Assessing Time-Dependent Density Functional Theory as a Computational Tool to Model Chromophores Intercalated into DNA Scaffolds

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Abstract

Understanding first-principles energy transport in organic molecules reveals novel energy harvesting systems, quantum computing, and solar power energy transportation and production. DiSC$_2$(5), also named Cy5, exhibits bright fluorescence signals and has shown promising lossless exciton transport properties, as well as tunable energy absorption and emission when conjoined with DNA. This paper focuses on functional groups of organic molecules, specifically the chromophoric red dye DiSC$_2$(5) and its interaction with H- and J-aggregates and with DNA. Density functional theory (DFT) and time dependent density functional theory (TD-DFT) are applied to investigate the chromophore Cy5 in vertically stacked (H-aggregates) and slipped assembly dyes (J-aggregates) arrangements in order to assess computational tools for the prediction of optimized structural characteristics and hypsochromic, bathochromic exciton behavior. Key Words: cyanine, chromophore, Cy5, DNA, quantum coherence, quantum computing, time-dependent density functional theory (TD-DFT)

Introduction

Since the breakthrough of DNA origami proposed by Rothemund in 2006 (2006), a plethora of interesting applications have been examined ranging from energy harvesting systems, photolithography (Beier & Hoheisel, 2000), drug delivery (Farokhzad & Langer, 2009; Shi, Votruba, Farokhzad, & Langer, 2010), organic photovoltaics (Lu, Willner, & Willner, 2013), miniaturization of computing systems (Calude & Paun, 2000; Widengren & Schwille, 2000), to large scale data storage (Cox, 2001; Lloyd, 1993), just to name a few. Nearly a decade and a half after its initial proposition, DNA sequencing costs are in exponential decline and the complexity of nucleic acid nanostructures continue to grow. DNA's unique addressability allows means of producing elaborate systems in which other molecules are attached via strong covalent bonding (Godard, Schmidtke, & Cassiman, 2003). Utilizing organic dyes properties, scientists propose the groundbreaking new means of photosynethic light harvesting antennas, potentially ushering in a new era of biomimetic molecular 'circuits' via photochemical reactions (Staden, 1980).

DNA-based nanoassemblies enable the arrangement of chromophores in well-defined configurations with sufficiently close spaces for coherent exciton energy transfer. It is suggested that excitons could work as carriers of information in quantum computing systems (Barz et al., 2013; Lloyd, 1993). Coherent exciton energy transfer is lossless and sufficiently fast. In order to create these coherent exciton-based devices, it is necessary to develop the chromophore-DNA-scaffold network arrays that enable to exhibit room temperature quantum coherence phenomena. Chromophores are covalently bonded into double stranded DNA (dsDNA). Coherent exciton energy transfer occurs between separated chromophores and is affected by the distance of the chromophores relative to each other.

This paper reviews the current status of computational tools to calculate interacting functional groups of chromophores and its interaction with DNA. Specifically, interacting chromophoric red dye indocrabocyanine-5 or DiSC$_2$(5) molecules aggregate in H- and J-formations and intercalate via covalent bonding into dsDNA arrangements.

Density functional theory (DFT) and time dependent density functional theory (TD-DFT) are viable methods to investigate the chromophore Cy5 in vertically stacked (H-aggregates) and slipped assembly dyes (J-aggregates) arrangements in order to computationally predict optimized structural characteristics, and hypsochromic and bathochromic exciton behaviors. Extensive literature reviews show that traditional XC functionals (functionals

used to approximate electron behavior) used with TD-DFT underperforms when calculating charge-transfer electronic transitions (Adamo, Jacquemin, Laurent, Adamo, & Jacquemin, 2014). Thus, we investigate the utilization of hybrid exchange-correlation (XC) functionals in quantum codes. Hybrid functionals provide sufficient deviations from theoretical and experimental results for the excitation energy and potential energy surfaces (Peach, Benfield, Helgaker, & Tozer, 2008). The sections below present the structures of DNA and Cy5, followed by a review of the current state of computational tools and results provided by DFT and TD-DFT methods, which can advance the understanding of experimental observations and guide future experiments.

Atomic structure DNA (deoxyribonucleic acid)

DNA is a nucleic acid that consists of nucleotide base pairs: adenine (A), guanine (G), cytosine (C), and thymine (T), where base pairs assemble anti-parallel strands in a double helix formation (Watson & Crick, 1953). Base pairs are comprised of a combination of hydrogen, oxygen, nitrogen, carbon, and phosphorus. The anti-symmetric helical strands create two adjacent voids called major and minor grove which are 22 Å and 12 Å wide, respectively (See Figure 1: Atomic Structure of DNA) (Wing et al., 1980). More recently, DNA origami has been discovered as a robust assembly technique that folds a single-stranded DNA template into a target structure by utilizing DNA's unique addressability (Seeman, 2003; Macfarlane, Lee, Jones, & Harris, 2011). DNA shows extreme promise for nanoscale processing techniques, specifically when aggregating with other organic functional groups. Furthermore, DNA nanoconjugates show reversible electrochemical behavior and improved electrochemical performances with respect to bare nanoparticles (Magro et al., 2015).
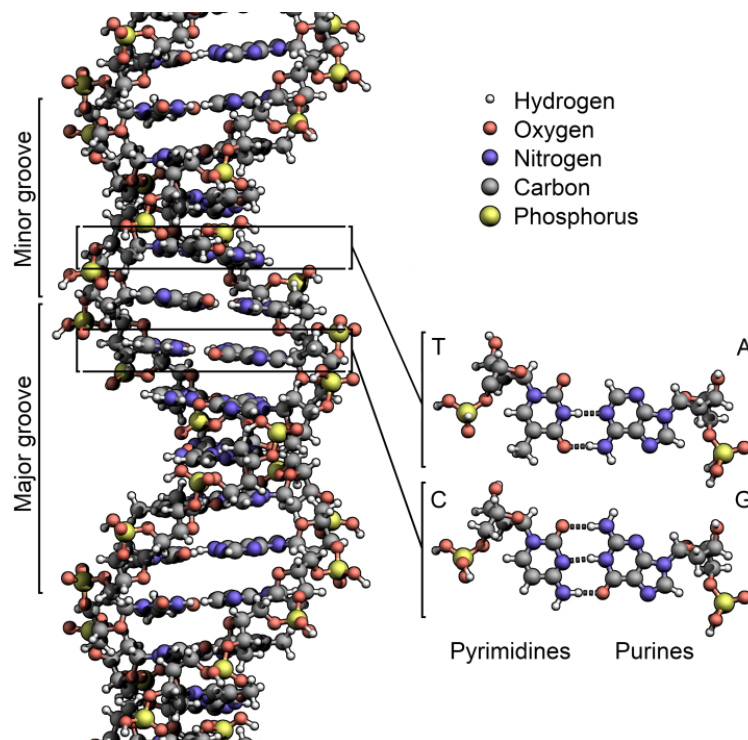

Figure 1. Atomic Structure of DNA demonstrating atomic arrangements, nucleotide base pairs, and major and minor grooves. *Figure Adapted (Zephyris, n.d.)

Cyanine dyes

Cyanine dyes exhibit bright fluorescence signals and hence practical applicable for investigating biological macro-scale interactions. $DiSC_2$ or Cy5 is a carboxyl cyanine flourophore which exhibits far-red spectral range (Maj, Jeon, Go, & Cho, 2012) (See Figure 1: Atomic Structure of Cyanine). Cyanine dyes function as monomers (single molecule) until steric interaction between two molecules are overcome; resulting in the formation of dimers, H-, and J-aggregates.
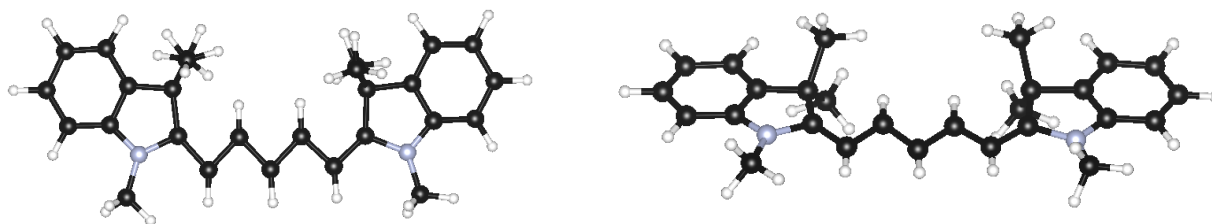
Figure 2. Monomer Cy5 displayed side (left) and top down (right) orientations. C, H, and N atoms are represented as black, white, and blue, respectively.

Dimers are two interacting monomers joined by strong intermolecular van der Waals (Kasha, 1963). H- and J-aggregates are defined as numerous arrangements of the monomer cyanine dyes and functions in two particular configurations of interest, which result in the shifting of absorbance spectrum. Cy5 two motifs are comprised of vertically stacked dyes (H-aggregates) and slipped assembly dyes (J-aggregates) which induce a hypsochromic shift (H-band) and bathochomomic shift (J-band), respectively (Maj et al., 2012). The three primary formations of aggregates are: ladder-type, staircase-type, and brickwork type (Amaresh Mishra, Rajani K. Behera, Pradipta K. Behera, Bijaya K. Mishra, & Behera*, 2000). A discussion of excitonics theory is outside of the scope of this document; however, the reader can refer to Kasha's work for understanding of the Molecular Exciton Model for molecular aggregates (Kasha, 1963).

Methods

Density functional theory

Density functional theory (DFT) is a quantum mechanical electron approximation which estimates the ground state behavior of periodic materials. Popular quantum codes provides a viable way of calculating electron-hole transfer (HT) and excess electron transfer (EET) for $DiSC_2$ and DNA interactions (Šebek & Bouř, 2008). Comprehensive studies of charge-transfer DFT modeling in DNA have been examined in thorough reviews with acceptable statistical deviations (Xifeng Li, Zhongli Cai, & Sevilla*, 2002). Felix et al. has successfully analyzed electronic couples for electron hole transfer in DNA (Becke, 1993). Moreover, while DFT can effectively analyze electron-hole pair, it also provides the excess electron transfer interactions (Becke, 1993). Results for DFT/TD-DFT have proven to be a successful approach in calculations of time dependent properties in many particle systems (Runge & Gross, 1984). Multiple studies have shown strong agreement of hybrid exchange-correlation functionals B3LYP (F Furche & Rappoport, 2005; Harl, 2008; M. A. L. Marques & Gross, n.d.) with empirically derived results, where BH&HLYP and HF overestimated charge transfer (M. a. L. Marques & Gross, 2004). It has also been shown that this method could accurately estimate energy potentials (M. A. L. Marques & Gross, 2003).

Discussion

The following sections firstly review TD-DFT screening articles spanning a breath of well-investigated chromophore systems. H- and J-dimer systems are then discussed with a focus on the Cy5 molecules. Finally, the current state of using time-dependent density functional codes in excited state calculations is addressed.

Benchmark calculations on chromophore systems

Chromophores encompass a large span of classes including but not limited to: carbonyl compounds, polyenes, aliphatic compounds, aromatic hydrocarbons, carbonyl compounds, and nucleobases (Thiel). While the scope of this document focuses on the cyanine chromophore, high-throughput computation screening work by Thiel et al. (Schreiber, Silva-Junior, Sauer, & Thiel, 2008), Tozer et al. (Peach et al., 2008), and Laurent et al. (Adèle D. Laurent & Jacquemin, 2013) offers insight into well-documented benchmark computational data and shortcomings of methods for multiple chromophore classes, including the Cy5 molecule.

Two decades of dye chemistry research utilizing TD-DFT has been presented in Laurent's work (Adele D Laurent, Adamo, & Jacquemin, 2014), including a summary of both seminal works of Tozer et al. and Theil et al. Generally, TD-DFT derived excited state (ES) vertical absorption energies and experimental absorption maxima are overestimated. Filippi et al. has proposed a means to reduce an overestimation of experimental observations ranging from 0.5-1.0 eV to values smaller than 0.3 eV (Filipp Furche & Rappoport, 2005). Hybrid quantum mechanics and molecular mechanics (QM/MM) methods are stated to be the best overall, with a few exceptions to robust hybrid functionals that do not scale well (Bathe-Salpeter Green's function [BSE]). New schemes have recently been developed to calculate the force field with polarization to include the response of the system when a chromophore absorbs light. The article discussed the polarizable continuum model (PCM) (Bansal, Bhattacharyya, & Ravi, 1995), solvent model (SMx) (Salomon-Ferrer, Case, & Walker, 2012), and the three-dimensional reference interaction site model (3D-RISM) (Becke, 1993; Wang, Cieplak, Kollman, & Kollman, 2000), which were widely used in the dye community for their efficiency and ease of use.

Monomer cyanine

Due to the robust nature of the TD-DFT calculation, typical calculations are limited to ~150 atoms (Adèle D. Laurent & Jacquemin, 2013). Works by West and Pearce reported experimental data on the dimer state of the 3,3-diethylthiacyine series (See Figure 2: Monomer Cy5 displayed side (left) and top down (right) orientations), identifying that the dimerization is greatest when the conjugated carbon length of the Cy5 derivate are closest to one vinylene group (West & Pearce, 1965). Scott and Radom reported that most errors in predicting vibrational and NMR (nuclear magnetic resonance) data can be corrected linearly (Hedegård, 2017). Further works by Zutterman et al. confirmed appropriate linear corrects can be made between experimental and TD-DFT to produce reasonable estimates, and vibrational modes can be mapped on the Cy5 structure using the BH and HLYP exchange-correlation and the Doktorov scheme (Champagne, Guillaume, & Zutterman, 2006). Hedegård's et al. proposed the ability to calculate the oscillator strength and excited state utilizing CAS short-range DFT (CAS-srDFT) (Hedegård, 2017), avoiding the well-known error of double-counting correlation effects, but it only works for small numbers of atoms (Hedegård, 2017).

Cyanine aggregates

Due to the minor energetic differences of aggregate formations, often research is directed towards utilizing the aggregates with a template (nucleic acids (Gibbs, Tinoco, Maestre, Ellinas, & Pasternack, 1988), peptides (Kobayashi, 2012), lipid assemblies (Yoo, Ozawa, & Nakashima, 2011)) to control growth.
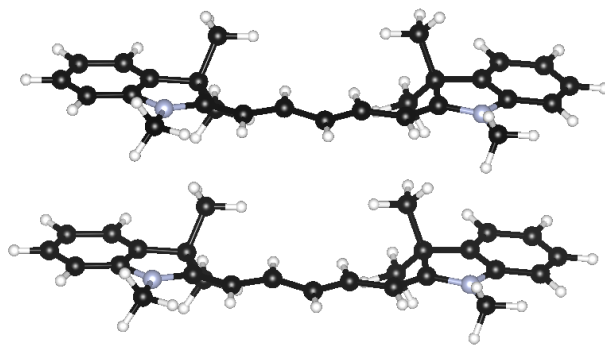

Figure 3. Two monomer cyanines stacked in H-dimer formation. C, H, and N atoms are represented as black, white, and blue, respectively.

However, the fundamental understanding of the self-association of cyanine dye is important in understanding chemical kinetics and photophysical effects. Nonetheless, computational studies of H- and J-aggregates using TD-DFT are significantly lacking. It is well known that subtle changes in structure of H- and J-assemblies result in dramatic shifts in absorption peaks (Asanuma, Fujii, Kato, & Kashida, 2012). I techniques that allow comparison

66

with typical techniques, such as NMR, correlation spectroscopy, and absorbance peaks data, would prove useful in providing novel and tunable photochemical behavior.
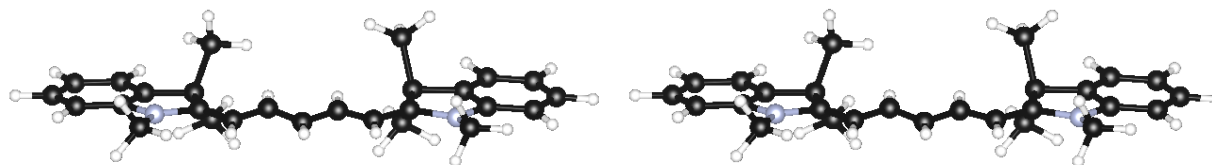

Figure 4. Two monomer cyanines in J-dimer formation. C, H, and N atoms are represented as black, white, and blue, respectively.

Cy5-conjugated DNA systems

DNA has gained significant interest from the (bio)organic dye community recently due to its unique assembly properties. DNA primarily functions as a template for aggregated dye molecules by two different means: (1) spontaneous bonding in the minor groove of DNA, (2) intercalating into the DNA sequence via organic linkers. Maj et al. thoroughly examines (1) with the utilization of molecular dynamics (MD) and TD-DFT methods to much success, by providing computational results in three models: electrostatic potential (TrESP), transition density cube (TDC), and fragment excitation different (FED) (Maj et al., 2012). The focus of this document is directed towards (2) and tools to calculate the excited states of covalently bonding cyanine dyes with the DNA structure.

Haner et al. explored cyanine dyes integration into A-C and T-G groups with organic linkers, establishing that electrical properties are uniform for H- and J-aggregates when binding to polymeric DNA (Ensslen & Wagenknecht, 2015). Peteanu et al. explored circular dichromism, an underreported computational result for TD-DFT, on J-type dimeric assemblies and reports on increased intensity of CD (circular dichroism) effects in a DNA duplex (Rachel A. Garoff, Elizabeth A. Litzinger, Rebecca E. Connor, Irene Fishman, & Armitage*, 2002). Asanuma and Kashida performed extensive work on cyanine dye systems intercalated into DNA (Kashida & Asanuma, 2012). Two useful publications by Asanuma were released in 2012 that provided insight into experimental techniques for control of interaction of chromophore by DNA design sequencing and resultant interactions of the sequenced dyes (Asanuma et al., 2012; Kashida & Asanuma, 2012). The articles extended the methods of the DNA duplex in order to control the orientation and sizes of dye aggregates and comprehensively compared theoretical predictions with experimental results of the H-aggregate cyanine dye. Asanuma reported that simple point-dipole model resulted in a large quantitate gap between experiments and could be attributed to the asymmetric structure of the dyes used and an oversimplified theoretical model (Asanuma et al., 2012).

Current state of cyanine and cyanine-DNA research

Although photochemical reactions show strong promise for novel materials, there are several drawbacks to large biochemical systems for photosynthetic light-harvesting. For the development of tunable photochemical reactions, one must understand sophisticated multi-chromophoric assemblies used to regulate and concentrate photoexcitations for a wide spectrum of irritancies. Experimental synthesis is still lacking in viable means for design and synthesis of a well understood antenna capable of replicating a system of numerous chromophores (6-10 molecules). Furthermore, it is understood that spatial and energetic cascades play an impactful role on the final effectiveness of energy producing reaction centers. A new interesting development suggests that quantum coherence may play a significant role in energy transfer mechanisms, which were produced using two-dimensional spectroscopy experiments (Collini et al., 2010; Collini & Scholes, 2009; Engel et al., 2007; Panitchayangkoon et al., 2010).

Extensive calculations are reported that examine the ground state (GS) and excited state (ES) of monomer chromophore dyes by large computation screens (typically with the CASPT code (Jones, 2015)). Computational research on H- and J-dimers, aggregates, and intercalated DNA is still significantly lacking. TD-DFT is computationally expensive and is likely to be primary reason why H- and J-systems have not been thoroughly investigated (Adèle D. Laurent & Jacquemin, 2013). Another shortcoming of TD-DFT is that the exchange correlational is often double counted with traditional codes, even with the inclusion of hybrid pseudopotentials (Jacquemin, Wathelet, Perpète, & Adamo, 2009). Proposed long-range-corrected hybrids (LCH) (Jacquemin et al.,

2009) allow for a fraction of the exchange correlation to be counted depending on the interelectronic distance (Jacquemin et al., 2009). Even with the inclusion of benchmarked methods, each unique system requires a different XC functional and there is no ideal method for each calculation—the need then arises to optimize XC functionals for each family of dyes and assemblies.

Nonetheless, TD-DFT provides a direct solution to time-dependent Schrödinger's equation, which was formally far too demanding for solving a direct solution. Paralleling experimental needs into the understanding of: photo-absorption cross sections of molecules and nanostructures, electron-ion dynamics in the excited state triggered by either weak or intense laser fields, application into new biological systems (chromophores), transport phenomena, optical spectra of solids and low-dimensional structures, TDDFT has met the challenges and continues to evolve with the current needs of experimental scientists (Rubio & Marques, 2009). Extensive benchmarks provide accurate estimates and show reasonable results for over 500 organic system (Adele D. Laurent et al., 2014). TD-DFT remains a viable means to predict max absorption behavior, electron-hole transfer and excess electron transfer, and circular dichroism (Asanuma et al., 2012).

Vertical contribution

TD-DFT articles primary report theoretical findings for vertical absorption energies, often notated as $E^{vert-absorb}$. The eigenvalue of the excited states and ground state are both calculated, E^{ES} and E^{GS} along with rotatory strength, R^{ES} of the excited states and the difference taken:

$$E^{vert-absor} = E^{ES}(R^{ES}) - E^{GS}(R^{ES}). \qquad (1)$$

These vertical contributions are often compared to λ_{max} and are relatively easy results to calculate because they are a direct output from the eigenvalues and eigenvectors of excited state and ground state. This method can easily be obtained from most *ab initio* packages. Although typically this value is underestimated, the max absorption still calculates in correct order per system so qualitative data may be extracted (Kuwahara, Kudo, Morisato, & Ohno, 2011).

Electron density differential

The concept of mapping the charge density of the ground state and comparing it to the excited states varies little from the vertical contribution. The only real difference is how the data is analyzed. Examining the perturbed time dependent electron density and comparing it with the ground state density and plotting selected HOMO with the lowest singlet $\pi\pi^*$ excited state, results in the understanding in which molecular orbital is responsible for the HOMO-LUMO transition (See Figure 3: Example of electron density of butadiene with π orbitals).
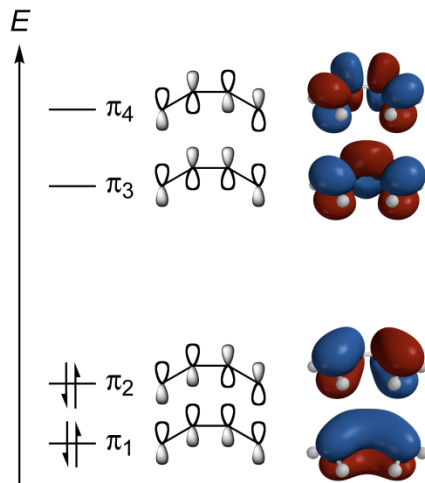

Figure 3. Example of electron density of butadiene with π orbitals. *Figure adapted.

Simulated CD

The calculation of the circular dichroism (CD) and optical rotatory dispersion (ORD) is extensive and beyond the scope of this document so only methods to obtain the data will be presented here. Most publications use built-in analysis tools that come with their density functional package that provide viable means of generating CD data. Two specific software, Gaussian and Q-CHEM 4.0, are mentioned in several studies (Shao et al., 2015).

Conclusion

This paper discusses the current state of photochemical materials science and the need for time dependent computational tools. The structure of DNA and cyanine are introduced followed by DFT, TD-DFT and variations of methods. DFT and TD-DFT are examined to investigate the chromophore Cy5 in vertically stacked (H-aggregates) and slipped assembly dyes (J-aggregates) arrangements in order to assess computational tools for the prediction of optimized structural characteristics and hypsochromic, bathochromic exciton behavior.

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