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Understanding the Use of DFT-Based Molecular Dynamics In Computational Biology

Short title: Understanding the Use of DFT-Based Molecular Dynamics

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ABSTRACT

Density-functional theory-based molecular dynamics is quickly becoming a go-to tool for biological and chemical models. In this article, we revisit the method's roots and explore its utility in practical contexts, as well as its present constraints and new helpful expansions. The importance of density functional theory molecular dynamics (DFT-MD) in the simulation of living systems is growing in significance. When it comes to solving many-body issues in quantum physics, the density functional theory is a powerful instrument. We discuss the benefits and drawbacks of the DFT-MD strategy, as well as its potential application as a complementary tool. Methods for future computations are outlined, and recent uses to systems of molecular and pharmaceutical relevance are addressed.

Keywords: Density functional theory, Molecular, Biology, Computational, Atoms

I. INTRODUCTION

Density functional theory is a tool used in solid state physics and chemistry for calculating and analyzing the electrical structure of quantum and solid-state systems. It combines elements of both quantum physics and classical molecular dynamics. "Quantum physics is used to explain the most important parts of a system." When the proper criteria are used, this technique is typically very precise. In order to account for the leftover elements, DFT employs molecular physics force fields. Due to the fact that this technique is not being applied to the focal area, it does not have to be as precise. Due to developments in DFT at the end of the 20th century, it is now used in many different areas of chemistry and physics. Recently, these computations have been applied to the description of chemicals in living organisms. However, even the smallest elements examined in biology are typically much larger than their physical science counterparts. If other Ab inito techniques were used, the processing expense would be prohibitive. DFT can be used for these massive systems because it strikes a nice equilibrium between precision and processing expense.

In the beginning, it was Hohenberg and Kohn who laid the groundwork for DFT. Based on Schrodinger's equation, they theorized that the ground-state energy is a special functional of the electron abundance. Minimizing the energy of the system in terms of the electron density also yields the energy of the system in its ground state. A methodical approach to chart the many-body issue, this

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offers a more attractive and flexible option. DFT considers all of the possible relationships between the system's components. It is often challenging to compute and understand the system's exchange energy and connection energy. Therefore, DFT, a potent mathematical instrument, is able to generate estimated forecasts of these terms and adds to a more precise ground state energy term. Constant research is being done to find solutions to DFT's issues. Problems have also been solved by employing densities functionals with more parameters.

There has been a recent boom in the application of DFT and DFT-MD techniques to problems in chemistry and materials science. Their use in science and biology, on the other hand, is just getting started. Evaluations of numerical strategies, such as merging DFT and conventional methods as a specific example of combined quantum-mechanical (QM) and molecular-mechanics (MM) approaches, or deriving crucial electronic factors for use in force fields and that are transferrable to bigger systems.

APPLICATION OF DENSITY FUNCTIONAL THEORY IN BIOLOGY

Density functional theory has only lately found a use in the study of complicated living processes. Consider the energy level of an enzyme before it attaches to its target. When an enzyme attaches to its substrate, a certain amount of energy is transferred to the enzyme, and when the enzyme drops its substrate, a different amount of energy is transferred. Each system state's unique energy terms can be calculated using DFT. Because of this, we can now begin to comprehend the energetics of protein networks. The energy barrier between a functional and misfolded protein can be calculated by selecting the high priority sections of the protein and applying DFT to different states. Therefore, the location of protein misfolding could be identified, which would aid studies of tumor development. The density functional theory has a wide range of potential applications. Several advances in our understanding of the complexity of biological systems have necessitated the introduction of density functional theory. Instead of relying on the force field situation, we need to learn the function of interatomic interactions and how to describe them correctly. The primary cause is that modeling a living system entails simulating a large number of events that are occurring concurrently.

II. REVIEW OF RELATED STUDIES

Kushwaha, Anoop. (2022) As more efficient methods and more powerful computers have become available, the scope and variety of first-principles density functional theory (DFT) uses have grown significantly in recent years. In order to anticipate and understand the behavior of complicated systems on the atomic scale, DFT is widely used in the fields of condensed matter physics, chemistry, materials science, and biology. Specifically, DFT is widely applied to study the effect of dopants on phase transformation, magnetic and electronic behaviour, spin and charge transport properties, etc. in material science/condensed matter physics; geometrical and electronic structure, dynamics, spectral hyperfine-interaction, excited-state, etc. in chemistry; interactive behaviour, bond formation and breaking, stabilization, etc. in the biological system. Additionally, a liquid is incorporated into the solvation models for realism and precision. Understanding the fundamentals of DFT is necessary for using DFT-embedded instruments for studying physical, molecular, and biological systems, including Gaussian, the Vienna Ab initio software program (VASP), Quantum espresso, and others. Because of this, I have condensed the details of DFT, including the basis set and solvation models, into a concise and accessible outline.

Mukhiemer, Sami. (2021) In the study of atomic, molecular, crystal, surface, cluster, and solid state physics, density functional theory (DFT) is a common tool. The purpose of this endeavor was to introduce the reader to DFT, examine the history of DFT's evolution into a time-independent theory, and create two potential DFT uses.

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Cole, Daniel & Hine, Nicholas (2016) The calculation of molecular structure using density functional theory (DFT) is now commonplace in physics, materials science, and chemistry. However, conventional DFT has a number of limitations that make it impractical to apply to issues in the biological sciences, primarily due to the unfavorable growth of the processing e ort with system size. In this article, we take a look back at some of the most significant software and utility advancements that have opened the door to performing illuminating electronic structure computations on systems with thousands upon thousands of atoms. Here, we provide an overview of the earliest uses of large-scale DFT for computing electronic characteristics and structures of biomolecules, as well as for solving fundamental issues in enzymology, metalloproteins, photosynthesis, and computer-aided drug design. "Our goal in writing this study was to show how close we are to being able to describe cellular structure-function connections using only first principles."

van Mourik, Tanja et al., (2014) Density functional theory (DFT) has gone from being an emerging figure to a significant participant in the field of computational quantum chemistry over the past few decades. In this Theme Issue, published fifty years after the Hohenberg-Kohn theorems that established the basis of modern DFT were first published, we discuss the successes and difficulties of the field as it stands today. This Theme Issue is not meant to be exhaustive, but rather to provide a taste of various facets of DFT.

Burke, Kieron. (2012) The amazing achievements of density functional theory (DFT) cannot be overstated. Due to its cheap processing cost and practical (but not yet molecular) precision, DFT is now a common method across the board in the chemical and materials sciences. Problems with electronic structure are being worked on in a wide range of disciplines right now. "However, DFT suffers from a number of drawbacks in its current state, including the need for too many estimates, inability to predict highly coupled systems, being too sluggish to predict liquids, etc." This viewpoint considers both completed and continuing tasks.

III. DFT–MD/MM APPROACH

Warshel and Levitt's seminal work from the late 1970s presented the ideas underlying QM/MM techniques, of which the ‘modern’ strategy merging DFT and MM is a particular example. Aimed especially at the simulation of enzymatic reactions, the QM/MM approach consists in partitioning the enzyme into two subsystems in order to treat the portion directly involved in the catalytic reaction at the QM level (the QM subsystem); the remainder, where events such as bond breaking and bond formation do not take place, is represented with an MM force field (the MM subsystem). QM/MM techniques require clever handling of the link between the two components, despite the simplicity of the underlying theory and the lack of specialized numerical skills required for actual application. Apart from the specific force field used for the MM subsystem and the specific method (theoretical as well as computational) used for the QM subsystem, the model chosen for the description of the interface and the definition of coupling as well as of the information to be exchanged comprise the distinguishing features of the various applications deployed so far.

As a logical expansion of the CP technique, several efforts have been made to merge the DFT-MD and MM approaches, with the CPMD code for the QM portion interfaced with conventional force-field codes. An interesting example of applications to biologically relevant systems is that of exploiting the possibility of comparing, within the same framework, the activity of a real enzymatic system treated with the hybrid approach to that of low-molecular-weight analogs (biomimetic compounds) treated fully at the DFT level. This line of inquiry has led to the realization that tiny synthesized analogs can be developed that replicate the activity of the actual system, as in the case of

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the copper enzyme galactose oxidase. This was based on the identification of a structural difference between a real synthetic analog that renders it much less active than the real enzyme, and also on the fact that in these calculations the structural and electronic properties of the QM portion (~80 atoms) appear to be insensitive to the behavior of the MM region.

However, as stated above, it is only when much bigger systems are handled, on the order of a few hundred to a thousand atoms, that the benefit of using DFT and in particular the plane-wave method (as in CPMD) for the QM component becomes apparent. In fact, increasing the size of the system to be modeled does not imply simply that one can explicitly treat a larger number of atoms around the active region at a higher level of theory, but rather that the problem of 'how to treat the interface' becomes much less critical because the MM subsystem is farther away from the active region. Indeed, it should be emphasized that most of the problems encountered in QM/MM applications that are related to detailed modeling of the interface, such as the definition of the constraints that must be imposed on the frontier bonds to avoid artifacts in the chemical behavior of the system, arise from the limited size of the QM component, or at least are greatly amplified. Moreover, the method based on plane waves permits a clearer definition of the orientation of the electronic wave functions, and it eliminates the precision issue linked to the basis superposition error, in comparison to a QM approach using localized functions.

Recently, we have considered BamHI within the DFT-MD/MM framework. BamHI is a prototypical Type II restriction enzyme, and it is responsible for a specific fragmentation of short DNA segments on both strands, resulting in 59-phosphate and 39-hydroxyl groups. The structure of BamHI-DNA compounds has been revealed by numerous experimental structural investigations. Although some speculations have been made about the process of the catalytic reaction, much remains unknown. It is well established, for instance, that divalent metal particles like Mg, Mn, Co, Zn, or Cd are necessary for the catalytic processes to take place. Ca, on the other hand, inhibits the enzyme process for unknown reasons, while the rest of them function as catalysts whose differences lie only in their catalytic effectiveness. It's obvious that we can't treat metal ions like point charges, and if we make any suppositions about the difference between the cations, we could potentially skew the results. We have chosen to use DFT-MD/MM calculations to examine BamHI in tandem with Ca and with Mg to address these issues, which requires an ab initio method.

Using laboratory data to inform our modeling and calculations, we were able to determine that the catalytic reaction causes only small structural changes in the BamHI-DNA complex. The RMS variation for the C locations is only 0.33 between the pre-reactive structure measured with the blocking calcium ion and the post-reactive structure measured in the presence of Mn. As shown in Figure 1, we started with the complex in its pre-reactive state with Ca as the starting arrangement and then performed local optimization within our strategy to further improve its overall structure.'

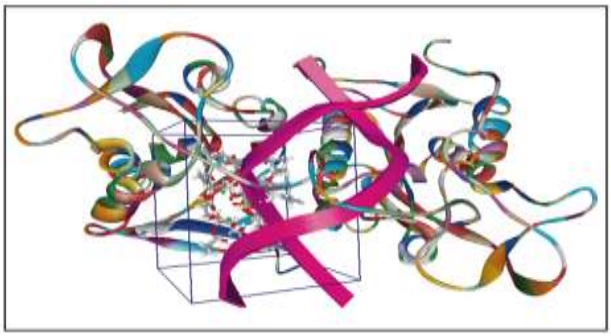
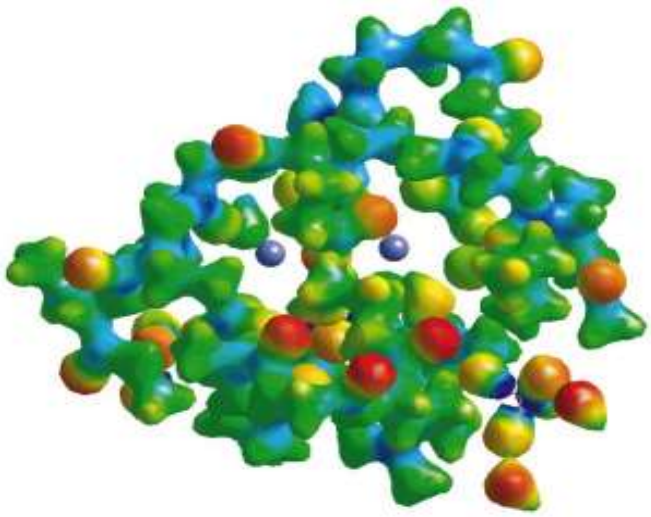


Figure 1: Structure of the BamHI–DNA complex. The 'ball-and-stick' model within the box represents the QM subsystem

ISSN: 0975-3583, 0976-2833 VOL12, ISSUE05, 2021

Only 297 atoms (the protein and DNA backbone, plus crystalline water molecules and metal atoms) out of a total of about 6,000 were included in the QM component. "The complex was first solvated in water and equilibrated with GROMOS computations employing the SPC model, after which its shape was locked in place." Including electrostatic and Van der Waals interactions allowed us to account for the influence of the MM component, which was treated as a spatially set environment and encircled by an extra 2300 water molecules. The QM atoms' electrostatic potential was plotted over a three-dimensional grid, produced by MM atoms and computed with the standard GROMOS96 force-field charges. Due to the lack of structural alterations during the reaction, this computation needed to be run only once. At each iteration of optimization or MD, however, Van der Waals contacts between QM and MM elements were determined. "The GROMOS96 6-12 Lennard-Jones potential with a limit of 10 was used to symbolize these. During the full exercise, hydrogen atoms were used to completely fill the open bonds of the QM atoms at the QM/MM interface, thereby stabilizing the interface." This simple modeling of the interface was made possible by two considerations: on the one hand, the large size of the QM system (the atoms of the active region are at least 5 Å away from the interface), and on the other the a priori knowledge that the structure of the MM region is quite insensitive to the reaction. In conclusion, in the above scheme, the electronic structure of the QM portion is optimized under the influence of the MM system, represented by the electrostatic potential, and the updating of the atomic coordinates takes into account the Van der Waals contribution of the interaction with the MM atoms. There is little to no difference between the optimum structure of the pre-reactive complex with Ca and the experimental one. The RMSD calculated for all QM elements (water not included) is 0.2 /atom, while the Ca-Ca distance is constant at 4.3 and the Ca-O distance varies by only about 0.1. As predicted, the Mg-O lengths decrease by an average of 0.3 when Ca is substituted by Mg, but the total RMSD value, as computed above, comes out to be roughly 0.2 /atom.

One possible explanation for the dissimilar catalytic behavior of Ca and Mg is that Ca is more likely to contribute two electrons. However, it can be shown without a doubt that this is not the case by examining the computed electrical structure of the pre-reactive shapes. Two valence electrons are lost in either case, and the shifted charge is distributed across the protein in much the same way. Figures 2(a) and 2(b) show the electrostatic potential plotted on an isodensity hypersurface for the two instances, revealing the remarkable resemblance between the two.



(a)

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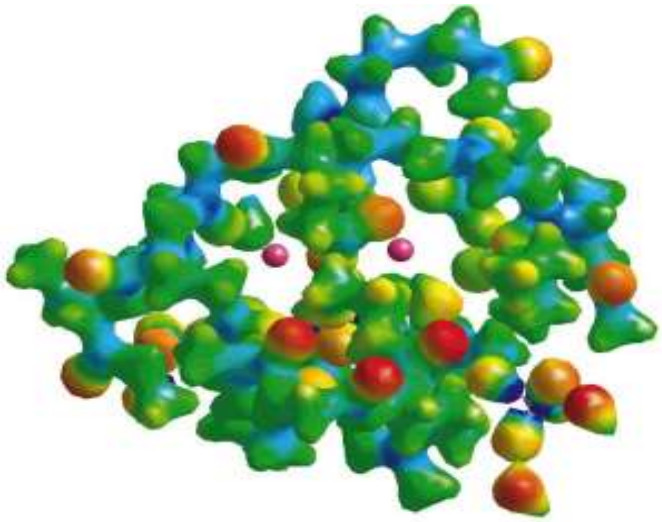

(b)

Figure 2: BamHI–DNA complex, depicting the QM subsystem: Electrostatic potential (using the convention of Figure 1 and mapped onto an isodensity surface) for the two choices of metal ion cofactors: (a) Ca; (b) Mg

Observing how and where the QM subsystem's charge distribution shifts as a result of its interplay with the MM subsystem is of analytical interest. The contrast between the QM area's electron density (also depicted on an isodensity surface) in isolation and after interacting with the MM region is shown in Figure 3. The change is significant, particularly considering the near proximity of DNA to the reactants. "Therefore, the ;300-atom component requires more than just a quantum mechanical approach."

We are presently simulating the cleavage reaction, which should provide usable insights into the mechanism of the catalytic reaction, and in particular the reasons why Ca cannot be used as a coenzyme.

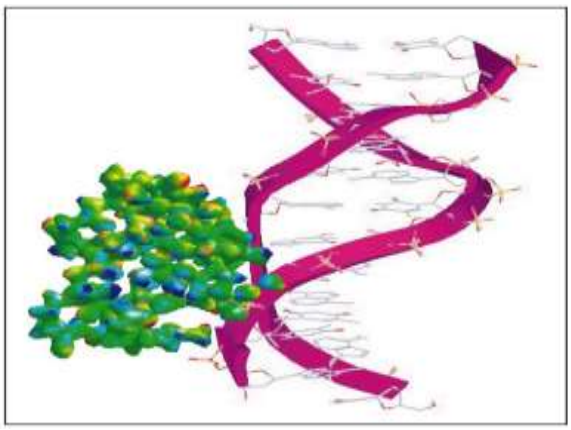

Figure 3: BamHI–DNA complex, depicting the electron density difference between the isolated QM and the QM system coupled with the MM system

IV. CONCLUSION

Increasing recognition of the worth and significance of computer models in biology is a sure sign of this. In addition, it is widely accepted that advancements in both technology and software are required for any appreciable effect to be realized. For the latter, not only will new codes be needed, but also new methods. From the scientific point of view, it is clear those computational chemistry methods,

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and in particular the combination of quantum-mechanical and molecular-dynamics methods, could make a difference by providing the degree of accuracy, reliability, and transferability that force fields generally do not offer. Science disciplines like chemistry and physics have made frequent use of this technique. Density functional theory is a potent instrument for studying complicated living systems due to the high number of interactions occurring at once.

REFERENCES:-

1. Kushwaha, Anoop. (2022). A Brief Review of Density Functional Theory and Solvation Model. 10.26434/chemrxiv-2022-vlhm0.
2. Mukhiemer, Sami. (2021). Density Functional Theory.
3. Srivastava, Ruby. (2019). Role of Density Functional Theory in 'Ribocomputing Devices'. 10.5772/intechopen.80491.
4. Zaharim, Wan Nurfadhilah & Sulaiman, Shukri & Bakar, S. & Ismail, N. & Rozak, H. & Watanabe, I.. (2018). Density Functional Theory Studies on Guanine and Cytosine. 85-91. 10.5220/0008887000850091.
5. Cole, Daniel & Hine, Nicholas. (2016). Applications of Large-Scale Density Functional Theory in Biology. 10.17863/CAM.1266.
6. Ilawe, Niranjan & Groulx, Marc & Wong, Bryan. (2016). Density Functional Theory Methods for Computing and Predicting Mechanical Properties. 10.1007/978-3-319-33480-6_4.
7. van Mourik, Tanja & Bühl, Michael & Gaigeot, Marie-Pierre. (2014). Density functional theory across chemistry, physics and biology Introduction. Philosophical transactions. Series A, Mathematical, physical, and engineering sciences. 372. 20120488. 10.1098/rsta.2012.0488.
8. Putz, Mihai & Mingos, D.Michael. (2013). Applications of Density Functional Theory to Biological and Bioinorganic Chemistry. 10.1007/978-3-642-32750-6.
9. Burke, Kieron. (2012). Perspective on Density Functional Theory. The Journal of chemical physics. 136. 150901. 10.1063/1.4704546.
10. Andreoni, W., Curioni, A., & Mordasini, T. (2001). DFT-based molecular dynamics as a new tool for computational biology: First applications and perspective. IBM J. Res. Dev., 45, 397-408.
11. DiMasi, J.A.; Grabowski, H.G.; Hansen, R.W. (2016) Innovation in the pharmaceutical industry: New estimates of R&D costs. J. Health Econ., 47, 20–33
12. Yu, W.; MacKerell, A.D. (2017) Computer-aided drug design methods. In Antibiotics; Springer: Berlin/Heidelberg, Germany,; pp. 85–106