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Unraveling Protein Assembly: The Interplay Of Hydrogen Bonding, Dispersion Forces, And Π-Interactions

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Abstract:
Biomolecular stability, assembly, as well as its functions rely on the interplay between hydrogen bonding and dispersion forces. Hydrogen bonds shows both structural specificity and directional stability, as seen in DNA base pairing, whereas dispersion forces reinforce stability through non-specific interactions like base stacking as well as protein folding. Despite its low strength, dispersion forces cumulatively enhance biomolecular resilience. Computational tools such as the Non-Covalent Interaction (NCI) index helps in visualizing these interactions by analyzing both reduced density gradient (RDG) and electron density (ρ). Understanding these forces is very essential for the advancement of biomolecular research, drug design, and biomaterials engineering.

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I. Introduction:

Non-covalent interaction, majorly divided into hydrogen bonding and dispersion forces, is the backbone of the biomolecular structures. The interplay between hydrogen bonding and dispersion forces is fundamental to the structural organization, stability and functionalities of biomolecules.[1-4] These non-covalent interactions shape the three-dimensional architecture and dynamic properties of macromolecules such as proteins and nucleic acids.[5-7] Hydrogen bonds, being a specific type of dipole-dipole interaction, occur when a hydrogen atom covalently bonded to an comparatively more electronegative element (such as oxygen, nitrogen, fluorine) interacts with another electronegative species.[7-8] With bond energies ranging from 1 to 40 kcal/mol, hydrogen bonds are generally stronger than dispersion forces.[5, 9] In biological systems, it plays a crucial role in maintaining macromolecular integrity. For instance, in DNA, hydrogen bonding facilitates precise base pairing, ensuring accurate genetic replication and transcription.[5, 10-11]

Beyond molecular structure, hydrogen bonding also influences physical properties such as boiling points.[6-7] Hydrogen bond network in water is responsible for its unusually high boiling point compared to other molecules of similar size.[12-13] This behaviour is essential for maintaining a remarkably stable cellular environment, which supports biochemical reactions as well as physiological processes.[14-15]

Dispersion forces, or London dispersion interactions, originate from temporary fluctuations in electron density resulting momentary dipoles.[16-17] While individually weaker than hydrogen bonds, these forces are universally present and collectively participate in large biological systems. Its influence extensively increases on surface contact.[18] Dispersion forces stabilize biomolecules by facilitating interactions between non-polar regions and modulating transient associations among polar groups, further reinforcing macromolecular cohesion.[19]

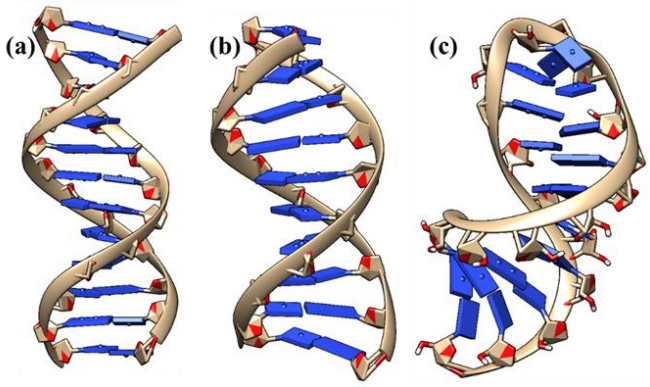

Figure 1: Molecular representations of biomolecular structures corresponding to the Protein Data Bank (PDB) entries: (a) 1D28, (b) 1CGC and (C) 1HlX

Combined effect of hydrogen bonding and dispersion forces create a balanced framework that sustains biomolecular structure and its important functions.[20-21]

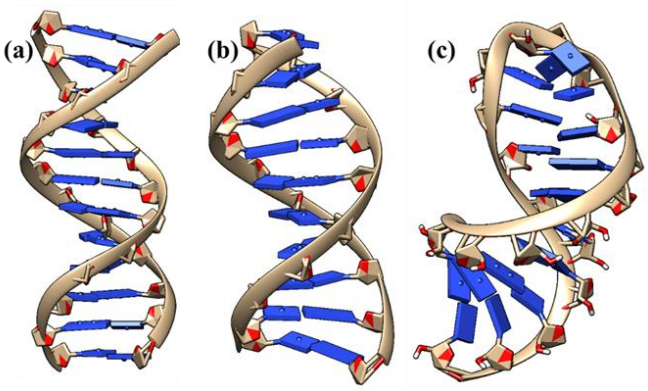

Figure 1 show the molecular representations of biomolecular structures corresponding to the Protein Data Bank (PDB) entries 1D28, 1CGC and 1HlX. Interestingly, these DNA double helix structures are mainly stabilized by cumulative effect of hydrogen bonding and dispersion interaction. Understanding these interactions provides valuable insights into biological processes. At the same time, it has significant implications for fields such as drug discovery and biomaterials development.[22]

II. Result And Discussion:

To explore the significance of non-covalent interactions in biomolecular stability, we have analyzed a representative protein structure (PDB ID: 2D94) and examine the behaviour of the non-covalent interaction in the iconic DNA double helix as a model system.(see

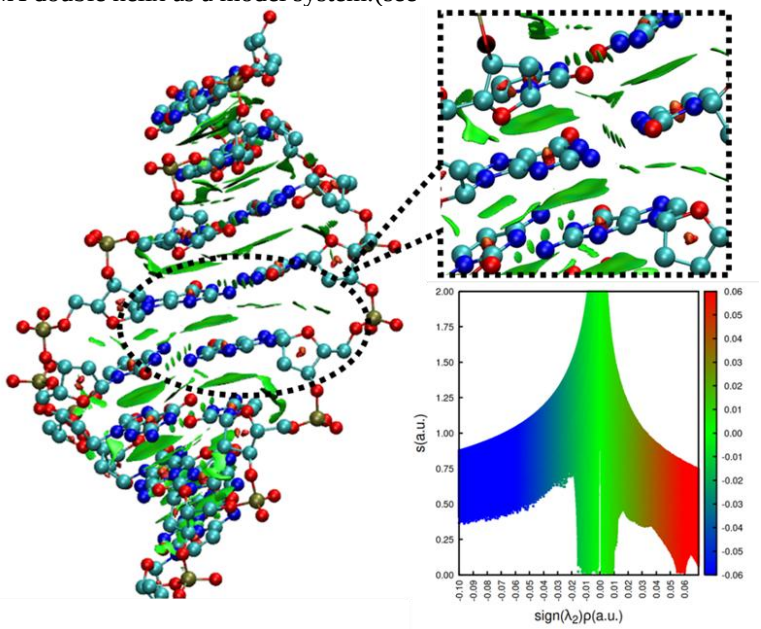

Figure 2) The structural integrity of the DNA and its functionalities rely on the combined effects of hydrogen bonding and dispersion interactions, which work in tandem to maintain its stability and biological efficacy.[2, 23]

Hydrogen bonding serves as the major stabilizing force in the DNA double helix structure by ensuring precise base pairing. Adenine, thymine, cytosine and guanine are the major components, which participate in hydrogen bonding. Adenine forms two hydrogen bonds with thymine, while guanine pairs with cytosine through three hydrogen bonds, reinforcing genetic fidelity.[5] These interactions involve an electron donor (typically nitrogen or oxygen bonded to hydrogen) and an acceptor with a lone electron pair.[24] Their directional nature ensures accurate strand alignment, reducing replication and transcription errors.[6] Additionally, the collective strength of multiple hydrogen bonds provides resilience, allowing DNA to remain stable even in aqueous environments where solvent interactions could otherwise disrupt its structure.[6-7]

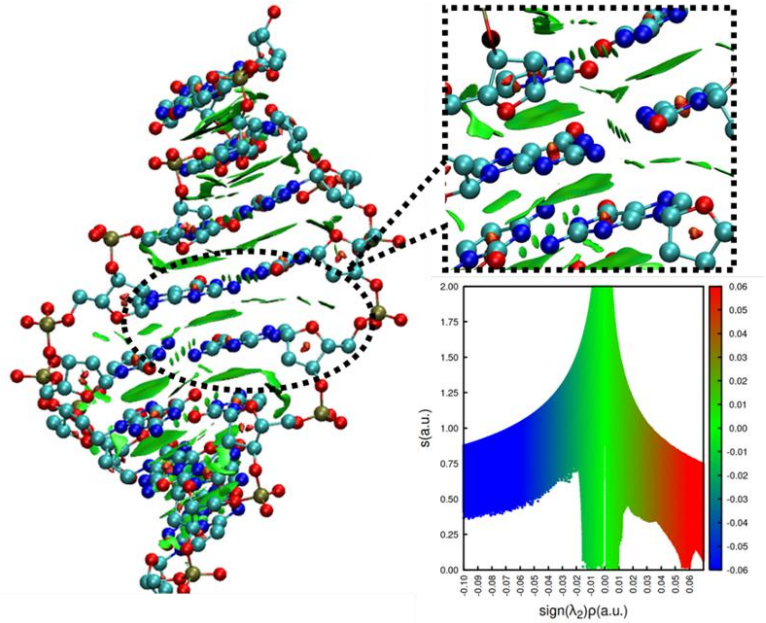

Figure 2: RDG plot as well as its Isosurface extractions of NCI analysis.[25-27]

Complementing hydrogen bonding, dispersion forces is the responsible glue for the base stacking interactions. This interaction contributes a lot to DNA's mechanical stability.[6-7] These interactions arise from transient electron density fluctuations. It further lead to π–π interactions between aromatic nucleotide bases along the helical axis.[28-30] The base stacking thus enhances DNA compactness and mitigates external perturbations. This supports the hydrophobic effect by shielding nucleotide bases from water therefore stabilizing the double helix.[28-30]

A deeper understanding of these interactions can be achieved through computational tools such as the Non-Covalent Interaction (NCI) index, which is shown in

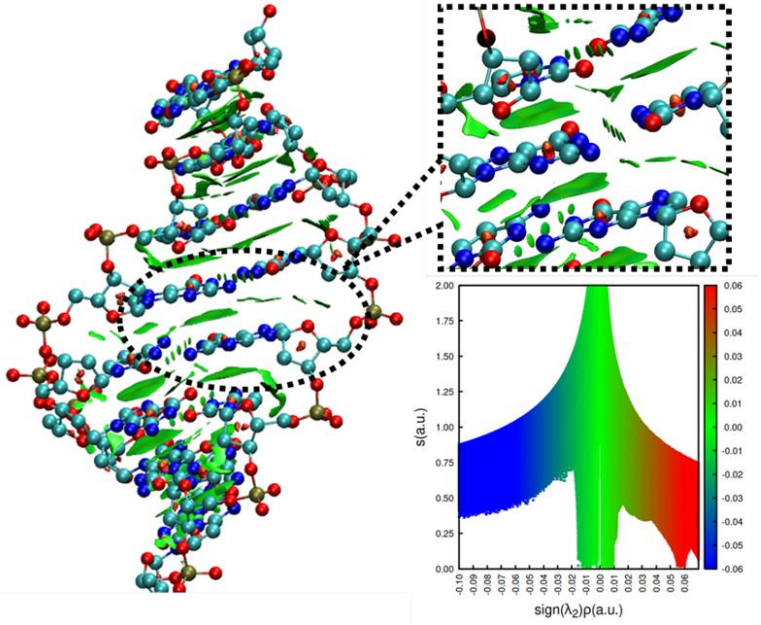

Figure 2. It is implemented using NCIPLOT software.[27] This method employs the reduced density gradient (RDG) and electron density (ρ) to understand various types of non-covalent interactions.[2, 23] In RDG versus ρ plots, the second Hessian eigenvalue (λ_2) serves as a key metric: negative λ_2 values indicate attractive interactions whereas the positive values denote repulsion and values near zero correspond to weak van der Waals forces.[26] These interactions are commonly visualized using color-coded representations. The blue colour represents the strong attractions whereas green is for dispersion forces, and red is for repulsions providing an intuitive means of identifying and characterizing non-covalent interactions in biomolecular systems.[27]

The combined influence of hydrogen bonding and dispersion forces extends across numerous biological phenomena, including protein folding, nucleic acid organization, and enzyme-substrate recognition.[7, 18] Hydrogen

bonds play a fundamental role in stabilizing secondary structures such as alpha-helices and beta-sheets in proteins, while dispersion interactions assist in maintaining tertiary structures by promoting hydrophobic associations among non-polar residues.[31-32] In nucleic acids, hydrogen bonding ensures accurate base pairing, whereas stacking interactions mediated by dispersion forces fortify the overall helical conformation.[28, 33] Enzymatic activity often relies on a dual contribution from these interactions, where hydrogen bonds provide substrate specificity, and dispersion forces contribute to binding stability.[29-30]

III. Conclusion

The balance between hydrogen bonding and dispersion forces plays a crucial role in maintaining biomolecular stability, function, and adaptability. While hydrogen bonds provide specificity and directional stability, dispersion forces reinforce structural cohesion and resilience. This interplay is fundamental to key biological processes such as nucleic acid replication, protein folding, and enzymatic activity. Gaining deeper insights into these interactions enhances our understanding of biomolecular behavior and paves the way for advancements in drug design and biomaterials engineering, where precise molecular recognition is critical for therapeutic and technological innovations.

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