Contribution ID : **83** Type : **Poster Presentation**

Predictive Quantitative Non-Covalent Interaction Index

Non-covalent interactions (NCIs) are fundamental to the structure, stability, and function of molecular systems across chemistry and biology [1]. The Non-Covalent Interaction (NCI) method offers a visual and intuitive means to identify regions of weak interactions by analysing low-density and low-gradient features in electron density data. Since its introduction, NCI has become a widely adopted qualitative tool owing to its ease of use, speed, and ability to provide clear visualizations of interaction zones [2]. However, establishing a direct quantitative link between NCI indices and interaction energies was a challenge [3].

In this work, we developed a quantitative framework linking the NCI index—obtained from integrating relevant volumes in electron density—to interaction energies with high accuracy. Using symbolic regression algorithms [4], we systematically analysed how the NCI index correlates with reference CCSD(T) energies across various small molecular complexes [5], including hydrogen-bonded and dispersion-dominated systems. Our results revealed a meaningful, interpretable equation that connects the NCI index with interaction energies, demonstrating reliable predictive capabilities. It furthermore enables the division of the energy into polar and non-polar components, see Figure 1.

The development of this quantitative model offers a computationally efficient alternative to conventional ab initio methods, enabling rapid estimation of interaction energies and paving the way for streamlined analysis of complex systems, such as biomolecular assemblies and materials, by providing fast and meaningful estimates of interaction energies directly from electron density data.

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