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THE DEVELOPMENT OF DENSITY FUNCTIONAL THEORY VIA JACOB’S LADDER FOR GENETIC MOLECULES

Nidaa A . Jasim
Assist Prof .in Physical Chemistry, Karbala Directorate of Education/Karbala / IRAQ, Email : nedaa.aljbory@gmail.com

ABSTRACT

This article provides a comprehensive review of the historical, technical, and methodological development of density function theory, based on the five-stage Jacobian ladder proposed by Purdue. It begins with the fundamentals of density function theory, progressing from the simplest approaches that treat electrons as a homogeneous gas and employ sample approximations, to highly accurate methods that begin by simulating the physical and chemical properties of the electron. The article analyzes how each rung of the ladder contributes to improving the accuracy of calculations relative to the computational cost. First-order modifications begin with the local density approximation (LDA) and progress to more complex degrees (B3LYP), which predict reaction energies and band gaps. Third-order approximations (GGA) currently represent the optimal balance between accuracy and efficiency for most complex chemical processes. This article discusses how each rung of the ladder improves the accuracy of predicting the properties of complex systems and aids in understanding the binding of molecules to nucleic acids and proteins—a crucial aspect of genetics. It highlights current challenges in addressing weak-strength and interconnected systems, while also pointing to the future of integrating artificial intelligence to develop higher degrees of the Jacob s ladder.

KEYWORD: density function theory , **Jacob s ladder**

INTRODUCTION

Density function theory plays a crucial and vital role in the fields of genetics, biomolecules, and understanding chemical reactions at the atomic level . (DFT) is the most widespread and successful method in physics and computational chemistry [1]. It represents a cornerstone of computational chemistry due to its ability to predict and understand the electronic and structural properties of complex molecules. This method strikes a balance between accuracy and cost compared to other methods. [2]. The theory of the two scientists (Hohenberg-Kohn) which functional theory is based shows that the properties of the quantum system and the total energy can be accurately determined by relying on the electron density instead of dealing with the complex wave function [3]. The first while the second theory posits ;theory posits that the external potential is a unique function of the electron density that the true electron density is for the ground state [4]. The Kohn-Sham approach (1965) is to highlight complex quantum systems and simplify the multi-electron problem and the basic idea instead of solving the complex Schrödinger equation containing N electrons (which depends on the 3N coordinates) into a hypothetical system containing three coordinates (x,y,z) . The electron density in a real system is represented by individual orbitals (Kohn-Sham orbitals).

For a non-reactive system. Then the Kuhn-Sham equation [5], which is similar to the Hartree-Fock equation, is solved, and the densities of these orbitals are summed to obtain the total electron density of the system. Despite the accuracy of Cohn-Sham's approach, the precise equation for exchange potential and correlation is unknown. Therefore, chemists rely on different approximations, such as the local density approximation (LDA), which depends solely on local density [6], and the generalized gradient approximation (GGA), which takes into account both density and its gradient to achieve higher accuracy . In 2000, physicist John perdew and his colleagues presented a theoretical framework for the organization and evolution of quantum chemistry , called the Jacob 's Ladder. This framework provided a theoretical and structural basis for the development of functions in terms of accuracy, aiming to move from simple approximations to high-precision solutions approaching the theoretical solutions to the Schrödinger equation[7] , Studying the evolution of density function theory allows us to more accurately and at a lower computational cost determine the impact of genetic mutations and chemical modifications on the stability of biomolecules, making it ideal for complex molecular systems in the world of genetics. Much like the rungs of a ladder connecting Earth to the sky. The ladder represents different levels of approximations: from the terrestrial level and simple approximations (LDA) that describe basic chemical systems , to more complex functions such as Perdew -burke-Ernzerh of 0 hybrid function (PBE0) These hybrid functions give accurate results because they combine the exchange energy calculated by (Hartree-Fock) with the exchange and correlation energies resulting from the GGA (density gradient and the generalized gradient approximation). John Perdreau's work was pivotal in the development of hybrid functions, which helped chemists improve the accuracy of simulating molecules and complex materials [8] . His development included calculating molecular energy using density function theory, moving beyond traditional methods based on local electron density to include electron density and orbital kinetic energy . [9].

Jacob s Ladder

Jacob's ladder in quantum chemistry is a conceptual framework used to describe the evolution in the accuracy of approximations used to calculate the energy of materials and molecules . It progresses from simple approximations (the base of the ladder) to high accuracy (the top of the ladder)[10]

**[1] First Rung (**local Density Approximation **LDA) **:It is the simplest and is used to describe the effect of exchange and correlation depending on the local electron density at a specific point in electronic systems

Main Idea At this level, the exchange and binding energy in electronic systems is described, where it is assumed that the exchange and binding energy of a heterogeneous, multi-density electronic system (atoms and molecules) , at a given point, is exactly equal to the energy of a uniform, homogeneous electron gas of the same density at the same point . The most important functions at this level that depend on electron density , Slater Exchange [11] .

$$E_{xc}^{LDA}[\rho] = \int \rho(\mathbf{r})\epsilon_{xc}^{unif}(\rho(\mathbf{r}))d\mathbf{r}$$

$\boldsymbol{E_{XC}^{LDA}}$ Exchange energy and correlation via an integral function dependent on local density

Exchange and bonding energy per electron in a uniform electron gas

Features and Uses: It is a fast option with lower accuracy, used to calculate the physical and chemical properties of solids, metals, and large systems[12].

Disadvantages:: Overestimation of bond energy, where the bond energy is much higher than reality; underestimation of bond lengths and energy gap, where estimates are much lower than the true values; and its inability to describe van der Waals forces, which is vital in organic and biological chemistry[13].

[2] **Second Rung: (Generalized Gradient Approximation – GGA)**

GGA transcends the first-order limits based on local density to consider electron density variations at each point[14].

Main Idea : While **LDA** assumes a homogeneous electron density **ρ** (a homogeneous electron gas), **GGA** considers that electron density varies and may increase or decrease in real molecules. Therefore, it depends on density and its derivatives **ρ∇** . These calculations are improved by taking into account the heterogeneous nature of electrons. Consequently[15], this approximation provides significantly better and more accurate results than **LDA** in calculating molecular bond lengths, bond energy, and solid structures. It yields excellent results for molecules where bonds are not perfectly Homogeneous **.** the important functions of this levels are Blyp , BP86 , BPEsol , RPBE [16] .

$$E_{xc}^{GGA}[\rho] = \int f(\rho(\mathbf{r}), \nabla\rho(\mathbf{r}))\, d\mathbf{r}$$

□ $\boldsymbol{E_{XC}^{GGA}}$: Exchange and correlation energy approximated to GGA

ρ(r) : Electronic density at point r

ρ∇ Electron density gradient at point r

f : A function that depends on its gradient and density

Features and Application : Its advantages include its reliance on energy gradients, greater accuracy in describing real chemical bonds, excellent results in bond lengths and angles, and its use in calculating the structures of more stable molecules, as well as calculating activation energy and studying the properties of solids such as crystal lattice energy and lattice constants. Its computational cost is considered moderate compared to more complex methods [17] .

Disadvantages : The most notable drawback of this model is the low value of the energy gap in insulators and semiconductors. In addition, it does not accurately describe van der Waals forces. At this level, it is not possible to describe materials in which their electrons are strongly bonded, such as transition metal oxides [18]

[3] Third Rung : Meta - Generalization Gradient Approximation (Meta- GGA)

Main Idea : This degree of calculation of exchange and correlation energy depends on the electron density (**ρ**) , in addition to the Electron density gradient (**ρ∇**) and orbital kinetic energy **τ(r) .** Among the most common functions at this level TPSS (Non-empirical) , M06-L, M05-L (empirical) , MS0, MS1, MS2 (Functions developed to improve the description of minerals [19]**.**

$$E_{xc}^{meta-GGA}[\rho] = \int f(\rho(\vec{r}), \nabla\rho(\vec{r}), \tau(\vec{r}))d\vec{r}$$

$$\tau(\vec{r}) = \frac{1}{2}\sum_i |\nabla\psi_i(\vec{r})|^2$$

ρ(r) : Electronic density at point r
ρ∇ Electron density gradient at point r
τ(r) Orbital kinetic energy

Features and Application : It improves the accuracy of orbital energy calculations and molecular geometry, provides an acceptable description of covalent bonds in organic and inorganic reactions, balances accuracy and cost, and is used in solids calculations , crystal lattice constants, and solid and magnetic structures[20].

Disadvantages The computational cost is slightly higher than GGA because it requires calculating the kinetic energy density derived from orbits, and weak forces (van der Waals forces) are not described. Furthermore, some functionals in this approach overestimate the formation energy in magnetic systems [21].

[4] Forth Rung : (Meta- Hybrid Function)

It combines the Exact exchange of Hartree-Fock (E_X^{HF}) , with the GGA or Meta -GGA Functions (exchange and correlation energy) Functions at this rung such as (B3LYB, PBE0 , HSE06)[22]

$$E_{xc}^{hybrid} = E_{xc}^{SL} + \alpha_x \left(E_x^{HF} - E_x^{SL} \right)$$

E_{xc}^{hybrid} : Hybrid exchange and correlation energy
E_{xc}^{HF} : Exact exchange (Hartree – Fock)
E_{xc}^{SL} Seme -Hybrid exchange and correlation energy (LDA , GGA , Meta- GGA)
E_x^{SL} Part of the local exchange used
α_x : Mixing Coefficient whose value ranges between 1 , 2 in B3LYP equal 0.25-0.20.

Features and Application: It addresses self-reaction errors at lower levels and improves the accuracy of calculations of bonds, energy gaps, and structural properties of complex molecules. It provides an excellent balance between the accuracy of chemical results and computational power[21], It is used in the study of macromolecules, metallic complexes, and the electronic properties of solids[23].

Disadvantages : Its disadvantages include: very high computational cost, as it requires calculations for occupied and unoccupied circuits, making it very slow and expensive when applied to large, complex systems. It also relies on non-local functions and hybrid exchange operators, further complicating its implementation[24].

[5] Fifth Rung :(Double Hybrid Functional)

It represents the peak or "sky" that aims for maximum chemical accuracy in density function theory, and is often called correlation and exchange functions based on unoccupied virtual orbitals (UNOP) or what is known as Random Phase Approximation (RPA)[25] . In the previous four levels (LDA, GGA, Meta-GGA, Hybrids) depended on electron density and occupied orbitals only , in the fifth level information from unoccupied orbitals (Virtual /Unoccupied Orbitals) is incorporated into the correlation and exchange functions . For double hybrid models such as B2PLYP, or RPA (Random Phase Approximation) models[26].

$$E_{xc}^{\mathrm{DH}} = c_x E_x^{\mathrm{HF}} + (1 - c_x) E_x^{\mathrm{DFT}} + c_c E_c^{\mathrm{MP2}} + (1 - c_c) E_c^{\mathrm{DFT}}$$

Double -Hybrid Exchange Correlation Energy E_{xc}^{DFT}
E_x^{HF} Hartree -Fock exchange
E_x^{DFT} Correlation energy resulting from DFT functions (Meta-GGA , GGA)
E_C^{MP2} Second -Order Mollar- Plesset Correlation

E_x^{DFT} Exchange energy derived from local or graded density theories (DFT exchange)
α , b Mixing Coefficients

Features and Application Level 5 represents the highest degree of accuracy, providing results very close to those based on wave functions. It also incorporates unoccupied orbitals into the calculations and provides a precise characterization of hydrogen bonds, combining density function theory(DFT) and disorder Density function theory plays a crucial and vital role in the fields of genetics, biomolecules, and understanding chemical reactions at the atomic level [28] .

Disadvantages : The computational cost is very high because it requires calculating virtual orbits, . theory(MP2). as well as strong sensitivity to correlation and size compatibility problems if not carefully designed [29].

SUMMARY

This article outlines the gradual development of density functional theory (DFT), providing a clear and distinct roadmap for improving functional approximations. DFT has revolutionized the simulation of complex molecules,

enabling the study of complex molecules such as DNA and proteins, from local density approximations (DFT) to functional hybridization and higher levels of the Jacob scale. It has successfully bridged the gap between theoretical and experimental results in terms of computational accuracy and cost. The Jacob scale has also facilitated the study of complex systems that were previously difficult to study experimentally. More recently, we have witnessed significant and widespread development in molecular modeling of systems containing thousands of atoms. The ultimate goal is to reach the pinnacle of development, as described by John Purdue, in the study of complex interactions and systems. DFT will remain the cornerstone of new materials design, with future research focusing on integrating artificial intelligence and machine learning to create novel exchange-correlation functions that transcend traditional scales. Density functional theory will continue to be the most powerful tool in materials chemistry and physicsv

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