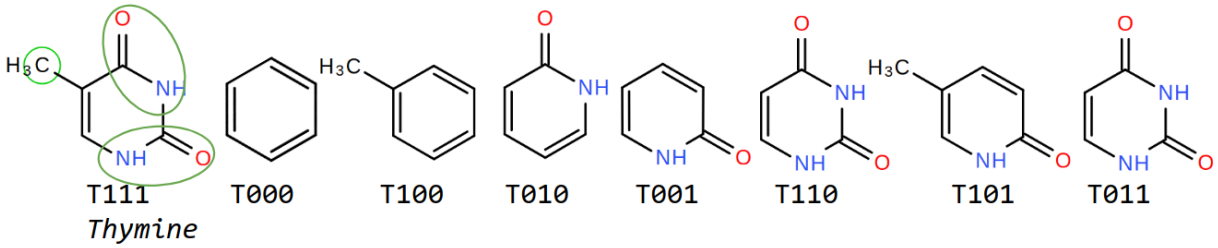


Chart 3 Structures of Representative Thymine Models

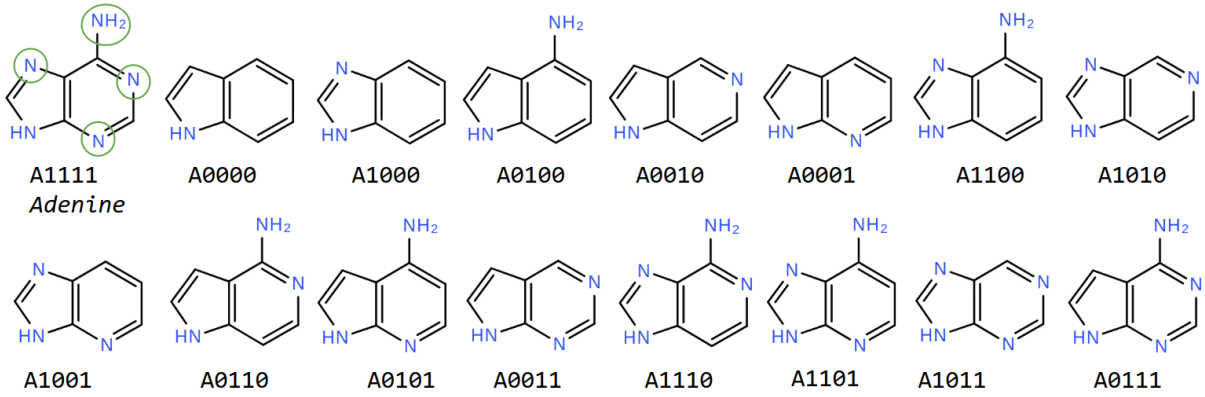


Chart 4 Structures of Representative Adenine Models

## 2.2 Model Construction

Representative structures for each nucleobase were generated by removing functional groups and substituting them with an appropriate number of $sp^2$ carbons and hydrogens. For example, to create a representative guanine structure without functional group Gu1, an $sp^2$ nitrogen from the 5-membered ring is replaced with an $sp^2$ carbon. This procedure yielded 16 guanine-representative, 8 cytosine-representative, 16 adenine-representative, and 8 thymine-representative structures were obtained.

Actual guanine was named Gu1111, where the 1's indicate the presence of all four functional groups. Gu0110 is a representative guanine with the first and fourth functional group (Gu1 and Gu4) replaced with carbons and hydrogens. Similarly actual cytosine was named Cy111, actual thymine is T111, and finally, actual Adenine is A1111.

All the structures were modelled carefully, maintaining their valence, and making sure each representative nucleobase is neutral

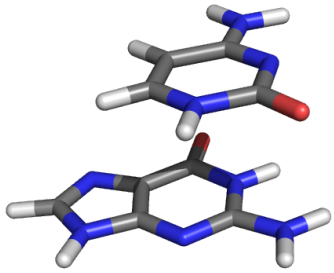

Figure 2 Guanine replaced with Gu0000

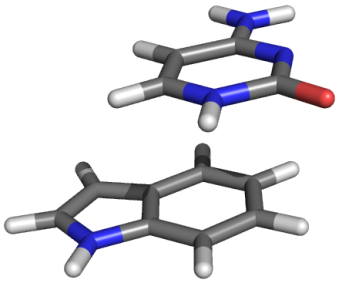

Figure 3 Guanine replaced with G0000

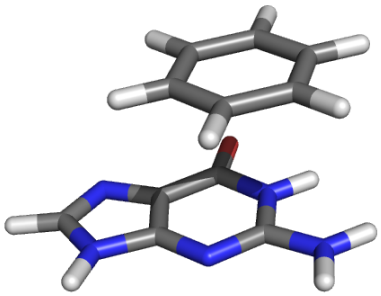

Figure 4 Cytosine replaced with C000

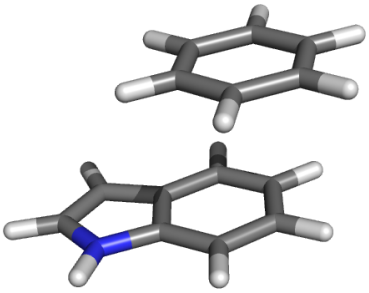

Figure 5 Cytosine replaced with C000, and Guanine replaced with G0000

### 2.3 Optimization and Alignment

The structures were initially optimized at MP2 level of theory using Dunning-type correlation consistent basis sets augmented with a set of diffuse functions, called aug-cc-PVDZ using Gaussian 09 program.

Optimized structures were used to generate stacked dimers of representative nucleobases, aligning them according to a standard dimer configuration from a B-DNA fragment.

This study included a comprehensive analysis of stacking interactions across all possible combinations of the four nucleobases: adenine, thymine, guanine, and cytosine. The pairs examined were adenine with adenine (AA), adenine with thymine (AT), adenine with guanine (AG), adenine with cytosine (AC), thymine with adenine (TA), thymine with thymine (TT), thymine with guanine (TG), thymine with cytosine (TC), guanine with adenine (GA), guanine with thymine (GT), guanine with cytosine (GC), guanine with guanine (GG), cytosine with adenine (CA), cytosine with thymine (CT), cytosine with guanine (CG), and cytosine with cytosine (CC).

The GC dimers had a total of 128 dimers for Guanine, and Cytosine (16 Guanine-Representative * 8 Cytosine-Representative), and similar for other pairs.

### 2.4 Calculation Details

The main challenge while trying to calculate base-stacking interactions (gas-phase) is to obtain a significant portion of the electron correlation energy. Acceptable results can be obtained with the inclusion of ΔCCSD(T) correction term. Results from MP2 calculations with medium sized basis sets are used to study qualitative effects in base stacking, and other type of stacking interactions. [26]

$$\Delta E_{\text{CBS}}^{\text{CCSD(T)}} = \Delta E_{\text{CBS}}^{\text{MP2}} + \left(\Delta E_{\text{CCSD(T)}} - \Delta E_{\text{MP2}}\right)_{\text{medium basis set}}$$

For our study, single point energy decomposition analysis (EDA) [27] were done at MP2 level of theory using the Resolution of Identity (RI) [28] approximation and employing aug-cc-PVDZ basis set using GAMESS program.

EDA calculations decompose the total interaction energy obtained from HF methods into electrostatic, exchange, repulsion, and polarization terms.

$$\Delta E_{\text{HF}} = \Delta E_{\text{electrostatic}} + \Delta E_{\text{exchange}} + \Delta E_{\text{repulsion}} + \Delta E_{\text{polarization}}$$

Electrostatic energy arises from the attraction between oppositely charged particles, such as positive nuclei and negative electrons. Repulsion energy, on the other hand, stems from the natural repulsion between like-charged particles, such as electron-electron repulsion. Exchange energy is associated with the Pauli exclusion principle, which prevents electrons from occupying the same quantum state. Polarization energy occurs when the electron cloud of a molecule is distorted by the electric fields of another molecule, altering the charge distribution. Lastly, dispersion refers to the interatomic interactions that arise from the attractive forces between the induced dipoles of interacting atoms.

Dispersion interaction energies were estimated as the difference in interaction energies calculated using Hartree-Fock and RI-MP2 methods. [27] Total interaction energy between the stacked nucleobases is the sum of HF energy and the dispersion term.

$$\Delta E_{\text{dispersion}} = \Delta E_{\text{interaction}} - \Delta E_{\text{HF}}$$

*Chapter 3*

# Results and Discussion

### 3.1 Dispersion Interactions Do Not Correlate With Total Interaction Energy

The dispersion and HF components of RI-MP2 interaction energies and the total interaction energy for the dimers is plotted in Figure 6 (Select values are given in Table 1. It is clear from the plot that interaction energies in dimers are dominated by dispersion with values in the range of -7.95 kcal/Mol to -14.74 kcal/Mol. The HF energy was found to be destabilizing in all but one of the complex where it was mildly stabilizing and the values lies in the range of -0.33 kcal/mol to 7.09 kcal/mol.

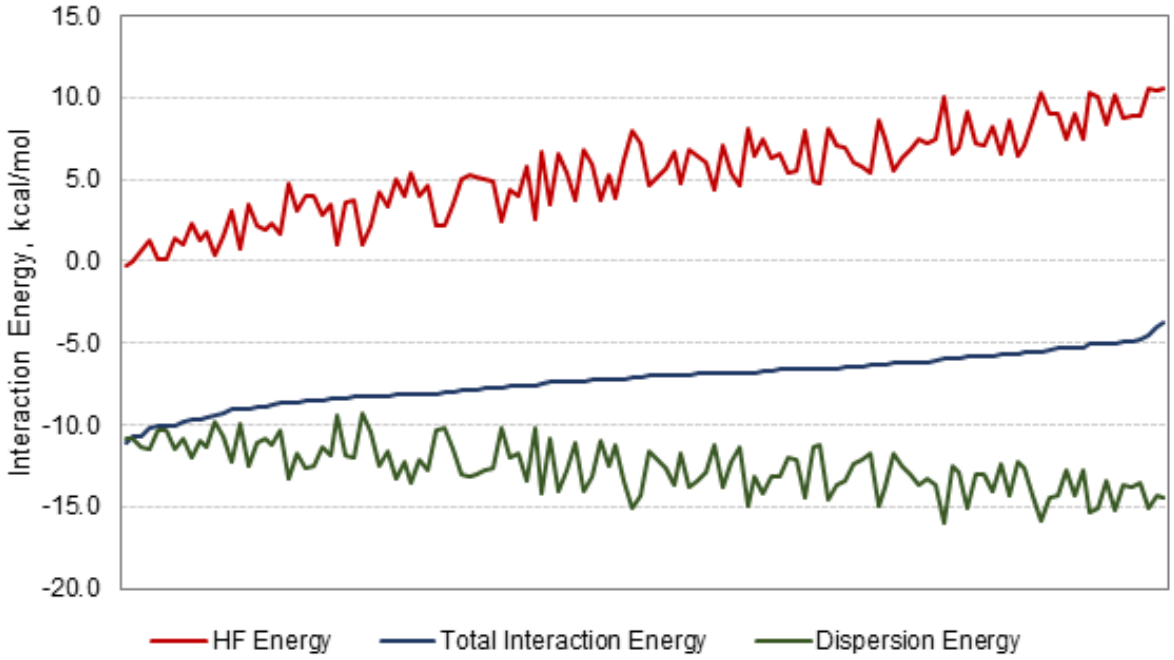


Figure 6 Dispersion Interactions Does Not Correlate with Total Interaction Energy

In an attempt to understand the relationship between the total interaction energy and the various components of HF energy namely electrostatic ($E_{HF}$), exchange, repulsion and polarization, and the dispersion energy, coefficient of determination, $\mathbf{R^2}$ were calculated. Plots of total interaction energy with dispersion energy and electrostatic component of HF energy are given in Figure 6. It was observed that dispersion energy, although dominant in determining the total interaction energy did not correlate with the quantity, $\mathbf{R^2} = 0.003$. A better correlation was observed between the electrostatic energy and the total interaction energy, $\mathbf{R^2} = 0.723$.

| | Interaction Energy (kcal/mol) | Dispersion | HF | Electrostatic |
|---|---|---|---|---|
| **Gu0000…Cy000** | -6.3 | -12.56 | 6.26 | -3.54 |
| **Gu1000…Cy000** | -6.42 | -12.31 | 5.89 | -3.87 |
| **Gu0100…Cy000** | -6.28 | -11.74 | 5.46 | -4.34 |
| **Gu0010...Cy000** | -7.14 | -13.25 | 6.11 | -3.39 |
| **Gu0001...Cy000** | -5.87 | -11.8 | 5.93 | -2.5 |
| **Gu0000…Cy100** | -6.97 | -14.04 | 7.07 | -3.53 |
| **Gu0000…Cy010** | -5.54 | -11.65 | 6.11 | -2.19 |
| **Gu0000…Cy001** | -7.04 | -11.62 | 4.58 | -3.79 |
| **Gu1111...Cy111** | -10.17 | -10.29 | 0.12 | -6.66 |

Table 1 RI-MP2 Interaction Energy, Dispersion Energy, HF energy and Electrostatic Energy of select dimers. Full Table, and values for other dimers has been included in the Supporting Information. (All values in kcal/mol)

Regression analysis with more than one energy components resulted in better correlation. The values were particularly high when one of the components taken was electrostatic. For example, the tri-variate regression of electrostatic energy, exchange energy and dispersion energy with the total interaction energy yielded a very good correlation, $\mathbf{R^2}$ =952. This result is plotted in *Figure 9*.

| COMPONENTS TAKEN FOR MULTIVARIATE REGRESSION | $R^2$ |
|---|---|
| **ELECTROSTATIC , EXCHANGE** | 0.725 |
| **ELECTROSTATIC , MP2-DISPERSION** | 0.769 |
| **ELECTROSTATIC , POLARIZATION** | 0.774 |
| **ELECTROSTATIC , REPULSION** | 0.725 |
| **ELECTROSTATIC , EXCHANGE , MP2-DISPERSION** | 0.952 |
| **ELECTROSTATIC , EXCHANGE , POLARIZATION** | 0.776 |
| **ELECTROSTATIC , EXCHANGE , REPULSION** | 0.758 |
| **ELECTROSTATIC , POLARIZATION , MP2-DISPERSION** | 0.793 |
| **ELECTROSTATIC , REPULSION , MP2-DISPERSION** | 0.957 |
| **ELECTROSTATIC , REPULSION , POLARIZATION** | 0.758 |

Table 2 Coefficient of determination obtained on multivariate linear regression of various combinations of energy components with the total interaction energy. Only combinations with R2 values greater than 0.7 are included here

The various combinations of bivariate and tri-variate linear regressions which had high values of $\mathbf{R^2}$ are tabulated in Table 2 Coefficient of determination obtained on multivariate linear regression of various combinations of energy components with the total interaction energy. Only combinations with **R2** values greater than 0.7 are included here. All the graphs for linear regressions are included in the supplementary information.

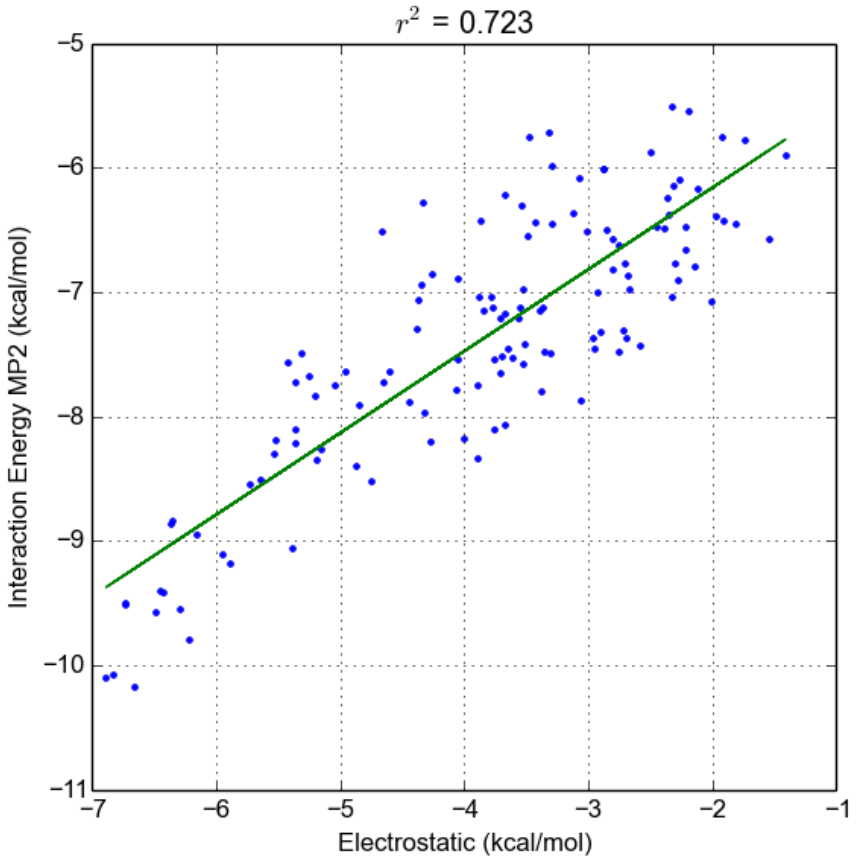


Figure 7 RI-MP2 interaction energy weakly correlates with the electrostatic component of the HF energy (Plot for the G…C stack)

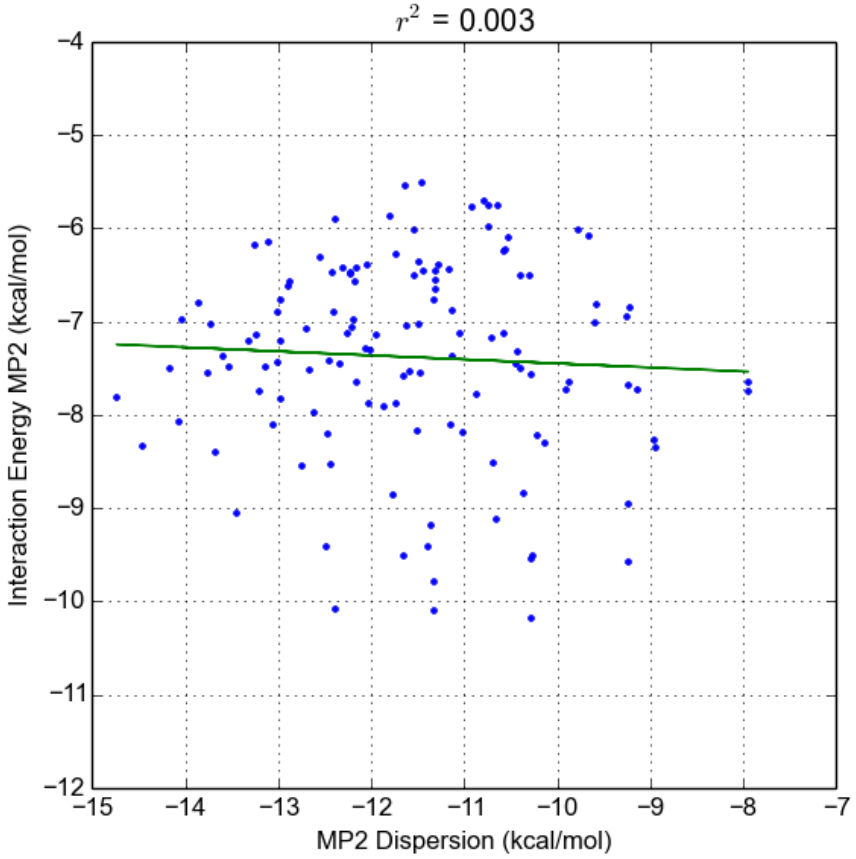


Figure 8 Although dispersion component is shown to be the major contributor to total interaction energy, no systematic correlation is seen between the two quantities (Plot for the G…C stack)

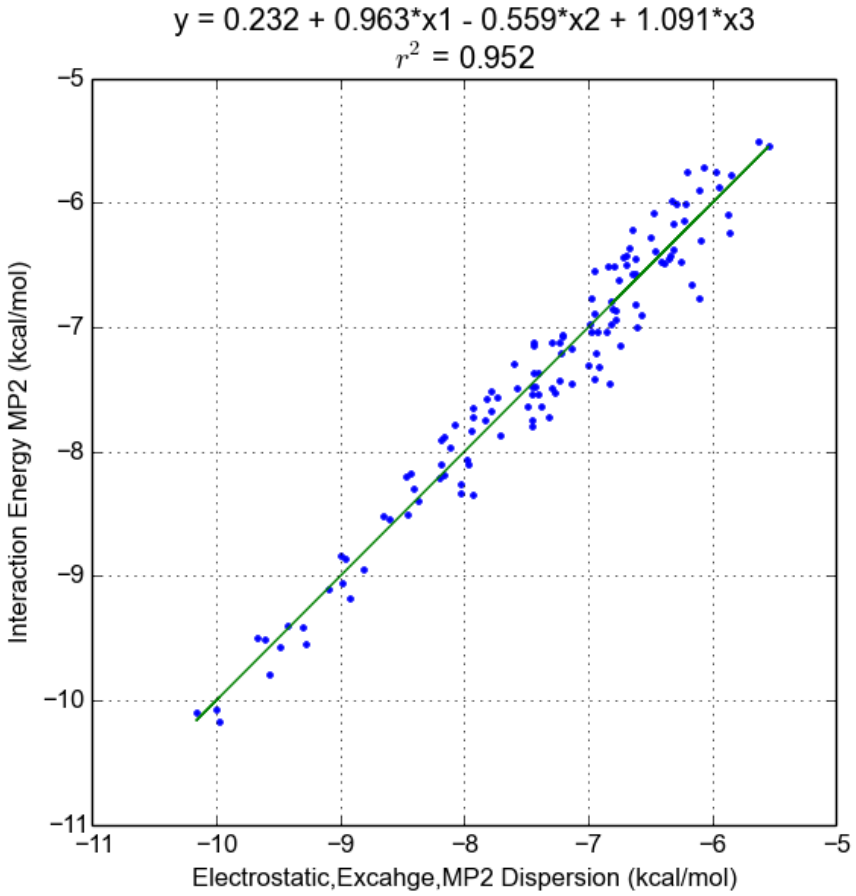


Figure 9 Linear regression of Interaction Energy with Electrostatic, Exchange and Dispersion
Although interaction energy is greatly affected by the electrostatic interactions, its final value is due to combined effects of more than one component. (All units in kcal/mol)

Another important observation is that the dimers with more number of functional groups were more stable irrespective of the identity of the functional group. In fact, the total interaction energy for the Gu1111…Cy111 (-10.17 kcal/mol) i.e. the actual Guanine-Cytosine dimer was 3.87 kcal/mol lower than that of Gu0000...Cy000 (-6.3kcal/mol) i.e. the indole-benzene dimer. This observation is consistent with previous findings of Sherrill and coworkers [29] and Lewis et al. [25] that any substitutions to the benzene-benzene dimer lowers the total interaction energy irrespective of the nature of the substituent.

The above discussion indicates that the interaction energy of stacked nucleobases is not due to one specific component but is rather a combined effect of more than one component, electrostatic, dispersion and the exchange-repulsion terms being the more important. Electrostatics play a modulating role, i.e. unfavourable electrostatics can destabilize a stack. The polarization term was not found to be playing a significant role, quantitatively or qualitatively in determining the overall interaction energy.

### 3.2 Unfavourable electrostatics can destabilize a stack

In the previous section we found that among all the component of total interaction energy, the electrostatic component most strongly correlates. In *Figure 10* we've plotted the electrostatic potential maps of benzene and the four nucleobases—adenine, guanine, cytosine, and thymine. It highlights the complex nature of electrostatics in the nucleobases.

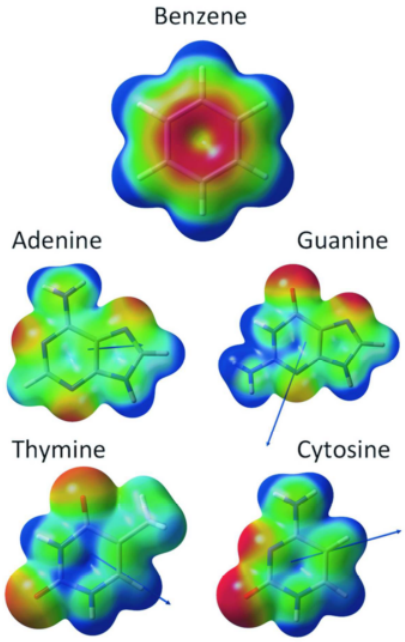


Figure 10 Electrostatic Potential maps of benzene and the four nucleobases

Electrostatic potential maps of the four nucleobases—adenine, guanine, cytosine, and thymine—reveal significant insights into how these molecules might interact in stacked configurations. ESP map of benzene is also plotted as a reference of a symmetrical distribution. Each molecule displays unique patterns of electrostatic potentials indicated by varied colour intensities, which represent areas of different electron densities. The blue lines on these maps denote the dipole moment vectors, indicating the direction of net molecular polarity.

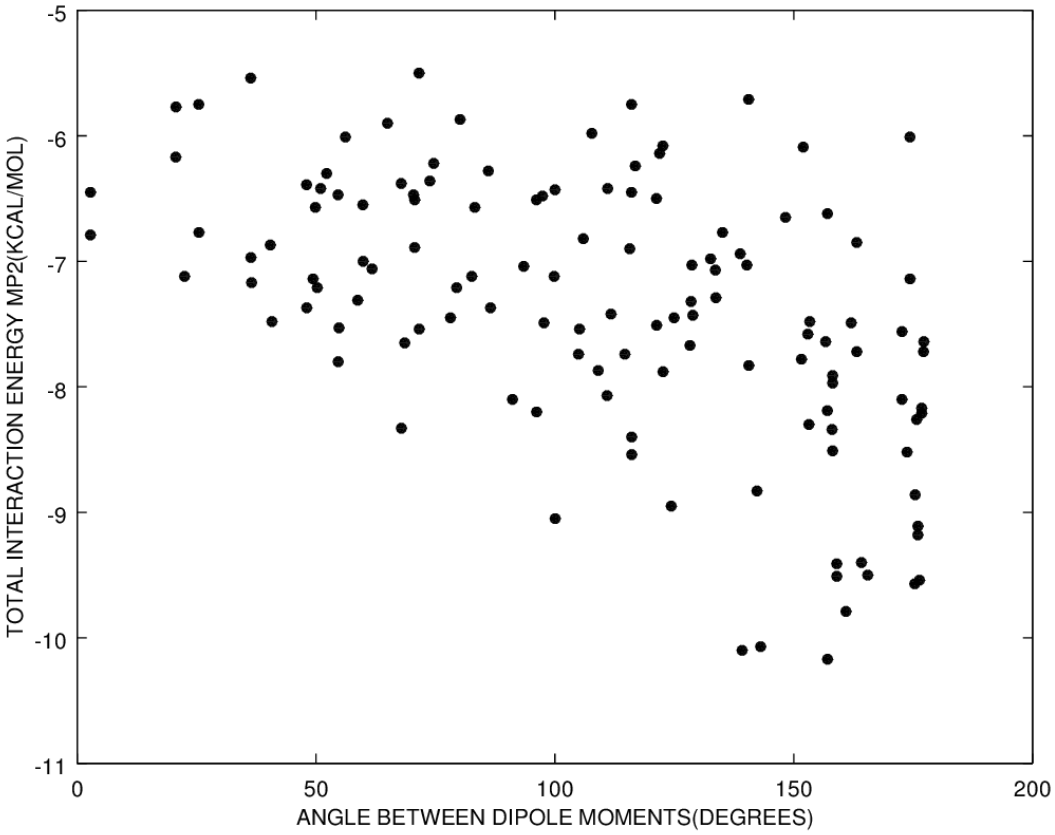


Figure 11 Parallelly aligned dipole vectors are lesser stable; However, oppositely aligned dipole vectors may not necessarily more stable.

A plot of total interaction energy versus the angle between dipole moments helps in quantifying the electrostatic contribution to stacking stability. As observed in the graph, systems with dipole moments aligned parallelly tend to exhibit less stability compared to those with oppositely aligned vectors. This trend suggests that although parallel alignment may lead to repulsive electrostatic forces, opposite alignments do not guarantee enhanced stability due to the complex nature of molecular interactions.

### 3.3 Effects Due To Functional Groups Are Additive

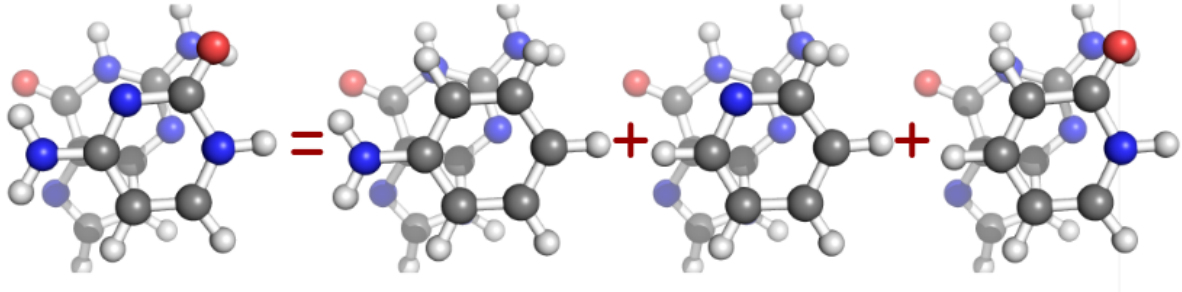

Figure 12 Illustration of the additivity behaviour of total interaction energy

According to Wheeler-Houk picture [21] the effect of substituent groups on pi stacking could be explained by the direct interactions of the substituent groups with the other ring. According to this model the substituent effects are a result of local interactions between the substituents and the unsubstituted ring. Substituents do not interact with the whole of the other ring, but only the nearest vertex. An interesting implication of the local direct interaction picture is that substituents operate independently and their effects are additive. [30] This additivity holds as long as the local environment of a substituent is not changed i.e. changes are made only to the distal side of either of the rings.

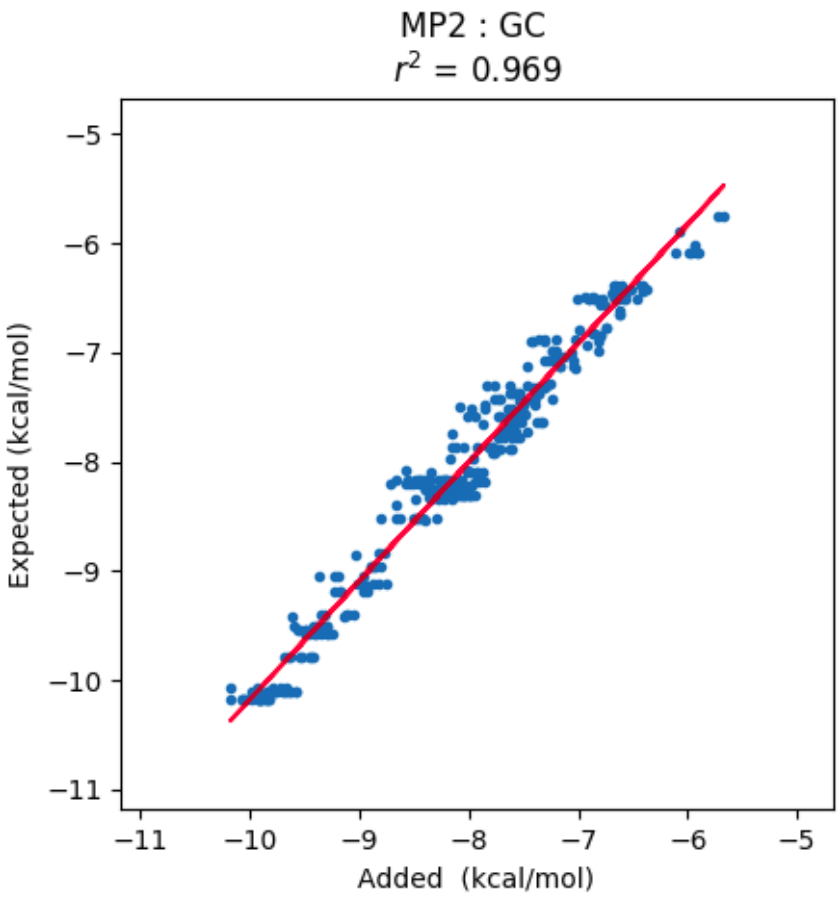


Figure 13 Correlation of Added and Expected Interaction Energies in Guanine-Cytosine Stacks. linear relationship between added and expected interaction energies for GC stacked dimers. he high coefficient of determination (0.969). This underscores the additivity of interaction energies, suggesting that the cumulative effect of individual interactions can predictably influence the overall stacking behaviour.

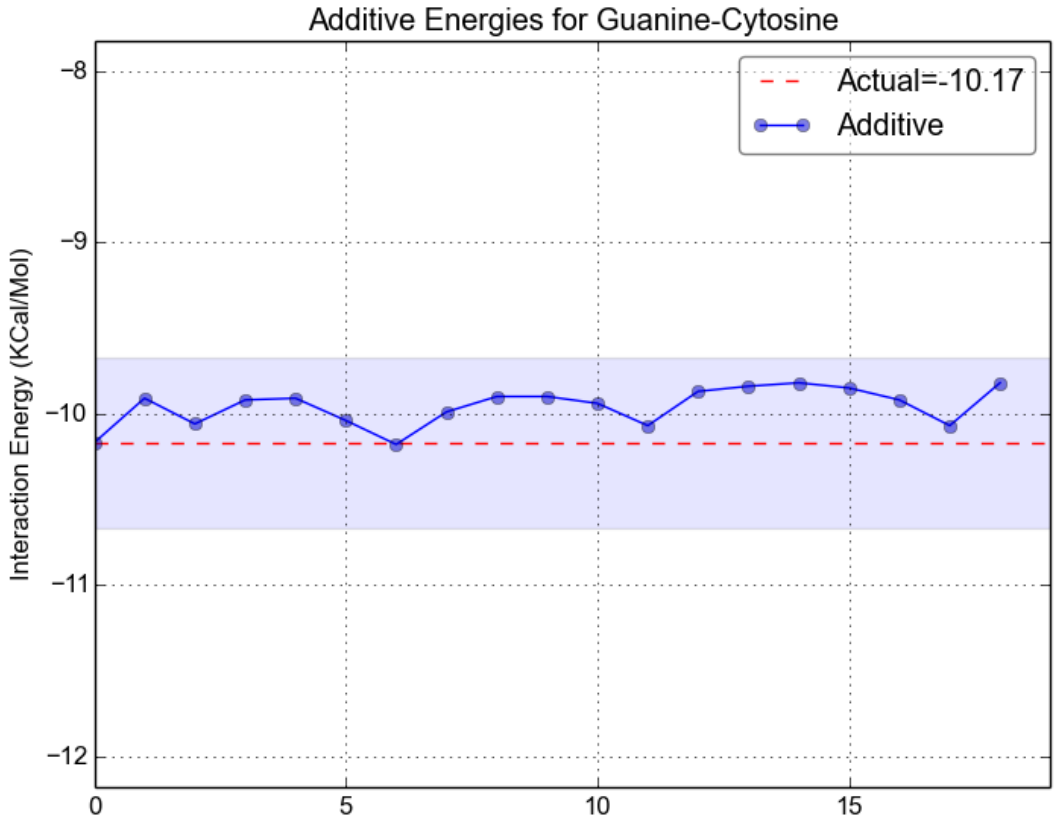


Figure 14 Additivity of effects due to functional groups. Red line is the target value of total interaction energy of Gu1111…Cy111, i.e. the actual Guanine-Cytosine dimer. Blue dots are the values of interaction energy by adding energies of dimers with lesser number of functional groups. Blue boundary is the region of +0.5 and - 0.5kcal/mol deviation from the target value

To check whether the local direct interaction model holds in our systems we checked whether the effects due the functional groups were additive. Taking the total interaction energy of Gu1111…Cy111 dimer as the target value, we tried to obtain a similar value by adding up interaction energies of dimers with lesser number of functional groups. According to this scheme, the target value could be obtained by adding up energies of Gu1100…Cy111 and Gu0011...Cy111 and subtracting interaction energies of Gu0000…Cy111 or by adding up energies of Gu1111…Cy100, Gu1111…Cy010, Gu1111…Cy001 and subtracting twice the energy of Gu1111…Cy000 to account for counting the same interactions multiple times. By keeping one of the two rings the same as that of target dimer we ensured that the local environment for the functional groups remains the same. The values obtained using these scheme were remarkably close to the target values in all the 18 possible combinations to obtain the target value, largest deviation being 0.35 kcal/mol. This data is plotted in Figure 14.

### 3.4 Role of the ring in substituent group additivity

We had also tried to obtain the target value by taking dimers in which changes to both the rings were made, an example of which would be adding Gu1100...Cy110 and Gu0011…Cy001. However, this scheme was less successful than the previous scheme. Successful additivity of functional group effects due to the first scheme and not so by the second scheme could be explained using the local direct interaction model. In the second scheme, the local environment for the functional groups were being changed by making changes to both the rings simultaneously.

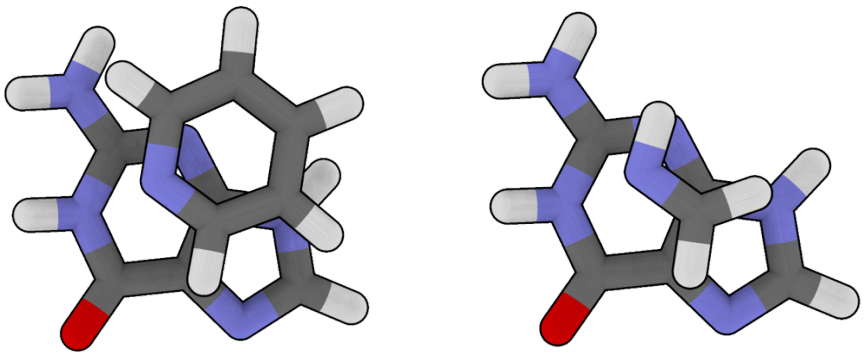

Figure 15 Schematic comparing stacking in
a. ring-ring dimer Gu1111…Cy010, with
b. ring-fragment dimer Gu1111…cm010

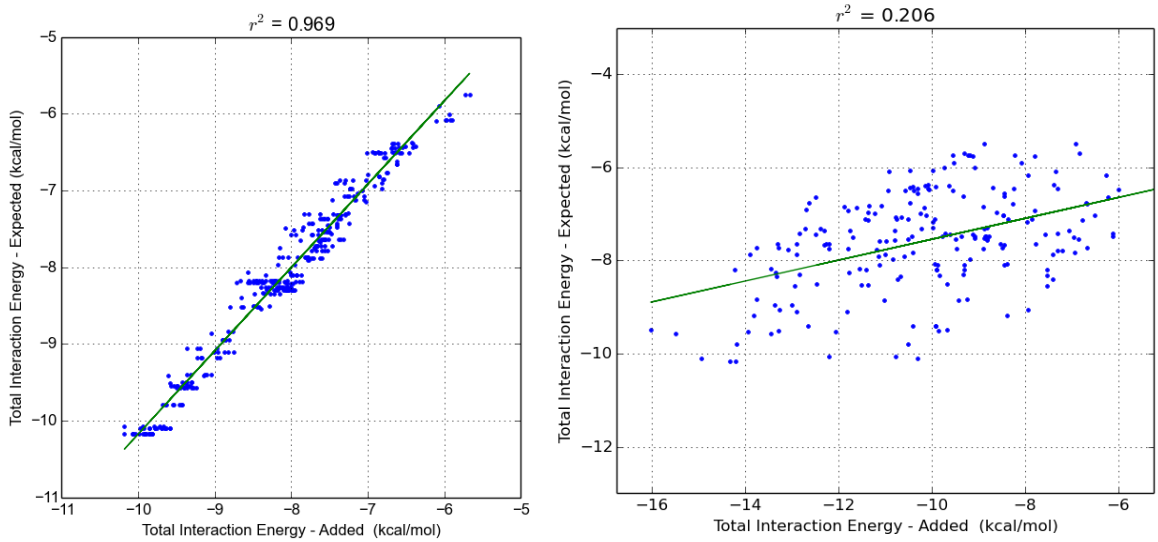


Figure 16 Comparison of additivity with and without rings.

Values of GC dimers with more than one substitutions are plotted along the y-axis. In the x-axis energy values for the target system using the described additivity scheme are plotted.

a. Additivity with functional groups attached to the rings
b. Additivity using fragmented functional groups.

To study the role of the rings in representative nucleobases in the additivity we calculated energy values for dimers where one of the two molecules was a representative nucleobase and the other molecule was a functional group fragment without the ring. Figure 15 is a schematic showing the stacking between ring-ring dimer Gu1111…Cy010 and ring-fragment dimer Gu1111...cm010. Fragments corresponding to functional group Gu1, Gu2, Gu3 and Gu4 are named gm1000, gm0100, gm0010 and gm0001.

Similarly fragments corresponding to functional groups Cy1, Cy2 and Cy3 are named cm100, cm010 and cm001 respectively. Using the energy values of theses fragmented system it should be possible to obtain the energies of the representative nucleobase stacks we had discussed earlier. e.g. Adding up energies of Gu1111...cm100 , Gu1111...cm010 and Gu1111...cm001 should give a value close to that of Gu1111…Cy111 or adding up energy values of gm1000...Cy111 and gm0110…Cy111 should give that of Gu1110...Cy111.

If the ring does not play an important role in stacking, the energy values obtained after adding up the fragmented systems should correlate with the energy values of target representative nucleobase stacks.

Taking the interaction energies of representative nucleobase stacks as target, energies were calculated using the ring-fragment systems by applying the additivity scheme discussed above. For comparison, energies for the same target systems were calculated using lesser substituted representative nucleobase stacks. The results are plotted in Figure 16 with the actual values of the target systems along the y axis and values obtained after additivity along the x axis. It is

clear from the plots that additivity does not work for the fragmented systems whereas it gives near perfect results when the systems have a ring. Therefore we can conclude that the rings in nucleobases play a very important role in determining the stacking interactions.

Although the local direct interaction model was developed by studying substituted benzene systems, our results show that the idea can be extended to more complex ring systems. Unlike substitutions to the sides of a ring, addition of some functional groups in our systems changes the identity of the ring, but the behaviour of both changes is very similar. Additivity of functional groups in this manner further validates the point that substituent effects are relatively independent and are transferable [31]. The idea of transferability is another implication of the local direct interaction model and states that interactions of substituted dimers are identical across systems as long as the local interactions are conserved.

*Chapter 4*

# Summary

For a complete understanding of DNA stability, it is crucial to explore the vertical stacking of nucleobases and the diverse factors influencing their interactions. In this study we examined the stacking interactions between guanine, cytosine, adenine and thymine employing advanced ab initio quantum mechanical calculations. Our findings reveal that while interaction energies in the dimers are primarily influenced by dispersion forces, they are significantly modulated by electrostatic interactions. Notably, although there is a strong correlation with the electrostatic component, the interaction energies are not governed solely by any single force. Instead, they result from a complex interplay of dispersion, electrostatic, and exchange-repulsion forces.

The study also demonstrates that the modification of nucleobase rings by adding functional groups has effects akin to those observed when substituent groups are added to the sides of a ring. Moreover, the additivity of effects from these functional groups supports their independent influence, as postulated by the Direct Interaction Model [24]. This additivity allows for the replication of interaction energies in more highly substituted systems using systems with fewer substitutions.

These results suggest that the principles governing stacking in nucleobase systems are comparable to those in simpler substituted benzene systems, indicating that methodologies developed for the latter can be effectively applied to understand interactions in nucleobase stacks. This insight enhances our grasp of molecular interactions within DNA, contributing to broader applications in biochemical and pharmaceutical research.

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# Supporting Information

| ELECTROSTATIC ENERGY(kcal/mol) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| GU/CY | 000 | 001 | 010 | 100 | 011 | 101 | 110 | 111 |
| 0000 | -3.54 | -3.53 | -2.19 | -3.79 | -2.32 | -3.57 | -2.37 | -2.39 |
| 0001 | -3.87 | -4.05 | -2.33 | -3.88 | -2.76 | -3.9 | -2.27 | -2.67 |
| 0010 | -4.34 | -5.2 | -3.32 | -5.32 | -4.39 | -6.37 | -4.35 | -5.64 |
| 0100 | -3.39 | -3.38 | -2.22 | -3.52 | -2.33 | -3.31 | -2.3 | -2.28 |
| 1000 | -2.5 | -2.12 | -1.74 | -3.68 | -1.41 | -3.37 | -2.93 | -2.68 |
| 0011 | -4.67 | -5.73 | -3.48 | -5.42 | -4.85 | -6.73 | -4.26 | -5.95 |
| 0101 | -3.71 | -3.89 | -2.35 | -3.65 | -2.75 | -3.68 | -2.22 | -2.58 |
| 1001 | -2.88 | -2.71 | -1.92 | -3.77 | -1.91 | -3.71 | -2.81 | -2.96 |
| 0110 | -4.05 | -4.88 | -3.3 | -5.37 | -4.32 | -6.43 | -4.65 | -5.89 |
| 1010 | -3.29 | -3.84 | -2.88 | -5.25 | -3.55 | -6.35 | -5.04 | -6.16 |
| 1100 | -2.45 | -2.14 | -1.81 | -3.61 | -1.54 | -3.35 | -2.95 | -2.72 |
| 0111 | -4.37 | -5.39 | -3.43 | -5.52 | -4.75 | -6.83 | -4.6 | -6.22 |
| 1011 | -3.67 | -4.44 | -3.08 | -5.36 | -4.07 | -6.73 | -4.96 | -6.49 |
| 1101 | -2.81 | -2.7 | -1.97 | -3.76 | -2.01 | -3.76 | -2.9 | -3.06 |
| 1110 | -3.12 | -3.7 | -2.85 | -5.36 | -3.53 | -6.45 | -5.19 | -6.29 |
| 1111 | -3.49 | -4.27 | -3.01 | -5.54 | -4.01 | -6.89 | -5.16 | -6.66 |

| EXCHANGE ENERGY(kcal/mol) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| GU/CY | 000 | 001 | 010 | 100 | 011 | 101 | 110 | 111 |
| 0000 | -19.27 | -20.86 | -16.16 | -16.53 | -18.04 | -18.81 | -13.81 | -16.13 |
| 0001 | -18.93 | -20.15 | -15.88 | -16.21 | -17.42 | -18.06 | -13.54 | -15.48 |
| 0010 | -18.33 | -19.66 | -15.5 | -15.48 | -17.07 | -17.49 | -13.02 | -15.04 |
| 0100 | -19.2 | -20.83 | -16.08 | -17.52 | -18.01 | -19.87 | -14.74 | -17.15 |
| 1000 | -16.27 | -17.81 | -13.44 | -14.06 | -15.27 | -16.26 | -11.54 | -13.81 |
| 0011 | -18 | -18.94 | -15.23 | -15.16 | -16.44 | -16.73 | -12.75 | -14.37 |
| 0101 | -18.9 | -20.14 | -15.84 | -17.19 | -17.43 | -19.1 | -14.46 | -16.48 |
| 1001 | -15.94 | -17.1 | -13.16 | -13.77 | -14.65 | -15.53 | -11.28 | -13.17 |
| 0110 | -18.33 | -19.7 | -15.49 | -16.33 | -17.13 | -18.39 | -13.83 | -15.94 |
| 1010 | -14.91 | -16.21 | -12.4 | -12.72 | -13.97 | -14.66 | -10.47 | -12.47 |
| 1100 | -16.59 | -18.14 | -13.65 | -15.43 | -15.53 | -17.67 | -12.84 | -15.19 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 0111 | -18.05 | -19.03 | -15.26 | -16.01 | -16.55 | -17.64 | -13.57 | -15.29 |
| 1011 | -14.62 | -15.53 | -12.16 | -12.45 | -13.36 | -13.94 | -10.24 | -11.83 |
| 1101 | -16.31 | -17.45 | -13.42 | -15.12 | -14.93 | -16.91 | -12.58 | -14.53 |
| 1110 | -15.45 | -16.77 | -12.8 | -14.11 | -14.42 | -16.08 | -11.8 | -13.89 |
| 1111 | -15.22 | -16.14 | -12.63 | -13.86 | -13.87 | -15.38 | -11.6 | -13.28 |

| REPULSION ENERGY(kcal/mol) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| GU/CY | 000 | 001 | 010 | 100 | 011 | 101 | 110 | 111 |
| 0000 | 30.49 | 33.01 | 25.68 | 26.32 | 28.63 | 29.98 | 22.13 | 25.87 |
| 0001 | 30.11 | 31.98 | 25.38 | 25.92 | 27.76 | 28.88 | 21.79 | 24.91 |
| 0010 | 29.39 | 31.49 | 24.99 | 25 | 27.48 | 28.22 | 21.18 | 24.43 |
| 0100 | 30.18 | 32.76 | 25.36 | 27.81 | 28.41 | 31.61 | 23.53 | 27.42 |
| 1000 | 25.8 | 28.23 | 21.31 | 22.4 | 24.19 | 25.95 | 18.41 | 22.1 |
| 0011 | 29.01 | 30.46 | 24.7 | 24.59 | 26.58 | 27.11 | 20.84 | 23.43 |
| 0101 | 29.86 | 31.78 | 25.12 | 27.39 | 27.58 | 30.48 | 23.19 | 26.45 |
| 1001 | 25.43 | 27.21 | 21.01 | 22.05 | 23.32 | 24.9 | 18.11 | 21.17 |
| 0110 | 29.18 | 31.34 | 24.76 | 26.25 | 27.36 | 29.57 | 22.39 | 25.79 |
| 1010 | 23.95 | 26.03 | 19.93 | 20.54 | 22.43 | 23.7 | 16.95 | 20.21 |
| 1100 | 26.14 | 28.61 | 21.49 | 24.51 | 24.47 | 28.17 | 20.44 | 24.26 |
| 0111 | 28.87 | 30.39 | 24.53 | 25.86 | 26.53 | 28.48 | 22.07 | 24.83 |
| 1011 | 23.64 | 25.06 | 19.69 | 20.23 | 21.58 | 22.67 | 16.69 | 19.28 |
| 1101 | 25.84 | 27.62 | 21.26 | 24.16 | 23.62 | 27.05 | 20.15 | 23.3 |
| 1110 | 24.67 | 26.78 | 20.43 | 22.71 | 23.01 | 25.93 | 19.05 | 22.44 |
| 1111 | 24.46 | 25.89 | 20.29 | 22.44 | 22.24 | 24.92 | 18.84 | 21.55 |

| POLARIZATION ENERGY(kcal/mol) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| GU/CY | 000 | 001 | 010 | 100 | 011 | 101 | 110 | 111 |
| 0000 | -1.42 | -1.54 | -1.22 | -1.42 | -1.29 | -1.48 | -1.61 | -1.59 |
| 0001 | -1.42 | -1.56 | -1.2 | -1.38 | -1.3 | -1.44 | -1.54 | -1.54 |
| 0010 | -1.27 | -1.47 | -1.09 | -1.28 | -1.24 | -1.45 | -1.48 | -1.55 |
| 0100 | -1.48 | -1.6 | -1.29 | -1.73 | -1.36 | -1.75 | -1.92 | -1.88 |
| 1000 | -1.09 | -1.21 | -0.97 | -1.11 | -1.04 | -1.19 | -1.35 | -1.34 |
| 0011 | -1.31 | -1.58 | -1.1 | -1.28 | -1.32 | -1.5 | -1.44 | -1.57 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 0101 | -1.47 | -1.62 | -1.26 | -1.67 | -1.35 | -1.7 | -1.83 | -1.8 |
| 1001 | -1.07 | -1.2 | -0.93 | -1.06 | -1.01 | -1.13 | -1.27 | -1.27 |
| 0110 | -1.28 | -1.48 | -1.11 | -1.51 | -1.26 | -1.67 | -1.71 | -1.77 |
| 1010 | -0.99 | -1.16 | -0.87 | -1.01 | -0.99 | -1.17 | -1.22 | -1.28 |
| 1100 | -1.14 | -1.25 | -1.03 | -1.41 | -1.09 | -1.48 | -1.65 | -1.64 |
| 0111 | -1.29 | -1.57 | -1.1 | -1.48 | -1.32 | -1.7 | -1.66 | -1.77 |
| 1011 | -1.01 | -1.24 | -0.87 | -1 | -1.04 | -1.2 | -1.17 | -1.28 |
| 1101 | -1.1 | -1.23 | -0.98 | -1.33 | -1.06 | -1.42 | -1.55 | -1.55 |
| 1110 | -0.97 | -1.14 | -0.88 | -1.23 | -0.99 | -1.4 | -1.44 | -1.51 |
| 1111 | -0.97 | -1.21 | -0.86 | -1.19 | -1.03 | -1.42 | -1.38 | -1.5 |

| MP2 DISPERSION ENERGY(kcal/mol) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| GU/CY | 000 | 001 | 010 | 100 | 011 | 101 | 110 | 111 |
| 0000 | -12.56 | -14.04 | -11.65 | -11.62 | -13.12 | -13.33 | -10.58 | -12.23 |
| 0001 | -12.31 | -13.76 | -11.46 | -11.49 | -12.9 | -13.21 | -10.54 | -12.2 |
| 0010 | -11.74 | -12.98 | -10.79 | -10.4 | -12.06 | -11.77 | -9.26 | -10.7 |
| 0100 | -13.25 | -14.74 | -12.23 | -12.46 | -13.74 | -14.17 | -11.34 | -13.02 |
| 1000 | -11.8 | -13.26 | -10.93 | -10.71 | -12.39 | -12.26 | -9.6 | -11.14 |
| 0011 | -11.54 | -12.75 | -10.64 | -10.29 | -11.87 | -11.66 | -9.23 | -10.66 |
| 0101 | -12.99 | -14.46 | -12.05 | -12.34 | -13.53 | -14.07 | -11.32 | -13.02 |
| 1001 | -11.54 | -12.98 | -10.74 | -10.58 | -12.17 | -12.17 | -9.58 | -11.14 |
| 0110 | -12.41 | -13.68 | -11.31 | -11.15 | -12.62 | -12.49 | -9.91 | -11.36 |
| 1010 | -10.75 | -11.96 | -9.79 | -9.24 | -11.06 | -10.37 | -7.96 | -9.25 |
| 1100 | -12.43 | -13.87 | -11.44 | -11.6 | -12.89 | -13.15 | -10.45 | -12.02 |
| 0111 | -12.22 | -13.45 | -11.17 | -11.03 | -12.44 | -12.39 | -9.88 | -11.34 |
| 1011 | -10.56 | -11.74 | -9.66 | -9.14 | -10.88 | -10.28 | -7.95 | -9.24 |
| 1101 | -12.19 | -13.6 | -11.28 | -11.48 | -12.7 | -13.07 | -10.44 | -12.03 |
| 1110 | -11.49 | -12.68 | -10.4 | -10.23 | -11.66 | -11.4 | -8.95 | -10.29 |
| 1111 | -11.31 | -12.48 | -10.3 | -10.14 | -11.51 | -11.33 | -8.96 | -10.29 |

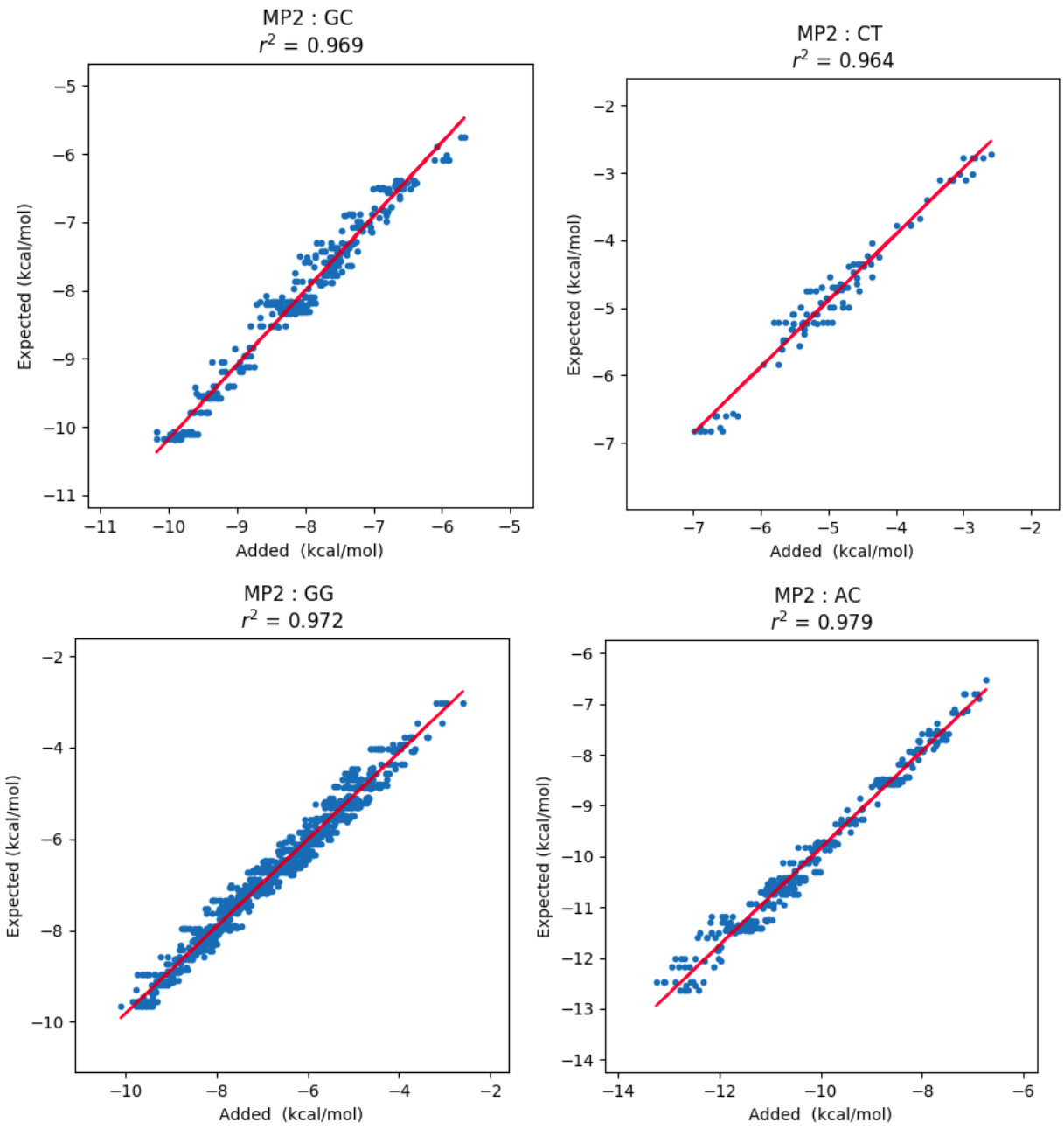
| TOTAL INTERACTION ENERGY HF OR DFT(kcal/mol) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| GU/CY | 000 | 001 | 010 | 100 | 011 | 101 | 110 | 111 |
| 0000 | 6.26 | 7.07 | 6.11 | 4.58 | 6.98 | 6.13 | 4.33 | 5.75 |
| 0001 | 5.89 | 6.22 | 5.96 | 4.46 | 6.28 | 5.48 | 4.45 | 5.23 |

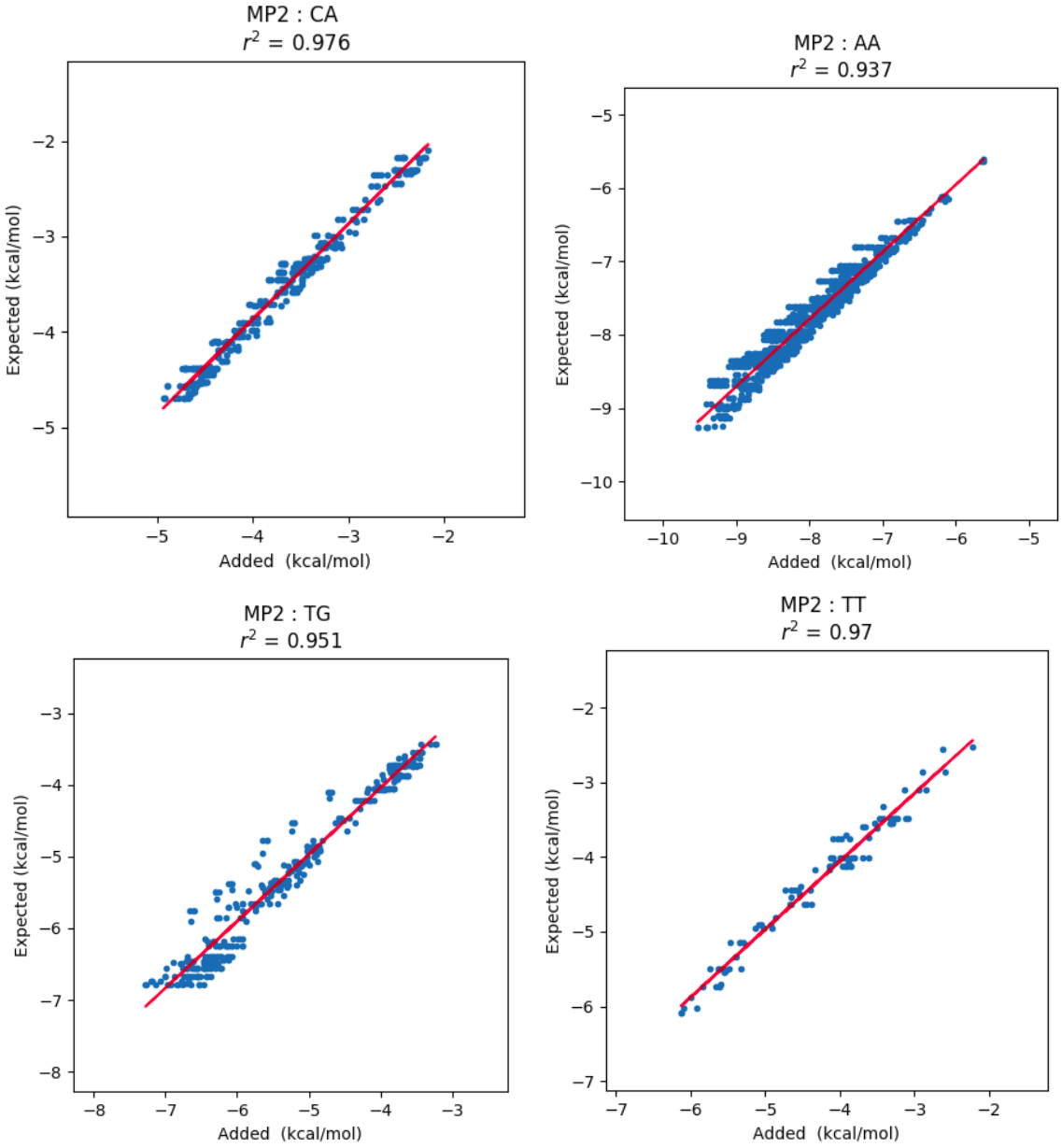
| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 0010 | 5.46 | 5.16 | 5.08 | 2.91 | 4.77 | 2.91 | 2.33 | 2.19 |
| 0100 | 6.11 | 6.94 | 5.76 | 5.04 | 6.71 | 6.68 | 4.57 | 6.12 |
| 1000 | 5.93 | 7.09 | 5.16 | 3.54 | 6.48 | 5.14 | 2.6 | 4.27 |
| 0011 | 5.04 | 4.21 | 4.89 | 2.73 | 3.96 | 2.15 | 2.38 | 1.55 |
| 0101 | 5.78 | 6.13 | 5.67 | 4.89 | 6.05 | 6 | 4.67 | 5.59 |
| 1001 | 5.54 | 6.21 | 4.99 | 3.46 | 5.75 | 4.52 | 2.76 | 3.78 |
| 0110 | 5.53 | 5.27 | 4.86 | 3.04 | 4.65 | 3.08 | 2.19 | 2.18 |
| 1010 | 4.77 | 4.83 | 3.78 | 1.57 | 3.93 | 1.54 | 0.22 | 0.3 |
| 1100 | 5.97 | 7.08 | 4.99 | 4.08 | 6.32 | 5.67 | 3 | 4.71 |
| 0111 | 5.16 | 4.4 | 4.74 | 2.84 | 3.91 | 2.32 | 2.24 | 1.55 |
| 1011 | 4.34 | 3.86 | 3.58 | 1.42 | 3.11 | 0.78 | 0.31 | -0.33 |
| 1101 | 5.63 | 6.23 | 4.88 | 3.95 | 5.62 | 4.97 | 3.12 | 4.16 |
| 1110 | 5.12 | 5.17 | 3.9 | 2.02 | 4.08 | 2 | 0.61 | 0.76 |
| 1111 | 4.77 | 4.27 | 3.79 | 1.85 | 3.33 | 1.22 | 0.7 | 0.12 |

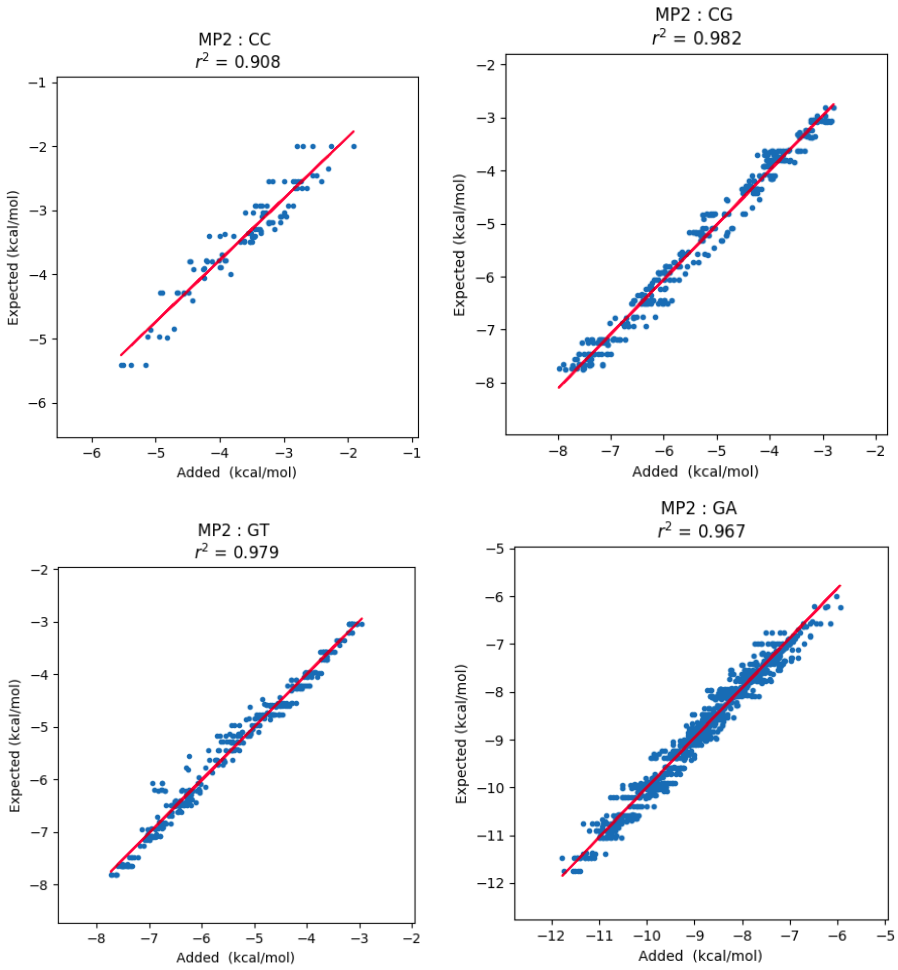
| TOTAL INTERACTION ENERGY MP2(kcal/mol) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| GU/CY | 000 | 001 | 010 | 100 | 011 | 101 | 110 | 111 |
| 0000 | -6.3 | -6.97 | -5.54 | -7.04 | -6.14 | -7.21 | -6.24 | -6.48 |
| 0001 | -6.42 | -7.54 | -5.5 | -7.03 | -6.62 | -7.74 | -6.09 | -6.98 |
| 0010 | -6.28 | -7.83 | -5.71 | -7.49 | -7.29 | -8.86 | -6.94 | -8.51 |
| 0100 | -7.14 | -7.8 | -6.47 | -7.42 | -7.03 | -7.49 | -6.77 | -6.9 |
| 1000 | -5.87 | -6.17 | -5.77 | -7.17 | -5.9 | -7.12 | -7 | -6.87 |
| 0011 | -6.51 | -8.54 | -5.75 | -7.56 | -7.91 | -9.51 | -6.85 | -9.11 |
| 0101 | -7.21 | -8.33 | -6.38 | -7.45 | -7.48 | -8.07 | -6.65 | -7.43 |
| 1001 | -6.01 | -6.77 | -5.75 | -7.12 | -6.42 | -7.65 | -6.82 | -7.37 |
| 0110 | -6.89 | -8.4 | -6.45 | -8.1 | -7.97 | -9.41 | -7.72 | -9.18 |
| 1010 | -5.98 | -7.14 | -6.01 | -7.67 | -7.12 | -8.83 | -7.74 | -8.95 |
| 1100 | -6.47 | -6.79 | -6.45 | -7.53 | -6.57 | -7.48 | -7.45 | -7.31 |
| 0111 | -7.06 | -9.05 | -6.43 | -8.19 | -8.52 | -10.07 | -7.64 | -9.79 |
| 1011 | -6.22 | -7.88 | -6.08 | -7.72 | -7.78 | -9.5 | -7.64 | -9.57 |
| 1101 | -6.57 | -7.37 | -6.39 | -7.54 | -7.07 | -8.1 | -7.32 | -7.87 |
| 1110 | -6.36 | -7.51 | -6.5 | -8.21 | -7.58 | -9.4 | -8.34 | -9.54 |
| 1111 | -6.55 | -8.2 | -6.51 | -8.3 | -8.17 | -10.1 | -8.26 | -10.17 |

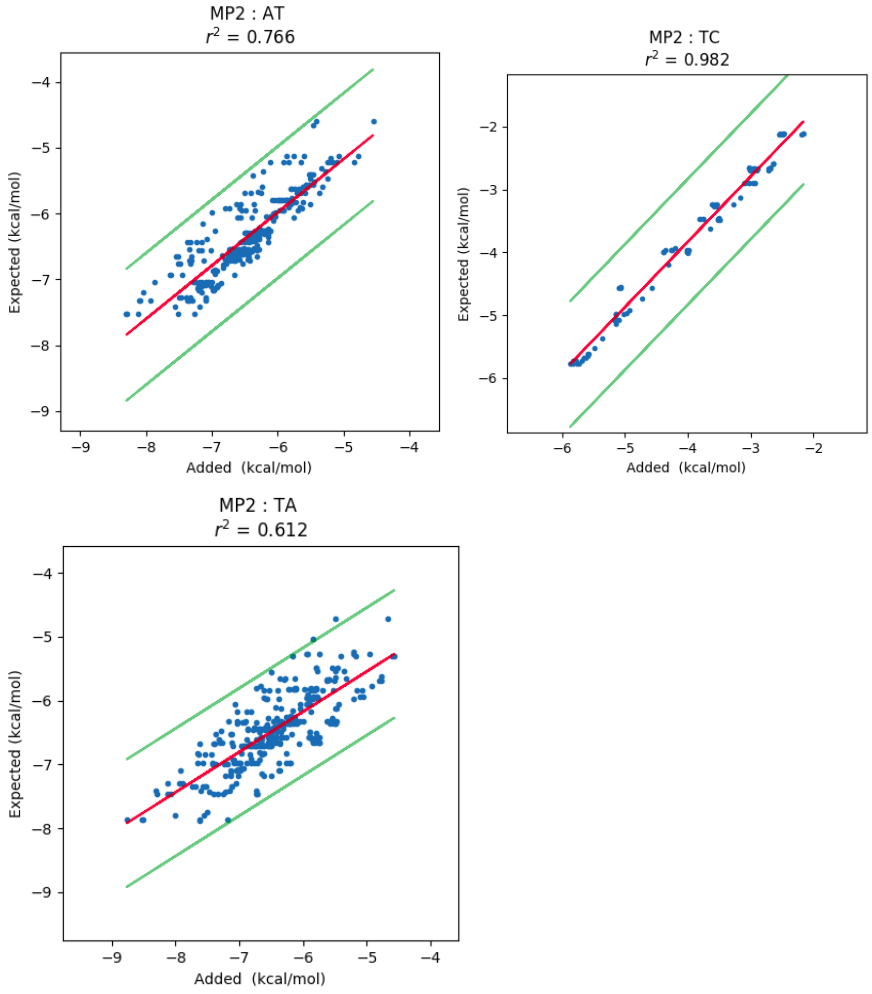
**Additivity**

| Scheme | Eint | Difference |
|---|---|---|
| **Gu1111..Cy111** | **-10.17** | **0** |
| Gu1111..Cy110+ Gu1111..Cy001-Gu1111..Cy000 | -9.91 | -0.26 |
| Gu1111..Cy101+ Gu1111..Cy010-Gu1111..Cy000 | -10.06 | -0.11 |
| Gu1111..Cy011+ Gu1111..Cy100-Gu1111..Cy000 | -9.92 | -0.25 |
| Gu1111..Cy001+ Gu1111..Cy010+ Gu1111..Cy100-2*Gu1111..Cy000 | -9.91 | -0.26 |
| Gu1110..Cy111+ Gu0001..Cy111-Gu0000..Cy111 | -10.04 | -0.13 |
| Gu0111..Cy111+ Gu1000..Cy111-Gu0000..Cy111 | -10.18 | 0.01 |
| Gu1011..Cy111+ Gu0100..Cy111-Gu0000..Cy111 | -9.99 | -0.18 |
| Gu1101..Cy111+ Gu0010..Cy111-Gu0000..Cy111 | -9.9 | -0.27 |
| Gu1010..Cy111+ Gu0101..Cy111-Gu0000..Cy111 | -9.9 | -0.27 |
| Gu1100..Cy111+ Gu0011..Cy111-Gu0000..Cy111 | -9.94 | -0.23 |
| Gu1001..Cy111+ Gu0110..Cy111-Gu0000..Cy111 | -10.07 | -0.1 |
| Gu1010..Cy111+ Gu0100..Cy111+ Gu0001..Cy111-2*Gu0000..Cy111 | -9.87 | -0.3 |
| Gu1100..Cy111+ Gu0010..Cy111+ Gu0001..Cy111-2*Gu0000..Cy111 | -9.84 | -0.33 |
| Gu1001..Cy111+ Gu0010..Cy111+ Gu0100..Cy111-2*Gu0000..Cy111 | -9.82 | -0.35 |
| Gu1000..Cy111+ Gu0010..Cy111+ Gu0101..Cy111-2*Gu0000..Cy111 | -9.85 | -0.32 |
| Gu1000..Cy111+ Gu0100..Cy111+ Gu0011..Cy111-2*Gu0000..Cy111 | -9.92 | -0.25 |
| Gu1000..Cy111+ Gu0001..Cy111+ Gu0110..Cy111-2*Gu0000..Cy111 | -10.07 | -0.1 |
| Gu0100..Cy111+ Gu0010..Cy111+ Gu1000..Cy111+ Gu0001..Cy111-2*Gu0000..Cy111 | -9.82 | -0.35 |


MP2 : GC
$r^2$ = 0.969
Expected (kcal/mol)
Added (kcal/mol)
MP2 : CT
$r^2$ = 0.964
Expected (kcal/mol)
Added (kcal/mol)
MP2 : GG
$r^2$ = 0.972
Expected (kcal/mol)
Added (kcal/mol)
MP2 : AC
$r^2$ = 0.979
Expected (kcal/mol)
Added (kcal/mol)

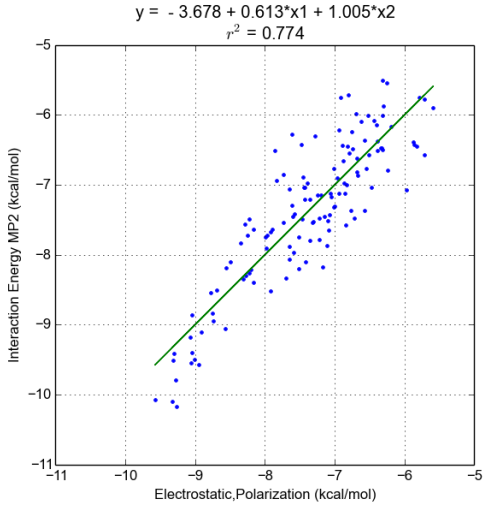

MP2 : CA
$r^2$ = 0.976
Expected (kcal/mol)
Added (kcal/mol)
MP2 : AA
$r^2$ = 0.937
Expected (kcal/mol)
Added (kcal/mol)
MP2 : TG
$r^2$ = 0.951
Expected (kcal/mol)
Added (kcal/mol)
MP2 : TT
$r^2$ = 0.97
Expected (kcal/mol)
Added (kcal/mol)

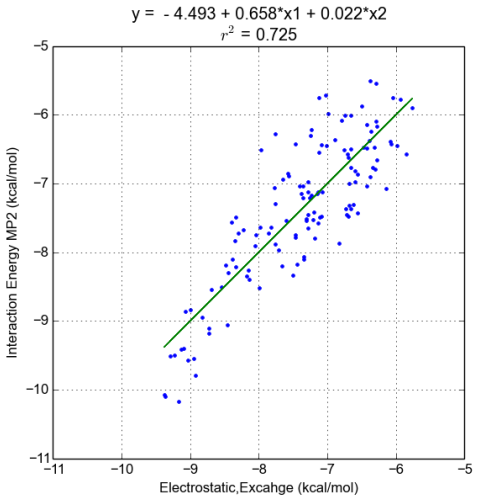

MP2 : CC
$r^2$ = 0.908
MP2 : CG
$r^2$ = 0.982
MP2 : GT
$r^2$ = 0.979
MP2 : GA
$r^2$ = 0.967
Expected (kcal/mol)
Added (kcal/mol)

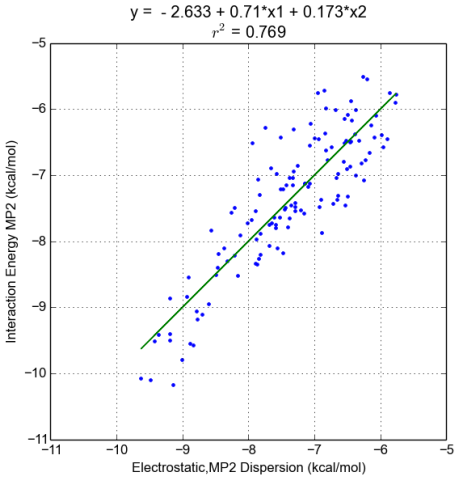

MP2 : AT
$r^2$ = 0.766
Expected (kcal/mol)
Added (kcal/mol)
MP2 : TC
$r^2$ = 0.982
Expected (kcal/mol)
Added (kcal/mol)
MP2 : TA
$r^2$ = 0.612
Expected (kcal/mol)
Added (kcal/mol)

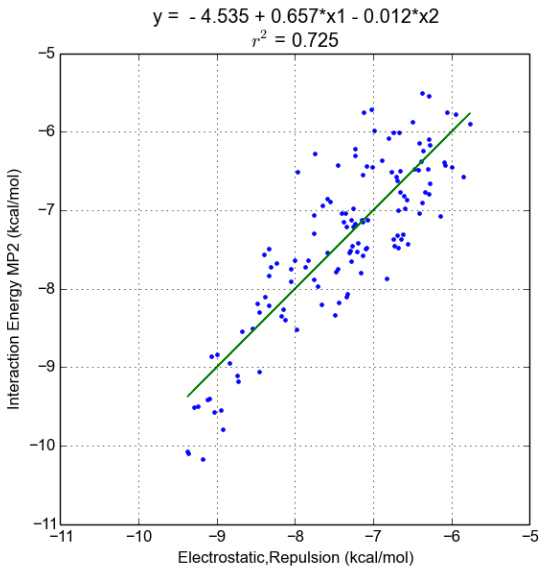
## Linear Regression Analysis

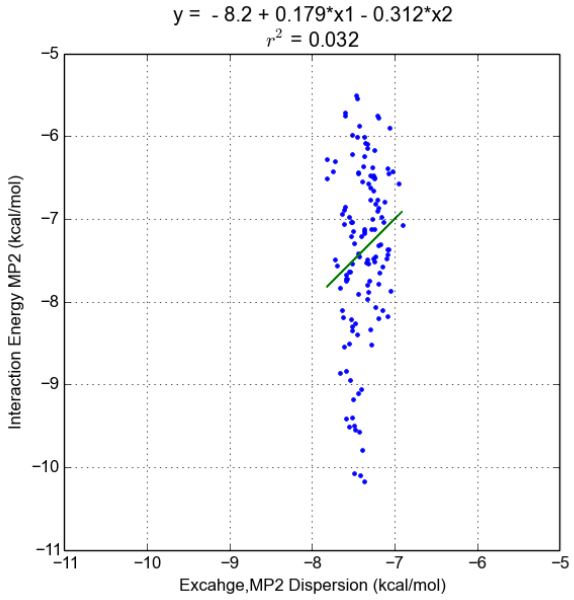
### Bivariate Regression

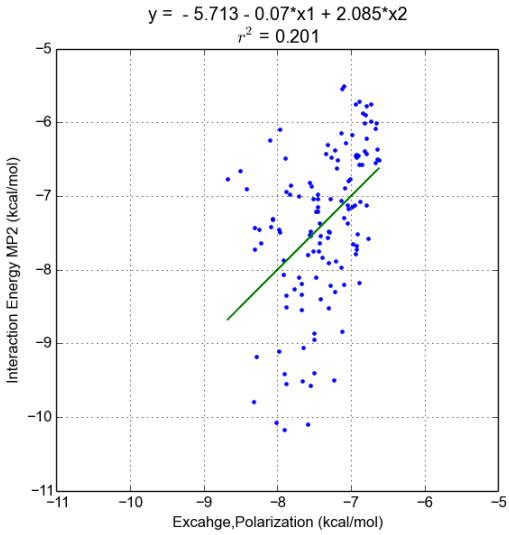


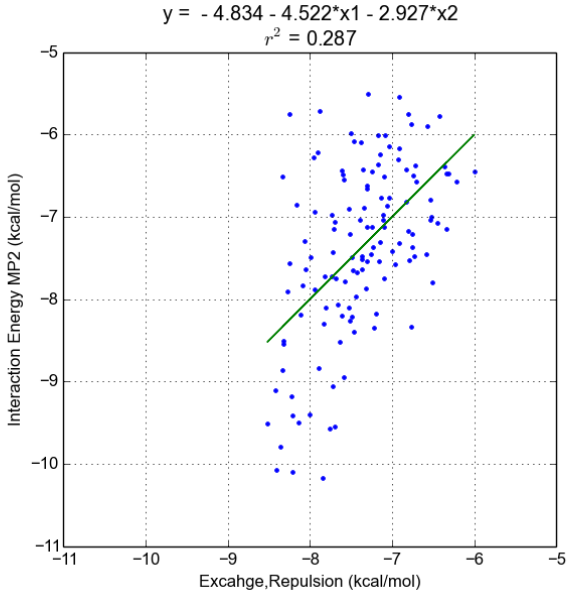



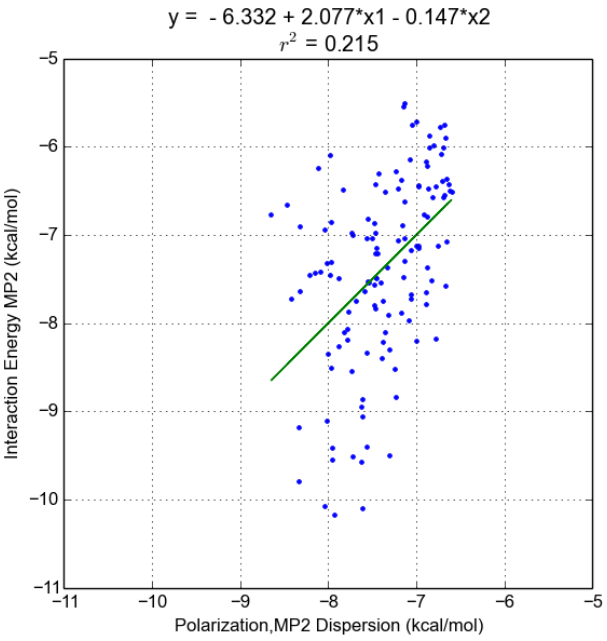



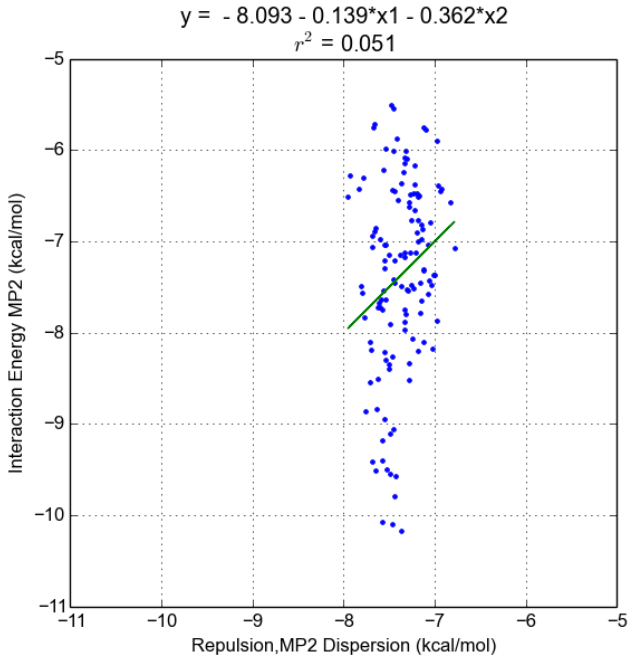

y = - 4.535 + 0.657*x1 - 0.012*x2
$r^2$ = 0.725
Interaction Energy MP2 (kcal/mol)
Electrostatic,Repulsion (kcal/mol)
−5
−6
−7
−8
−9
−10
−11
−11
−10
−9
−8
−7
−6
−5

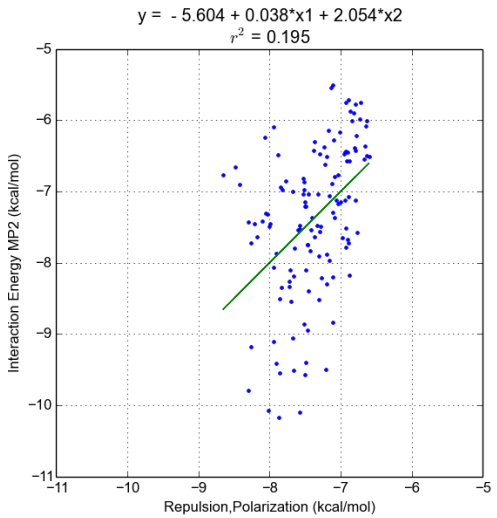

y = - 8.2 + 0.179*x1 - 0.312*x2
$r^2$ = 0.032
Interaction Energy MP2 (kcal/mol)
Excahge,MP2 Dispersion (kcal/mol)
−5
−6
−7
−8
−9
−10
−11
−11
−10
−9
−8
−7
−6
−5


y = - 5.713 - 0.07*x1 + 2.085*x2
$r^2$ = 0.201
Interaction Energy MP2 (kcal/mol)
Excahge,Polarization (kcal/mol)
−5
−6
−7
−8
−9
−10
−11
−11
−10
−9
−8
−7
−6
−5

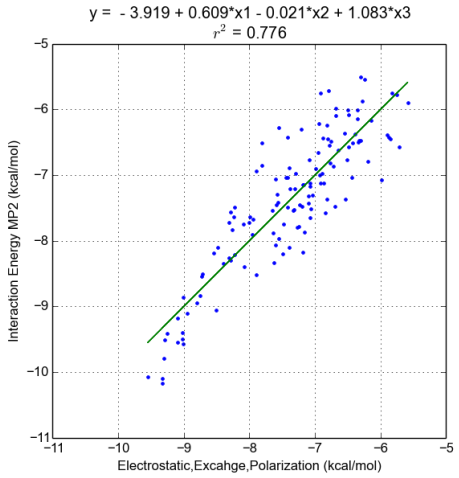

y = - 4.834 - 4.522*x1 - 2.927*x2
$r^2$ = 0.287
Interaction Energy MP2 (kcal/mol)
Excahge,Repulsion (kcal/mol)
−5
−6
−7
−8
−9
−10
−11
−11
−10
−9
−8
−7
−6
−5

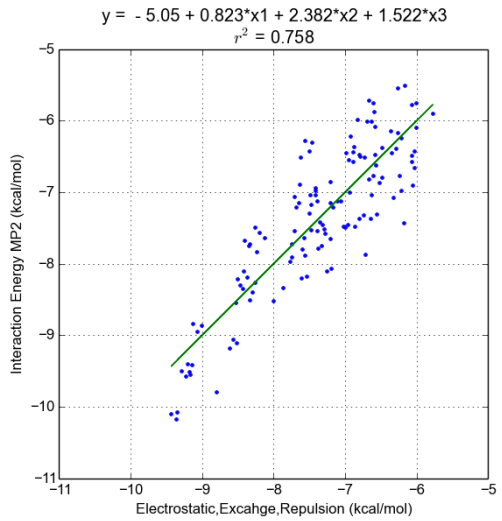

y = - 6.332 + 2.077*x1 - 0.147*x2
$r^2$ = 0.215
Interaction Energy MP2 (kcal/mol)
Polarization,MP2 Dispersion (kcal/mol)
−5
−6
−7
−8
−9
−10
−11
−11
−10
−9
−8
−7
−6
−5

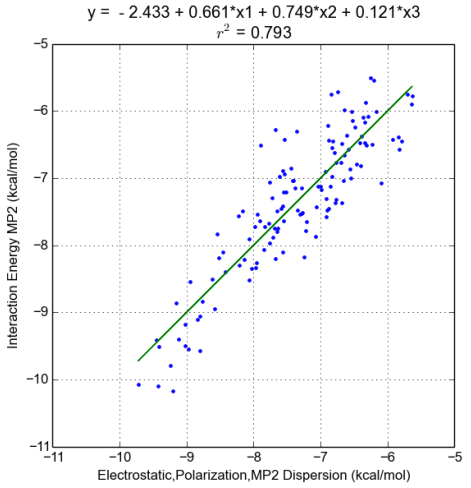

y = - 8.093 - 0.139*x1 - 0.362*x2
$r^2$ = 0.051
Interaction Energy MP2 (kcal/mol)
Repulsion,MP2 Dispersion (kcal/mol)
−5
−6
−7
−8
−9
−10
−11
−11
−10
−9
−8
−7
−6
−5

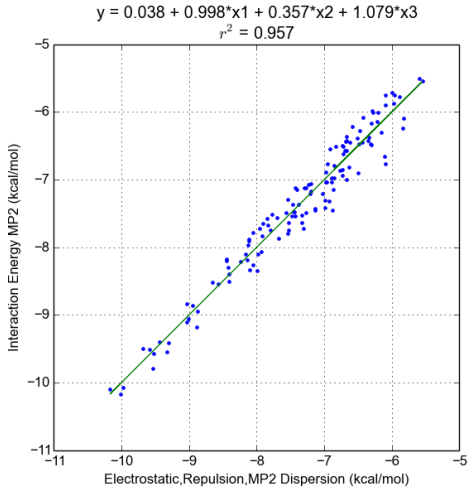


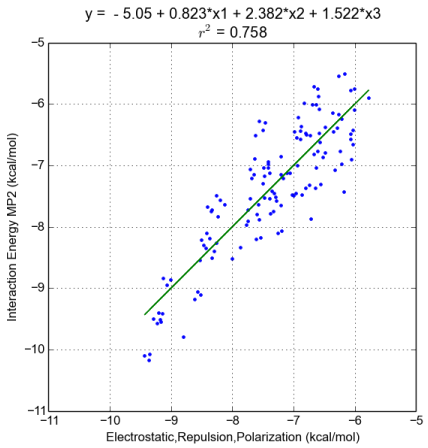

## Trivariate Regression

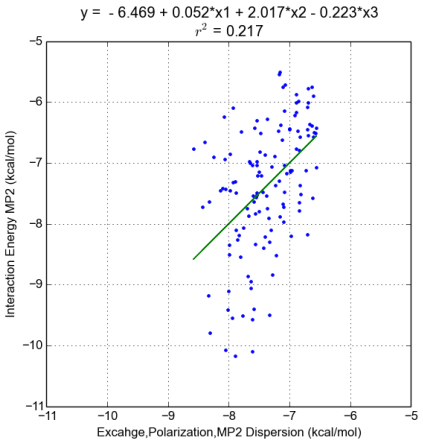


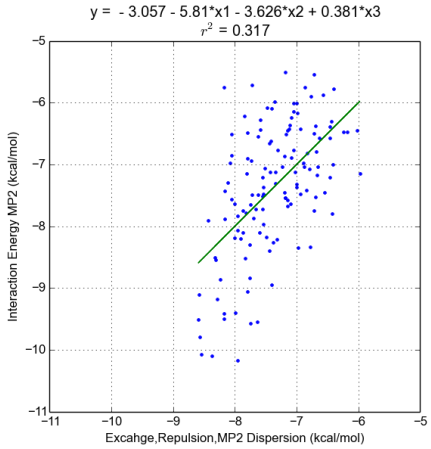

y = - 5.05 + 0.823*x1 + 2.382*x2 + 1.522*x3
$r^2$ = 0.758
Interaction Energy MP2 (kcal/mol)
Electrostatic,Excahge,Repulsion (kcal/mol)

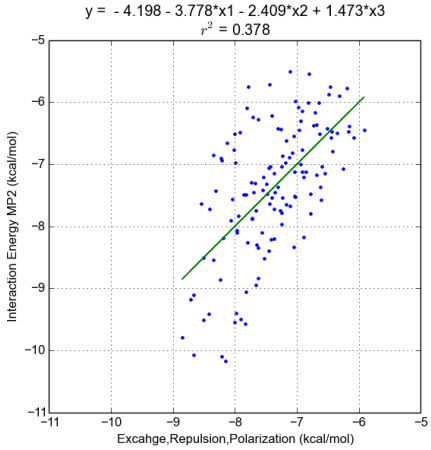

y = - 2.433 + 0.661*x1 + 0.749*x2 + 0.121*x3
$r^2$ = 0.793
Interaction Energy MP2 (kcal/mol)
Electrostatic,Polarization,MP2 Dispersion (kcal/mol)

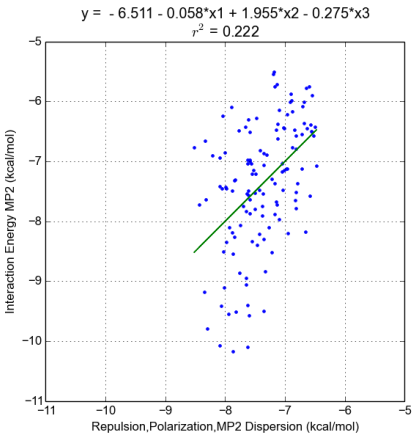

y = 0.038 + 0.998*x1 + 0.357*x2 + 1.079*x3
$r^2$ = 0.957
Interaction Energy MP2 (kcal/mol)
Electrostatic,Repulsion,MP2 Dispersion (kcal/mol)


y = - 5.05 + 0.823*x1 + 2.382*x2 + 1.522*x3
$r^2$ = 0.758
Interaction Energy MP2 (kcal/mol)
Electrostatic,Repulsion,Polarization (kcal/mol)

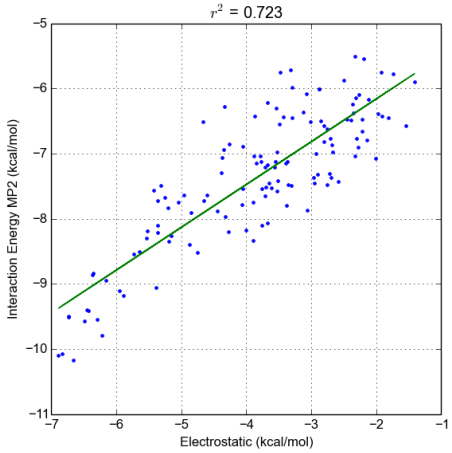

y = - 6.469 + 0.052*x1 + 2.017*x2 - 0.223*x3
$r^2$ = 0.217
Interaction Energy MP2 (kcal/mol)
Excahge,Polarization,MP2 Dispersion (kcal/mol)

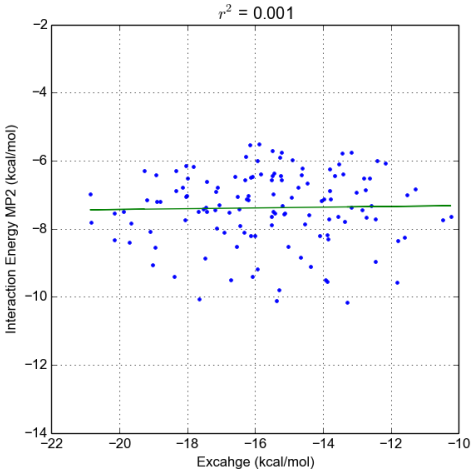

y = - 3.057 - 5.81*x1 - 3.626*x2 + 0.381*x3
$r^2$ = 0.317
Interaction Energy MP2 (kcal/mol)
Excahge,Repulsion,MP2 Dispersion (kcal/mol)

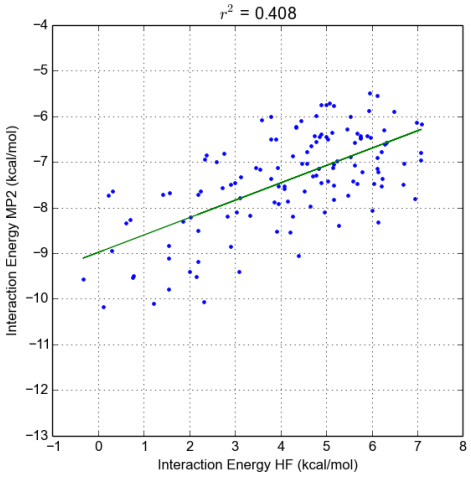

y = - 4.198 - 3.778*x1 - 2.409*x2 + 1.473*x3
$r^2$ = 0.378
Interaction Energy MP2 (kcal/mol)
Excahge,Repulsion,Polarization (kcal/mol)

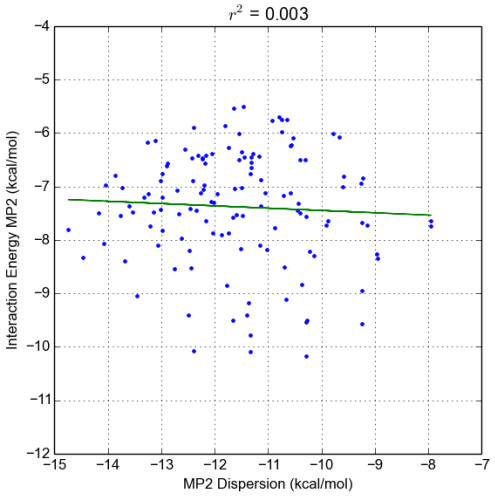

y = - 6.511 - 0.058*x1 + 1.955*x2 - 0.275*x3
$r^2$ = 0.222
Interaction Energy MP2 (kcal/mol)
Repulsion,Polarization,MP2 Dispersion (kcal/mol)

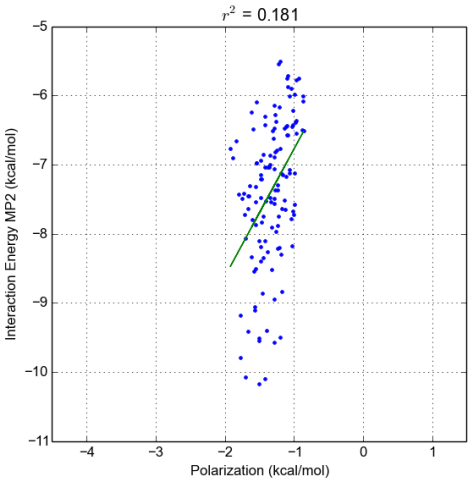
## Single Variate Correlation

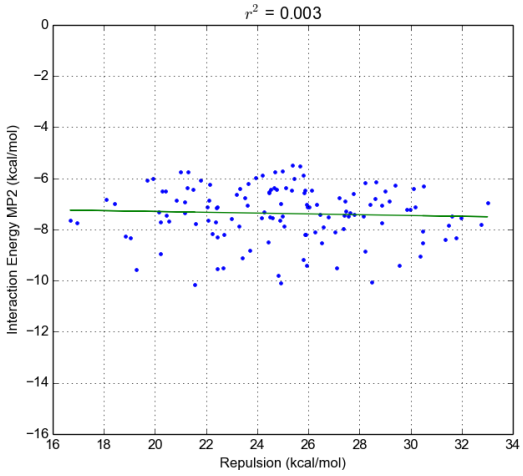



$r^2$ = 0.001
Interaction Energy MP2 (kcal/mol)
Excahge (kcal/mol)


$r^2$ = 0.408
Interaction Energy MP2 (kcal/mol)
Interaction Energy HF (kcal/mol)


$r^2$ = 0.003
Interaction Energy MP2 (kcal/mol)
MP2 Dispersion (kcal/mol)

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