COMPUTATIONAL MODELING AS A STRATEGIC TOOL FOR PROMOTING THE PRINCIPLES OF GREEN CHEMISTRY

https://doi.org/10.22533/at.ed.569112531037

Data de aceite: 13/10/2025

Mario Rodrigues Oliveira
Graduate Program In Chemistry (PGQUI), State University of Southwest Bahia, Jequié, BA, Brazil

Erenilson dos Santos Moreira
Graduate Program In Chemistry (PGQUI), State University of Southwest Bahia, Jequié, BA, Brazil

Júlia Ellen Barboza Aguiar
Graduate Program In Chemistry (PGQUI), State University of Southwest Bahia, Jequié, BA, BraziL

Luis Felipe Santana Aguiar
Graduate Program In Chemistry (PGQUI), State University of Southwest Bahia, Jequié, BA, Brazil

Alan Santana Benevides
Department of Science and Technology (DCT), State University of Southwest Bahia, Jequié, BA, Brazil

Jaime Dias da Silva Filho
Graduate Program In Chemistry (PGQUI), State University of Southwest Bahia, Jequié, BA, Brazil

ABSTRACT: Density Functional Theory (DFT) is one of the most relevant methods in computational quantum chemistry, used to study the electronic structure of molecular and solid systems based on electronic density. Originating from the theorems of Hohenberg and Kohn (1964) and consolidated by the Kohn-Sham method (1965), DFT revolutionized chemical modeling by reducing dependence on the wave function, simplifying calculations, and making them less computationally costly. This paper addresses the fundamental principles of DFT, its applications in docking studies, QSAR/QSPR, and green chemistry, as well as its current limitations compared to *ab initio* methods. DFT has proven to be a versatile tool, capable of assisting in yield estimation, toxicity prediction, and the development of more sustainable products, aligning with the goals of modern chemistry and the need to reduce environmental impacts and laboratory risks.

INTRODUCTION

Computational chemistry has established itself in recent decades as a strategic area for understanding complex

chemical systems, reducing costs and risks associated with traditional experimental methods. In this context, Density Functional Theory (DFT) emerges as one of the most important methodologies for studying the electronic structure of atoms, molecules, and solids. Based on the theorems of Hohenberg and Kohn (1964) and the Kohn-Sham method (1965), DFT brought a new paradigm by using electronic density instead of wave function, reducing the mathematical complexity of calculations and making them more accessible for large systems. In addition to its theoretical relevance, DFT has direct applications in different fields of chemistry, from molecular modeling to the design of new materials, interacting with green chemistry principles by enabling more efficient predictions of yield, toxicity, and sustainable synthetic routes. This work discusses the fundamentals, advances, applications, and limitations of DFT, highlighting its growing importance at the interface between materials science, theoretical chemistry, and technological innovation.

DENSITY FUNCTIONAL THEORY

Density functional theory (DFT) is a method of computational quantum chemistry used to study the electronic structure of atoms, molecules, and solids, based on electronic density rather than directly on the wave function. However, it was in 1964, with the publication of the Hohenberg and Kohn theorems, that the use of the method gained legitimacy and became popular in the academic world (Duarte, 2001). Hohenberg and Kohn's theorems show that there is an exact energy functional of electronic density and an exact variational principle for this functional. In 1965, Kohn and Sham developed a way to circumvent the problem of locating the exact energy functional proposed by the theory, called the "KS" method (Duarte, 2001).

The work of Hohenberg and Kohn (1964) states in its first theorem that "the ground state density of a system of interacting electrons, in the presence of an external potential, uniquely determines this potential, that is, the external potential is a density functional." The use of electron density as the main calculation parameter is what sets this method apart from other methods used in computational chemistry to simulate the chemical and physical properties of molecules, according to Lewars (2011):

> If electronic density r, instead of the wave function, could be used to calculate molecular geometries, energies, etc., this could be an improvement over the wave function approach because, as mentioned above, the electron density in a molecule with n electrons is a function of only the three spatial coordinates x, y, z, but the wave function is a function of 4n coordinates. Density functional theory seeks to calculate all the properties of atoms and molecules from the electron density. (Lewars, p. 448, 2011).

In the second theorem, according to Lewars (2011), "any test electron density function will produce an energy greater than (or equal to, if it were exactly the true electron density function) the true ground state energy." From the second Hohenberg–Kohn theorem, we

can conclude that electron density plays a central role in determining the energy of a system in the ground state, functioning analogously to the variational principle applied to the wave function.

This theorem ensures that any trial electron density that satisfies the basic physical conditions will result in an energy greater than or equal to the true ground state energy, provided that the energy functional used is exact. Although, in practice, the functionals used in DFT are approximate and do not always maintain the variational- y character, the theorem establishes the conceptual basis for treating the energy of the system as a functional of density, allowing quantum modeling to become more efficient and less costly than traditional *ab initio* methods (Lewars, 2011).

Thus, the DFT method, consolidated by the calculations and studies of the authors mentioned, presents itself as an excellent option for qualitative research involving molecular computational modeling. In addition to offering reliable results, this method allows for faster processing compared to other methods of quantum chemistry, while also requiring significantly lower computational costs.

TIME SAVINGS, WASTE REDUCTION, SAFETY

Over the years, Density Functional Theory has become one of the most important methods for calculating electronic structure in molecules and solids. Traditional wave function, variational, or perturbative methods can be applied to find highly accurate results in smaller systems, providing parameters for the development of density functionals, which can then be applied to much larger systems. This reduces computational cost and memory space used, establishing itself as a simple and accurate alternative method.

Many docking protocols have been developed to try to assess the probability of various orientations and positions of binding to the substrate. Initially, docking studies were used mainly by the pharmaceutical industry to establish drug binding and interactions and drug interactions with enzymes. However, these protocols can also be used to configure a QM/MM model to insert a substrate into a crystal structure without a substrate prior to minimization. Docking protocols typically use molecular information, including atom types and structure, as well as atomic/atomic/group charges and polarity, and compare the structural characteristics of the substrate with those of the protein surface to establish a lock-and-key match. A popular docking procedure is to use the online server called SwissDock (available at www.swissdock.ch). However, with systems that have hydrophobic active sites positioned far from the enzyme surface or when there is good evidence of the substrate binding position, it may be more advantageous to use one that incorporates grids and thus significantly decreases computation time. The Autodock software package includes “autogrid,” which can be used to drastically decrease the target area within the macromolecule available for substrate binding, while the “ e atomic affinity grid” can assist with substrate orientation. Grids are mainly used to speed up calculations, a goal that can often be aided by limiting the space to be probed.

To improve most QSAR models that predict biological activity for only one endpoint, multi-target QSAR has been suggested as a tool for creating models for multiple endpoints (Prado-Prado *et al.*, 2009; Prado-Prado *et al.*, 2010; Speck-Planche *et al.*, 2010). This design has attractive advantages, as it provides the user with a list of information with expected numerical data for groups of endpoints that affect the phenomenon under consideration, e.g., therapeutic effect, inhibition, biocidal potential, etc. (Toropov and Toropova, 2020).

Endpoints can be expressed through correlation weights of molecular features extracted from SMILES, and their similarities can be a heuristic tool for controlling biochemical knowledge (Toropova *et al.*, 2018; Toropova *et al.*, 2018; Toropova *et al.*, 2017). In principle, the spectrum of physicochemical conditions with a clear impact on biochemical endpoints (toxicity, therapeutic potential) is capable of providing clues for establishing similarity (dissimilarity) for two endpoints relevant to drug discovery, toxicity, risk assessment, and others (Toropov and Toropova, 2020).

CURRENT LIMITATIONS AND CHALLENGES

The *Ab initio* and DFT methods use quantum physics through the Schroedinger equation to obtain both the wave function (*Ab initio*) and electronic density (DFT) in order to describe the atom with greater complexity, as there is a visualization of its orbitals. Both methods are not parameterized, which means that there are no experimental parameters that will assist in obtaining results, although hybrid DFT has values that adjust the calculations, but not experimental ones. This absence of parameters makes the method computationally expensive.

The training of chemistry specialists needs to cover all or most of the options that may be constructive in their future profession and contribute to society, including computational chemistry. However, this recognition has not yet spread sufficiently in education, mainly because it is a new area and requires prior knowledge in various aspects, such as the phenomena that give rise to an infrared spectrum or the physical-chemical interactions of a species. Students' exposure to the potential and practices of this type of exploration between areas remains very inadequate. Undergraduate preparation focuses mainly on the training necessary for students to pass individual course exams, and graduate training focuses on the selected area of specialization. The space for discourse and exploration between areas remains limited or nonexistent (Mammino, 2022).

Even with improvements over the last decade, the QSPR/QSAR technique has some "disadvantageous peculiarities" that still persist. The possibility of "casual correlations," the possibility of overtraining, and the possibility of poor reproducibility of the statistical quality of a suggested approach. These peculiarities have led to other disadvantages of the technique, such as the gradual increase in the number of statistical characteristics used to measure the predictive potential of a model. This diversity of different criteria for predictive

potential is a tool for improving the quality of QSPR/QSAR models. However, this situation sometimes causes uncertainty in choosing the best model, and these contradictions in the recommendations of various criteria force the researcher to seek the best choice in a larger maze of possibilities. Another peculiarity that has emerged is that, naturally, the contribution of molecular structure is of primary importance for a parameter; however, most QSPR/QSAR has been developed without taking into account anything beyond molecular structure. It should be noted, however, that in some cases, molecular structure is not informative for creating a predictive model of endpoints. Meanwhile, defining a model with a mathematical function of experimental conditions, aligned with the molecular structure, is a shorter and, consequently, more attractive way to solve the corresponding task (Toropov and Toropova, 2020).

APPLICATIONS OF COMPUTATIONAL MODELING IN THE PRINCIPLES OF GREEN CHEMISTRY

Estimation of Yield and Byproducts through Simulations

Using computer simulations to predict yield, toxicity, and solvent efficiency is in line with the green chemistry principles of waste prevention, using methodologies that generate products with reduced toxicity, generating effective but non-toxic products, and reducing the potential for chemical accidents, which were introduced by Paul Anastas and John Warner in 1998 (Mohammed; Ali; Errayes, 2020; Rafi, 2023).

Predicting the yields of chemical reactions is a particularly challenging task because it is influenced not only by the variables of the reaction under study but also by all possible side reactions (Saebi *et al*., 2023, p. 4997). Computer-Aided Synthetic Planning (CASP) software such as Reaction Design for Organic Synthesis (EROS) and Chematica stand out for offering innovative and unusual alternatives, making it possible to prevent waste.

EROS assists chemists in identifying active functional groups using reactivity rules and calculations (Joshi, 2023, p. 9094). It is also capable of predicting reactions that have not been made available in the literature and allows the study of organic reactions such as general hydrolysis, amide hydrolysis, and electrophilic substitution (Wang *et al.,* 2021, p. 22). It is based on methods for calculating bond polarity, electronegativity in the molecule, and resonance effects to predict the results of reactions using nominal user-input reagents (Goel *et al.,* 2022, p. 5).

Another software, Chematica, stands out for its hybrid approach based on rules of reactions performed experimentally and published in the literature and network analysis. With a robust database containing millions of compounds and reactions, the system allows manual or fully automatic retrosyntheses to be performed, considering factors such as cost, selectivity, reagent availability, and even the need for protective groups (Engkvist *et al.,* 2018; Szymkuć *et al.,* 2016).

Objectivity in choosing the best route to take for the development of molecules using computer simulations provides a better approach to synthesis by ensuring the prevention of toxic waste formulations, reagent waste, and environmentally harmful by-products.

Toxicity Prediction in the Design of Less Hazardous Products

Through molecular properties, computational chemistry influences the design of products with less or no toxicity. The stages of molecular docking and molecular dynamics allow the selection of favorable structures from a range of possibilities. This ensures that only promising molecules are synthesized for experimental testing (Mammino, 2023).

Quantitative structure-activity relationship (QSAR) models used to predict the biological activity, such as toxicity, of chemicals are useful tools for screening molecules prior to synthesis. These models are based on machine learning or neural networks, where they are trained with structural characteristics and/or physicochemical properties from a large amount of existing data (Krebs; McKeague, 2020).

One proposed tool is ToxinPred3.0, a web server that predicts the toxicity of peptides. It is based on machine learning and deep learning methods that have been trained on a large dataset of experimentally validated toxic and non-toxic peptides (Gupta *et al.*, 2013). The open-source application Toxtree uses machine learning to estimate toxic risks, specifically the decision tree. Toxtree proves to be a useful tool for facilitating the systematic toxicological evaluation of compounds that may pose a risk to human health (Patlewicz *et al.,* 2008).

In silico studies guarantee results in the research and development of new products, as they allow computational modeling, simulation of molecules, and toxicological properties even before synthesis and laboratory testing. This guides researchers in the generation of effective non-toxic products or products with reduced toxicity to human health and the environment.

CONCLUSION

Density Functional Theory has established itself as one of the most powerful and accessible approaches in modern quantum chemistry, balancing reliability and computational efficiency. Despite its challenges, such as dependence on approximate functionals and some limitations in accurately describing complex interactions, DFT remains an essential tool for molecular modeling and the design of new materials and drugs. Its integration with advanced simulation methods, such as QSAR, QSPR, and molecular dynamics, further expands its potential, allowing not only for the theoretical understanding of systems, but also for practical applications in green chemistry, toxicology, and synthetic planning. In this sense, DFT is not just a calculation methodology, but a link between theory, innovation, and sustainability, making it indispensable for the scientific and technological advancement of contemporary chemistry.

REFERENCES

A. Grosdidier, V. Zoete, O. Michielin, Nucleic Acids Res. 2011, 39, W270 – 277.

ANASTAS, P. T.; WARNER, J. C. *Green Chemistry: Theory and Practice*. Oxford University Press, 1998.

BUCKLEY, Timothy J. et al. Cutting-edge computational chemical exposure research at the U.S. Environmental Protection Agency. Environment International, v. 178, p. 108097, 2023. DOI: 10.1016/j.envint.2023.108097.

BURKE, K. and others. The ABC of DFT. Department of Chemistry, University of California 2007.

DUARTE, H. A. Índices de reatividade química a partir da teoria do funcional de densidade: formalismo e perspectivas. Química Nova, v. 24, n. 4, p. 501-508, 2001.

ENGKVIST, Ola *et al.* Computational prediction of chemical reactions: current status and outlook. Drug Discovery Today, [*s. l.*], vol. 23, nº 6, p. 1203–1218, 2018.

G. M. Morris, R. Huey, W. Lindstrom, M. F. Sanner, R. K. Belew, D. S. Goodsell, A. J. Olson, J. Comput. Chem. 2009, 30, 2785 – 2791.

GOEL, Shruti *et al.* Ai's Assistance in Amplifying the Competence of Chemists. SSRN Electronic Journal, [*s. l.*], 2022. Disponível em: https://www.ssrn.com/abstract=4055501. Acesso em: 10 maio 2025.

GUPTA, Sudheer *et al.* In Silico Approach for Predicting Toxicity of Peptides and Proteins. PLoS ONE, [*s. l.*], vol. 8, nº 9, p. e73957, 2013.

KREBS, F. C.; McKEAGUE, M. *Machine learning and QSAR: A powerful alliance for green chemistry*. 2020.

KREBS, Johanna; MCKEAGUE, Maureen. Green Toxicology: Connecting Green Chemistry and Modern Toxicology. Chemical Research in Toxicology, [*s. l.*], vol. 33, nº 12, p. 2919–2931, 2020.

JOSHI, Payal B. Navigating with chemometrics and machine learning in chemistry. Artificial Intelligence Review, [*s. l.*], vol. 56, nº 9, p. 9089–9114, 2023.

LEWARS, E. G. *Computational Chemistry*: *Introduction to the Theory and Applications of Molecular and Quantum Mechanics*. New York: Springer, 2011.

LOGARUŠIĆ, Marijan et al. Harnessing the potential of deep eutectic solvents in biocatalysis: design strategies using CO_2 to formate reduction as a case study. Frontiers in Chemistry, v. 12, 2024. DOI: 10.3389/fchem.2024.1467810.

MACCHIA, Andrea et al. Prediction of green solvent applicability in cultural heritage using Hansen solubility parameters, Cremonesi method and integrated toxicity index. Sustainability, v. 17, n. 7, p. 2944, 2025. DOI: 10.3390/su17072944.

M. D. Cummings, R. L. DesJarlais, A. C. Gibbs, V. Mohan, E. P. Jaeger, J. Med. Chem. 2005, 48, 962–976. [32]

MAMMINO, L. Computational chemistry and green chemistry: Familiarizing chemistry students with the modes and benefits of promising synergies. Sustainable Chemistry and Pharmacy. 2022, 29, 100743.

MAMMINO, Liliana. Green chemistry and computational chemistry: A wealth of promising synergies. Sustainable Chemistry and Pharmacy, [*s. l.*], vol. 34, p. 101151, 2023.

MAMMINO, L. *Green chemistry in computational studies: Applications and theoretical developments*. 2023.

MOHAMMED, Wanisa Abdussalam; ALI, Amna Qasem; ERRAYES, Asma O. Green Chemistry: Principles, Applications, and Disadvantages. Chemical Methodologies, [*s. l.*], vol. 4, nº 4, p. 408–423, 2020.

MUHIEDDINE, Mohamad H. et al. Model-based solvent selection for the synthesis and crystallisation of pharmaceutical compounds. Chemical Engineering Science, v. 264, p. 118125, 2022. DOI: 10.1016/j.ces.2022.118125.

PATLEWICZ, G. *et al.* An evaluation of the implementation of the Cramer classification scheme in the Toxtree software. SAR and QSAR in Environmental Research, [*s. l.*], vol. 19, nº 5–6, p. 495–524, 2008.

PRADO-PRADO, F.J.; de LA VEGA, O.M.; URIARTE, E.; UBEIRA, F.M.; CHOU, K.-C.; GONZÁLEZ-DÍAZ, H. Unified QSAR approach to antimicrobials. 4. Multi-target QSAR modeling and comparative multi-distance study of the giant components of antiviral drug-drug complex networks. Bioorg. Med. Chem. 2009, 17, 569–575.

PRADO-PRADO, F.J.; GARCÍA-MERA, X.; GONZÁLEZ-DÍAZ, H. Multi-target spectral moment QSAR versus ANN for antiparasitic drugs against different parasite species. Bioorg. Med. Chem. 2010, 18, 2225–2231.

RAFI, Iftear Kazim. Green Chemistry and its Implementation for Better and Healthy Environment. Green Chemistry and its Implementation for Better and Healthy Environment, [*s. l.*], vol. 4, nº 8, p. 838–845, 2023.

R. D. Taylor, P. J. Jewsbury, J. W. Essex, J. Comput.-Aided Mol. Design 2002, 16, 151 – 166

SAEBI, Mandana *et al.* On the use of real-world datasets for reaction yield prediction. Chemical Science, [*s. l.*], vol. 14, nº 19, p. 4997–5005, 2023.

SPECK-PLANCHE, A.; KLEANDROVA, V.V.; LUAN, F.; CORDEIRO, M.N.D.S. Rational drug design for anti-cancer chemotherapy: Multi-target QSAR models for the in silico discovery of anti-colorectal cancer agents. Bioorg. Med. Chem. 2012, 20, 4848–4855.

STEIN, T.; KRONIK, L.; BAER, R. Reliable Prediction of Charge Transfer Excitations in Molecular Complexes Using Time-Dependent Density Functional Theory. J. Am. Chem. Soc. 2009, 131, (8), 2818-2820.

SZYMKUĆ, Sara *et al.* Computergestützte Syntheseplanung: Das Ende vom Anfang. Angewandte Chemie, [*s. l.*], vol. 128, nº 20, p. 6004–6040, 2016.

TOLMACHEV, Dmitry et al. Computer simulations of deep eutectic solvents: challenges, solutions, and perspectives. International Journal of Molecular Sciences, v. 23, n. 2, p. 645, 2022. DOI: 10.3390/ijms23020645.

TOROPOV, A.A.; TOROPOVA, A.P. QSPR/QSAR: State-of-Art, Weirdness, the Future. Molecules 2020, 25, 1292.

TOROPOV, A.A.; TOROPOVA, A.P.; BENFENATI, E.; SALMONA, M. Mutagenicity, anticancer activity and blood–brain barrier: Similarity and dissimilarity of molecular alerts. Toxicol. Mech. Methods 2018, 28, 321–327.

TOROPOVA, A.P.; TOROPOV, A.A.; BEGUM, S.; ACHARY, P.G.R. Blood brain barrier and Alzheimer's disease: Similarity and dissimilarity of molecular alerts. Curr. Neuropharmacol. 2018, 16, 769–785.

TOROPOVA, A.P.; TOROPOV, A.A.; VESELINOVI´C, A.M.; VESELINOVI´C, J.B.; LESZCZYNSKA, D.; LESZCZYNSKI, J. Quasi-SMILES as a Novel Tool for Prediction of Nanomaterials' Endpoints. In Multi-Scale Approaches in Drug Discovery: From Empirical Knowledge to In silico Experiments and Back, 1st ed.; Speck-Planche, A., Ed.; Elsevier Science: Amsterdam, The Netherlands, 2017; pp. 191–221.

WANG, Zheng *et al.* Mapping the resources and approaches facilitating computer-aided synthesis planning. Organic Chemistry Frontiers, [*s. l.*], vol. 8, nº 4, p. 812–824, 2021.