A Systematic Computational Protocol for Deconstructing Non-Covalent Interactions: BerchNCI 1.0

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Dedication: This work is dedicated to Professor Stefan Grimme, whose development of dispersion corrections has revolutionized the accurate modeling of non-covalent interactions.

Abstract: Non-covalent interactions constitute the fundamental organizing principles of supramolecular assemblies; however, the accurate modeling of these subtle, dispersion-driven forces remains a formidable challenge in theoretical chemistry. In this work, we formally propose the *Berchmans Protocol for Modelling Non-Covalent Interactions 1.0* (BerchNCI 1.0), a comprehensive, hierarchical computational workflow designed to decipher the electronic anatomy of NCIs with benchmark precision. The BerchNCI 1.0 protocol systematizes the characterization of weak interactions by integrating geometry optimization via dispersion-corrected functionals with a range of analytical descriptors. This strategy employs the Non-Covalent Interaction index, Quantum Theory of Atoms in Molecules, and the Independent Gradient Model based on Hirshfeld partition to visualize and quantify interaction topologies. The physical driving forces of molecular association, including electrostatics, dispersion, and Pauli repulsion, are dissected using Local Energy Decomposition analysis. Uniquely, this protocol extends beyond static analysis by incorporating *ab initio* Molecular Dynamics to assess the thermodynamic stability and temporal evolution of these assemblies. We present BerchNCI 1.0 as a standardized methodology for resolving competitive interactions and rationalizing molecular recognition across diverse chemical environments.

Keywords: non-covalent interactions; QTAIM; IGMH; LED; CVB; NBO

1. Introduction

Non-covalent interactions (NCIs) represent a spectrum of forces that, while not involving the sharing of electrons typical of covalent bonds, are fundamental to the structure and function of matter [1–4]. These interactions, including hydrogen bonds, halogen bonds,

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carbon bonds, tetral bonds, van der Waals forces, and π-system interactions, are the organizing principles that govern molecular recognition, dictate the three-dimensional structures of proteins and nucleic acids, and control the assembly of supramolecular architectures [5–8]. The double helix of DNA, for instance, is stabilized by a network of hydrogen bonds and π-π stacking interactions between base pairs. Similarly, the efficacy of a drug molecule is often determined by its non-covalent binding affinity within the active site of a target protein [9]. Though individually weak, typically ranging from 1 to 15 kcal/mol, the cumulative effect of numerous NCIs within an extensive system is decisive, controlling everything from the physical properties of materials, such as boiling points and solubility, to the intricate mechanisms of biological catalysis [10,11].

The nature of these forces presents a significant challenge for both experimental and theoretical chemists. While experimental techniques like X-ray crystallography and NMR spectroscopy provide invaluable structural data, they often have limitations in resolving the fine electronic details and dynamic fluctuations inherent to weak interactions. Prof. E. Arunan has used microwave spectroscopy studies to evaluate the nature of the weak chemical bonds [12–15] But a complete picture is not always possible with experimental studies due to the weak nature of these interactions. This elevates the importance of computational chemistry as an indispensable partner to experiment [3,16].

This paper aims to provide a critical and comprehensive survey of the state-of-the-art theoretical and computational methodologies our research group employed to study, visualize, and quantify non-covalent interactions. A central theme is that an understanding of these complex phenomena cannot be achieved through a single computational lens. This paper is structured to present this workflow, illustrating its power and versatility through a series of case studies from the author's published research across diverse chemical domains, including drug-solvent interactions, biomolecular solvation, nanomaterial complexation, and the fundamental competition between different non-covalent forces. The author prefers to call it the *Berchmans Protocol for Modelling Non-Covalent Interactions 1.0* (BerchNCI 1.0), in honour of his alma mater.

2. A Lexicon of Non-Covalent Interactions

A detailed understanding of the theoretical toolbox requires an understanding of the interactions it is designed to probe. Non-covalent interactions encompass a range of forces with distinct physical origins, strengths, and geometric characteristics.

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2.1. Hydrogen Bonding

The hydrogen bond is the archetypal directional non-covalent interaction, arising from the electrostatic attraction between a hydrogen atom covalently bonded to a highly electronegative atom (the donor, e.g., O, N) and another nearby electronegative atom (the acceptor). The strength of hydrogen bonds varies significantly, from weak (2–5 kcal/mol) in many neutral organic systems to strong (>10 kcal/mol) in charged species, and this strength dictates their function. These interactions are critical in determining the structure of biomolecules, such as in the stabilization of protein secondary structures and the solvation of drugs and amino acids, as has been demonstrated in computational studies of prontosil, resveratrol, and various amino acids in polar solvents. Modern interpretations also classify the hydrogen bond as a specific type of σ-hole interaction, where the positive electrostatic potential is located along the axis of the covalent bond to hydrogen [17,18].

2.2. Halogen Bonding and Other σ-Hole Interactions

Analogous to hydrogen bonding, other σ-hole interactions arise from an anisotropically distributed electron density around a covalently bonded atom from Groups 14–17 of the periodic table. This anisotropy creates a region of positive electrostatic potential, the σ-hole, on the side of the atom opposite to the covalent bond. This positive region can then interact favorably with a nucleophilic site, such as a lone pair on an oxygen or nitrogen atom. When the σ-hole donor is a halogen atom (Cl, Br, I), the resulting interaction is termed a halogen bond. These interactions are highly directional and have become a powerful tool in crystal engineering and drug design. The competition between halogen bonding and the more conventional hydrogen bonding presents a subtle chemical problem, as explored in studies of halogenated coumarins, where the choice between the two interaction motifs can be finely tuned and computationally resolved [19–23].

2.3. π-Interactions

Aromatic and other π-conjugated systems engage in a variety of non-covalent interactions driven by their delocalized electron clouds. The most common of these is π-π stacking, where the faces of two aromatic rings interact favorably. These interactions are crucial for the stability of the DNA double helix (base stacking), the packing of molecules in organic crystals, and the formation of many supramolecular assemblies. The interaction strength is highly dependent on the relative orientation and the electronic nature of the aromatic rings. Other important π-interactions include cation-π interactions, where a cation is attracted to the electron-rich face of a π-system, and anion-π interactions, where an anion interacts with an electron-deficient π-system [24].

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2.4. Van der Waals Forces

Van der Waals (vdW) forces are a general class of interactions that occur between all atoms and molecules, arising from correlations in the fluctuating polarizations of nearby particles. They are fundamentally composed of two parts: long-range attractive forces, known as London dispersion forces, which result from instantaneous induced dipoles; and short-range repulsive forces, known as Pauli repulsion, which arise from the overlap of electron clouds when atoms get too close, and they are weak (typically ~0.5–2 kcal/mol). [25–28].

3. The Analytical Toolbox for Visualizing and Quantifying Interactions

Density Functional Theory is widely used to model the NCI's. Several functionally suitable models for NCI are available, and hence benchmarking is very important [29]. Once a quantum mechanical calculation is complete, a suite of analytical tools is required to translate the resulting wavefunction or electron density into chemically intuitive concepts. These methods make the invisible world of weak forces visible and quantifiable, forming a synergistic workflow for a comprehensive NCI analysis.

3.1. Topological Analysis of Electron Density

The electron density, $\rho(r)$, is a fundamental physical observable that contains all the information about a system. Topological analysis methods parse this scalar field to identify and characterize bonding interactions.

3.1.1. The Non-Covalent Interaction (NCI) Index

The NCI index, based on the Reduced Density Gradient (RDG), is a powerful and popular tool for visualizing non-covalent interactions in three-dimensional real space. The RDG is a dimensionless quantity defined as: $s(r) = 2(3\pi2)1/31\rho(r)4/3 \mid \nabla\rho(r) \mid$. In regions characterized by low electron density, the Reduced Density Gradient (RDG) approaches zero specifically where the density gradient is minimal, a condition typical of the interface between non-covalently interacting fragments. These interactions are identified by plotting the RDG against electron density, where they appear as spikes at low density values; to classify the nature of these interactions, the sign of the second eigenvalue ($\lambda2$) of the electron density Hessian matrix is employed. By plotting RDG versus $(\lambda2)\rho$, interaction types are separated and subsequently mapped onto 3D RDG isosurfaces using a color-coded scheme: blue indicates strong attractive interactions, such as hydrogen bonds $\lambda2<0$.green denotes

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weak van der Waals interactions $\lambda 2 \approx 0$.and red signifies strong repulsive interactions, such as steric effects ($\lambda 2 > 0$) [30–32]. NCI can be easily visualised using tools like Multiwfn [33] and atomistica.online [34].

3.1.2. Quantum Theory of Atoms in Molecules (QTAIM)

While the NCI index provides a qualitative visualization, the Quantum Theory of Atoms in Molecules (QTAIM), developed by Richard Bader, offers a rigorous, quantitative framework for analyzing chemical bonding based on the topology of the electron density.[35], [36] The central concept in QTAIM is the Bond Critical Point (BCP), a point of minimum electron density along the path of maximum density (the bond path) that links two interacting atomic nuclei. The existence of a BCP and its associated bond path is a necessary condition for a chemical interaction. The properties of the electron density at the BCP, such as the density itself ($\rho(r)$), its Laplacian ($\nabla 2\rho(r)$), and the total energy density ($H(r)$), are used to classify the nature and strength of the interaction. For non-covalent interactions, particularly hydrogen bonds, Popelier's criteria are often used: a low value of $\rho(r)$ and a positive value of $\nabla 2\rho(r)$ are characteristic of a closed-shell interaction. The consistent application of QTAIM across studies of resveratrol, alachlor, and amino acids provides the quantitative evidence needed to confirm and characterize the interactions first visualized by NCI [37–39].

3.1.3. Advanced and Complementary Visualization Methods

The quest for more precise and more informative visualizations of NCIs has led to the development of several advanced methods that complement NCI and QTAIM. Independent Gradient Model based on Hirshfeld Partition (IGMH) is a powerful evolution of the gradient-based approach that not only visualizes interactions but also quantifies the contributions of individual atoms and fragments to the interaction. It decomposes the total density gradient into intra- and inter-fragment components. The inter-fragment component, δg^{inter}, specifically highlights the regions of non-covalent interaction. [40, 41] Interaction Region Indicator (IRI) and Density Overlaps Region Indicator (DORI) are also efficient methods. IRI is a modified version of the RDG that is capable of clearly displaying both strong covalent bonds and weak non-covalent interactions simultaneously [42]. DORI is a related tool that highlights regions where electron densities from different fragments overlap, providing a clear picture of bonding and interaction sites [43, 44].

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3.2. Decomposing the Energetics of Interaction

Generally, after a quantum chemical calculation, one gets the total energy of the system. That is not sufficient enough to get the complete picture of the process, especially, weak chemical bonds. Energy decomposition analysis methods dissect this total energy into physically meaningful components, revealing the underlying drivers of molecular association.

3.2.1. Energy Decomposition Analysis (EDA)

EDA schemes partition the total interaction energy (ΔEint) into components such as electrostatics (Eelstat), Pauli repulsion (Erep), polarization/induction (Epol), dispersion (Edisp), and charge transfer (ECT) [45–48] A particularly powerful scheme is the Local Energy Decomposition (LED) analysis, which is designed to be fully compatible with the high-accuracy DLPNO-CCSD(T) method. This synergy is crucial, as it allows for the decomposition of a benchmark-quality interaction energy. The LED approach has been consistently used to explain *why* a given complex is stable. For example, in the reported prontosil-methanol and deucravacitinib-ethanol systems by this author, LED analysis revealed that the strong stability arises from the dominance of attractive electrostatic and dispersion forces over Pauli repulsion [49–58]. Xiamen Energy Decomposition Analysis (XEDA) is a useful study where LMO-EDA, GKS-EDA and their extensions are used to quantitatively analyse NCI and strong chemical bonds in various environments [4].

3.2.2. Natural Bond Orbital (NBO) Analysis

NBO analysis provides a complementary perspective, interpreting interactions in the language of localized Lewis-like bonding orbitals. It identifies donor-acceptor interactions between filled (donor) and empty (acceptor) orbitals. For hydrogen bonds, this typically involves charge transfer from a lone pair (LP) on the acceptor atom to the antibonding orbital ($\sigma*$) of the donor bond (e.g., $LP(O)\rightarrow\sigma*(N-H)$). The strength of this interaction is quantified by the second-order perturbation stabilization energy, E(2). NBO analysis is a cornerstone of the workflow presented here, used in nearly every case study to pinpoint and quantify the specific orbital interactions that constitute the hydrogen bonds visualized by other methods [59–61].

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3.3. Specialized Descriptors for Hydrogen Bonding

For the specific and crucial case of hydrogen bonding, highly specialized descriptors have been developed to provide a clear and concise measure of bond strength. The Core-Valence Bifurcation (CVB) Index is derived from the topology of the ELF. The ELF maps regions of high electron pair localization. The CVB index measures the difference in ELF values at two key bifurcation points. Its sign and magnitude correlate directly with hydrogen bond strength. A negative CVB index indicates a strong, partially covalent H-bond, while a positive value indicates a weaker, closed-shell interaction. This index has been effectively used to provide a quantitative ranking of hydrogen bond strengths in systems like amino acid-water complexes [62, 63].

3.4. Dynamic Perspectives: Ab Initio Molecular Dynamics (AIMD)

Normal quantum mechanical calculations are typically performed on static, optimised, and energy-minimized structures using appropriate tools. Even if this provides an accurate description of the system, real chemical systems at a finite temperature are dynamic and constantly fluctuating. *Ab Initio* Molecular Dynamics (AIMD) bridges this gap by generating dynamical trajectories using forces computed on the fly from electronic structure calculations, effectively creating a molecular movie, even though it is computationally expensive. It allows for the observation of transient hydrogen bond formation and breaking, solvent reorganization, conformational changes, and even chemical reactions. This aids in the study of the stability and complexation time of the NCI system [64–68].

4. Berchmans Protocol for Modelling Non-Covalent Interactions (BerchNCI) 1.0

The proposed protocol, which the author wishes to call BerchNCI 1.0, is a combination of the above methods. Here, we do not propose any new theoretical tools, but use the already available theoretical frameworks in a systematic way to get a better picture of the weak interactions. In our reported papers, we generally optimise the geometry of the molecular assemblies using a DFT with the aid of functionals that can account for dispersion interaction after searching for stable conformations. Later, the interaction energy is evaluated, followed by energy decomposition analysis. The nature of the interaction is well studied using natural bond orbital methods and QTAIM, which help to understand the electronic delocalisation and topological descriptions, respectively. The stability of the molecular assembly is evaluated using *ab initio* molecular dynamics (AIMD). The qualitative aspect of the interaction is evaluated using NCI/RDG plots followed by ELF-based CVB index, IMGH, IRI,

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DORI, etc. In our opinion, this protocol can effectively model all the aspects of weak interactions, like the energy, stability of the molecular assembly, nature of the energy contribution, topological studies, and qualitative aspects of interactions. This may not be an exhaustive model, but we may update the model in the future with exhaustive tools.

5. Conclusion and Future Outlook

This paper proposes the first version of a systematic computational plan, named the Berchmans Protocol for Modelling Non-Covalent Interactions 1.0 (BerchNCI 1.0), for studying NCIs in molecular systems. It starts with geometry optimization using dispersion-corrected DFT, followed by calculating the interaction energy and performing LED to understand the separate contributions of forces, followed by the use of NBO analysis and QTAIM for a detailed electronic and topological description of the interactions. The qualitative picture is supported by visualization tools such as the NCI index and the IGMH method. Finally, AIMD is used to check the stability and movement of the assembly over time. This sequence allows us to model all significant aspects of weak interactions, including their energy, stability, nature of energy contribution, and qualitative appearance. We present BerchNCI 1.0 as a standardized tool for analyzing the competition and function of NCIs. Since this is the initial version, the protocol may be updated in the future based on feedback from the scientific community and further testing of the methods' accuracy and limitations. However, the accurate data generated by this comprehensive protocol is important because it provides the essential high-fidelity information needed to train future ML models for predicting molecular properties.

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