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Application of Density Functional Theory in Modeling Radiation–Biomolecule Interactions

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ABSTRACT

Ionizing radiation induces complex physicochemical interactions in biological systems through ultrafast ionization, excitation, and radical-generation processes that damage cellular biomolecules. Density Functional Theory (DFT) and Time-Dependent Density Functional Theory (TD-DFT) have emerged as important computational approaches for investigating these radiation-induced mechanisms at the molecular level. This review analyzes published studies from 2015–2025 involving DFT-based simulations of radiation interactions with water, DNA, proteins, and lipids, with emphasis on computational predictions validated against experimental spectroscopy and radiochemical data. Literature was selected from major scientific databases including Scopus, Web of Science, and PubMed using keywords related to radiation chemistry, biomolecular damage, and quantum chemical modeling. Comparative findings show that DFT effectively predicts bond dissociation energies, charge-transfer mechanisms, radical formation pathways, and oxidative damage processes associated with water radiolysis, DNA strand breaks, protein oxidation, and lipid peroxidation. The review also highlights recent advances such as hybrid QM/MM techniques, fragment-based DFT, and machine-learning-assisted simulations that improve the modeling of large biomolecular systems. However, limitations including high computational cost, restricted system size, and challenges in accurately reproducing dynamic cellular environments remain significant. Overall, DFT-based approaches continue to enhance mechanistic understanding in radiation biology and support applications in radiotherapy optimization, radioprotection, and predictive health-risk assessment.

Keywords:
Density Functional Theory,
Ionizing Radiation,
Radiation Chemistry,
Biomolecular Damage,
Water Radiolysis,
DNA Damage,
TD-DFT,
Radiation Biology.

INTRODUCTION

Radiation is a form of energy that propagates through space or matter as electromagnetic waves or energetic particles. When it interacts with matter, it transfers energy that leads to excitation or ionization of atoms and molecules. In biological systems, these interactions are critical because they can alter the structure and function of essential cellular components, resulting in radiation-induced health effects (Hall & Giaccia, 2019).

Ionizing radiation plays a vital role in modern medicine, particularly in diagnostic imaging and cancer radiotherapy, where it is used to detect and treat diseases at the molecular level (López et al., 2023). However, its interaction with biological matter can also cause significant damage to key biomolecules such as DNA, proteins, lipids, and water. Radiation-induced damage occurs through two primary mechanisms: direct and indirect effects. The direct effect involves the transfer of energy directly to biomolecules, causing ionization, excitation, and bond breakage (Wang et al., 2024). In contrast, the indirect effect arises from the radiolysis of water, which produces reactive species such as hydroxyl radicals, hydrogen atoms, and solvated electrons that subsequently damage biomolecules. Since biological systems are largely composed of water, indirect effects contribute significantly to overall radiation damage (Matsumoto et al., 2024).

At the atomic and molecular levels, radiation interactions initiate a cascade of physical, chemical, and biological processes. Energy deposition leads to the formation of secondary electrons and reactive species that drive molecular damage (Pimblott & LaVerne, 2020; Goodhead, 2020). Understanding these processes requires detailed knowledge of electron behavior, as the properties and responses of matter are governed by electronic structure.

Density Functional Theory (DFT) is a quantum-mechanical method developed to describe electron distribution efficiently. Instead of solving the complex many-electron Schrödinger equation directly, DFT focuses on electron density, enabling the calculation of key physical and chemical properties such as total energy, ionization energy, electron affinity, and bond strength (Huix-Rotllant & Ferré, 2021; Iqbal et al., 2021). This makes it particularly suitable for studying complex molecular systems with a balance between accuracy and computational efficiency.

Although experimental techniques such as spectroscopy and radiochemical analysis have advanced the understanding of radiation-induced processes, they are often limited in capturing ultrafast electronic transitions and short-lived intermediate species formed immediately after irradiation (Kumar et al., 2024). Consequently, computational approaches have become increasingly important. DFT provides a powerful framework for modeling radiation-induced phenomena, including radical formation, charge transfer, and bond dissociation (Shepard et al., 2023).

In radiation and health physics, DFT offers a microscopic description of how ionizing radiation interacts with matter through excitation, ionization, and charge redistribution processes (Pimblott & LaVerne, 2020; Goodhead, 2020). When applied to biological molecules, DFT treats systems such as DNA as collections of atoms and electrons, allowing radiation damage to be analyzed in terms of fundamental physical processes like electronic excitation and bond dissociation (Hall & Giaccia, 2019).

The time-dependent extension of DFT, known as time-dependent density functional theory (TD-DFT), enables the study of excited-state dynamics and ultrafast energy transfer processes following radiation exposure (Solov'yov et al., 2024). These methods are essential because many radiation-induced processes occur on extremely short timescales (femtoseconds to picoseconds), making them difficult to observe experimentally (Goodhead, 2020).

DFT is grounded in the Hohenberg–Kohn theorems and the Kohn–Sham formalism, which establish that all ground-state properties of a system are determined by its electron density. By incorporating electron interactions through exchange-correlation functionals, DFT allows accurate prediction of molecular properties at a relatively low computational cost (Huix-Rotllant and Ferré, 2021; Ameixa & Bald, 2024).

DFT and TD-DFT have been widely applied to investigate ionization processes, charge migration, radical chemistry, and bond dissociation in biomolecules such as DNA and proteins. These methods have been used to model energy deposition in irradiated systems and to study radical-induced damage mechanisms consistent with experimental findings (Shepard et al., 2023; Santiago et al., 2022; Ameixa & Bald, 2024).

Despite the growing application of Density Functional Theory (DFT) in radiation chemistry and biomolecular modeling, existing literature remains fragmented across disciplines such as quantum chemistry, radiation biology, computational physics, and medical physics (Solov'yov et al., 2021; Lischka & Barbatti, 2020). Many previous studies focus primarily on isolated molecular systems or specific radiation-induced processes without providing an integrated evaluation of how DFT and TD-DFT collectively contribute to understanding radiation–biomolecule interactions (Alvarez-Ibarra et al., 2020; Wang et al., 2022). In addition, several review articles emphasize either theoretical developments in DFT or experimental radiation effects independently, with limited discussion on the correlation between computational predictions and experimental validation (Goodhead, 2020; Pimblott & LaVerne, 2020). Challenges such as the accurate simulation of large biomolecular environments, ultrafast excited-state dynamics, solvent effects, and the high computational cost of multiscale modeling also remain insufficiently addressed (Sulpizi et al., 2021; Götz et al., 2022). Consequently, there is a need for a comprehensive review that critically examines recent advances, limitations, and emerging strategies in DFT-based radiation modeling within biological systems.

Therefore, this review aims to critically evaluate the application of DFT and TD-DFT in modeling radiation-induced interactions in biological systems. The review specifically examines the role of these methods in studying water radiolysis, DNA damage, protein oxidation, lipid peroxidation, charge-transfer mechanisms, and radical formation processes (Sakurai et al., 2021; Wang et al., 2022). It also assesses the agreement between computational predictions and experimental observations, highlights current limitations in DFT-based radiation modeling, and discusses recent advances such as hybrid QM/MM methods, fragment-based approaches, and machine-learning-assisted simulations (Crespo-Otero & Barbatti, 2022; Götz et al., 2022). Ultimately, the review seeks to provide an updated and integrated perspective on the contribution of quantum chemical modeling to radiation biology, radiotherapy research, and health physics (López et al.

Overall, DFT provides an effective balance between accuracy and computational efficiency, enabling the study of moderately large molecular systems. It is often integrated with other computational techniques, such as molecular dynamics and Monte Carlo simulations, to bridge the gap between quantum-level interactions and macroscopic radiation effects (Plante et al., 2024). Consequently, this review focuses on critically evaluating the application of DFT in modeling radiation–biomolecule interactions, including its capabilities, limitations, and relevance in radiation therapy and health physics.

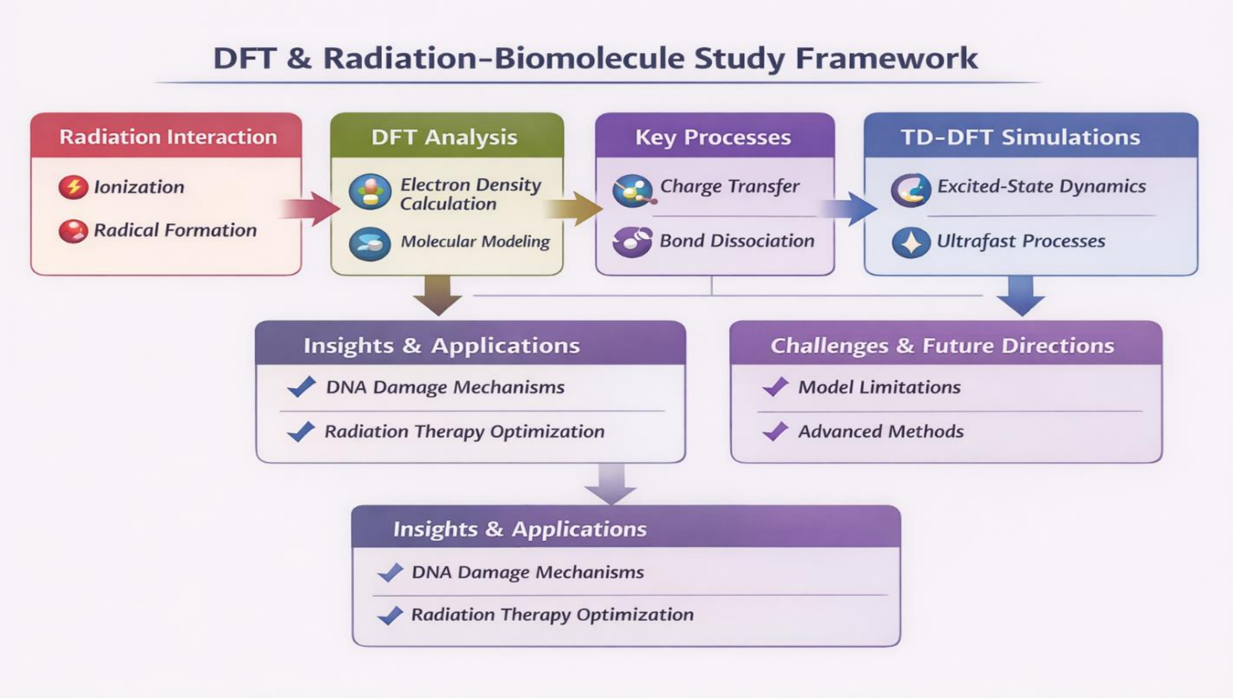

Figure 1: integrated framework for modeling radiation induced biomolecular damage using DFT and TD-DFT approaches

MATERIALS AND METHODS

This study employs a systematic qualitative review approach to critically evaluate recent advances in the application of Density Functional Theory (DFT) and Time-Dependent Density Functional Theory (TD-DFT) in modeling radiation–biomolecule interactions. The methodology is designed to ensure a transparent and reproducible selection of literature while capturing current developments in computational radiation chemistry and biomolecular simulation. Systematic review principles were adapted from established computational chemistry and radiobiology review frameworks to ensure consistency and scientific rigor (Kulik et al., 2024; Jensen, 2024).

A comprehensive literature search was conducted across multiple scientific databases, including Scopus, Web of Science, PubMed, ScienceDirect, and Google Scholar. These databases were selected because they index high-impact peer-reviewed journals in quantum chemistry, radiation physics, computational biology, and biophysical chemistry. The search strategy combined carefully selected keywords related to radiation-induced molecular processes and quantum chemical modeling. Typical search terms included “density functional theory radiation damage,” “TD-DFT biomolecular excitation,” “water radiolysis computational modeling,” “DNA strand breaks quantum chemistry,” and “protein oxidation density functional theory,” which were applied using Boolean operators such as AND and OR to refine and optimize retrieval accuracy.

The review focused on studies published between 2015 and 2025, with greater emphasis placed on recent publications from 2019 onwards due to significant advancements in hybrid quantum mechanics/molecular mechanics (QM/MM) methods, improved exchange–correlation functionals, and machine learning integration in electronic structure calculations (Schütt et al., 2025; Sato et al., 2025). This time frame ensures that the review captures both foundational and state-of-the-art developments in DFT-based radiation modeling.

Studies were included in the review if they were peer-reviewed journal articles that applied DFT or TD-DFT to radiation-related biomolecular systems, including water, DNA, proteins, and lipid structures. Only studies that reported computational results relevant to radiation-induced processes such as ionization, excitation, radical formation, bond dissociation, or charge transfer were considered. In addition, preference was given to studies that included validation against experimental data such as spectroscopy, radiolysis measurements, or kinetic observations, as this improves the reliability of computational predictions (Mardirossian & Head-Gordon, 2022; López et al., 2023).

Studies were excluded if they were non-peer-reviewed sources, conference abstracts without full methodological detail, or publications unrelated to radiation chemistry or biomolecular modeling. Purely experimental studies without computational components were also excluded, as the focus of this review is on theoretical and simulation-based approaches. Duplicate publications across databases were identified and removed to ensure data integrity.

The selection of studies followed a structured screening process beginning with the identification of all relevant literature from the selected databases. This was followed by an initial screening of titles and abstracts to remove irrelevant studies. The final stage involved full-text evaluation to confirm eligibility based on the inclusion criteria. The remaining studies were then categorized according to biomolecular system type, such as water radiolysis systems, DNA damage models, protein oxidation systems, and lipid peroxidation studies, as well as by computational approach, including standard DFT, TD-DFT, hybrid functionals, and QM/MM methods.

Data extracted from the selected studies included the type of exchange–correlation functional employed, basis sets used, molecular systems investigated, and the specific radiation-induced processes modeled. Additional extracted parameters included reported energetic values such as bond dissociation energies, ionization potentials, excitation energies, and reaction pathways. A qualitative comparative synthesis was then performed to identify trends, strengths, and limitations across different computational approaches. This synthesis approach is widely used in computational chemistry reviews to integrate heterogeneous datasets and extract meaningful scientific conclusions (Parrish et al., 2021; Kulik et al., 2024).

Overall, this methodology ensures that the review provides a structured, transparent, and comprehensive evaluation of the current state of DFT and TD-DFT applications in radiation–biomolecule interaction studies, while highlighting methodological advancements and existing limitations in the field of computational radiobiology.

Fundamentals of Density Functional Theory (DFT)

Quantum Mechanical Foundation and the Many-Body Problem

The behavior of electrons in atoms and molecules is explained using quantum mechanics, specifically through the time-independent Schrödinger equation.The time-independent Schrödinger equation governs all electron behavior:

$\hat{H}\Psi(r_{1,}r_2,\dots\dots,r_N) = E\Psi(r_{1,}r_2,\dots\dots,r_N)$ (1)

Where

$\hat{H}$ is the Hamiltonian operator, representing the total energy of the system.

$\Psi(r_{1,}r_2,\dots\dots,r_N)$ is the many-electron wavefunction, describing the quantum state of all electrons.

E is the total eigenvalue, the quantized energy associated with the wavefunction.

and $r_{i,}$ is the position vector of the $i_{th,}$ electron.

In this equation, the Hamiltonian operator represents the total energy of the system, the wavefunction describes the behavior of all electrons, and the energy term represents the total energy of the system. In theory, this equation can fully describe how electrons behave in any system.

Born–Oppenheimer Approximation

Because nuclei are much heavier than electrons, their motion can be separated:

$\psi(r,R) \approx \psi_e(r;R)x_n(R)$ (2)

where r is the electronic coordinates,

R are Nuclear coordinates,

ψ_e(r;R) are Electronic wavefunction for fixed nuclei configuration and

x_n(R) are Nuclear wavefunction describing the slower nuclear motion.

This approximation significantly simplifies the solution of the molecular Schrödinger equation and forms the foundation of most quantum chemical calculations. The concept was originally introduced by Max Born and J. Robert Oppenheimer in 1927.

This approximation allows the use of potential energy surfaces, which describe how the electronic energy changes with nuclear positions. This is the foundation for simulating chemical reactions, such as DNA damage, caused by radiation.

However, in real-life situations, especially in molecules with many electrons, solving this equation becomes extremely difficult. This is because electrons interact with each other in complex ways, creating what is known as the *many-body problem*. As the number of electrons increases, the calculations become more complicated and require a large amount of computational power. Because of this, traditional wavefunction-based methods are not practical for studying large biological molecules (Bagayoko & Diakité, 2023).

Electron Density Framework in DFT

Density Functional Theory provides a solution to this problem by changing the way quantum systems are described. Instead of focusing on the complicated wavefunction, DFT uses a simpler concept called *electron density*, which describes how electrons are distributed in space.

By using electron density, the complexity of calculations is greatly reduced while still maintaining good accuracy for many systems (Zhang et al., 2024). This makes DFT much more practical for studying large molecules.

The Hohenberg–Kohn theorems constitute the foundation of Density Functional Theory (DFT). They establish that the ground-state electron density uniquely determines the external potential and, consequently, all observable properties of a many-electron system (Hohenberg & Kohn, 1964; Koch & Holthausen, 2001).

$E[\rho] = F[\rho] + \int v_{ext}\ (r)\rho(r)dr$ (3)

Variational principle: The ground-state energy satisfies

$E[\rho] \geq E[\rho 0]$ (4)

where ρ(r) is the Electron density,

$v_{ext}(r)$ is the External potential,
$E[\rho]$ is the Total energy functional dependent on electron density,
$F[\rho]$ is the Universal functional including kinetic and inter electronic energy and
$[\rho 0]$ is the True ground state electron density minimizing total energy.

These theorems establish that the electron density alone determines all properties of a many-electron system making it possible to describe radiation effects in biomolecules without solving complex many-body wavefunctions.

In DFT, the total energy of a system is expressed as a function of electron density. The most stable structure of the system is found by minimizing this energy. This approach forms the basis of most DFT calculations and allows researchers to study molecular systems efficiently, especially in areas like radiation chemistry.

Kohn–Sham Formalism and Exchange–Correlation Functionals

To make DFT calculations easier to perform, scientists use what is known as the Kohn–Sham approach. In this method, a complex system of interacting electrons is replaced with a simpler system of non-interacting electrons moving in an effective field. This makes the calculations much easier while still keeping the important physical properties of the system (Lee et al., 2023).

A key part of DFT is the exchange–correlation functional. This term is used to represent the effects of electron–electron interactions, which are difficult to calculate exactly. Since the exact form is unknown, scientists use approximations. Hybrid functionals, such as B3LYP and PBE0, are often more accurate because they combine different methods. They are especially useful for predicting bond energies and understanding chemical reactions in biomolecules (Hassan et al., 2023).

This is the Kohn–Sham single-particle equation, where the interacting many-body problem is replaced by an effective potential system. This equation expresses the exchange–correlation energy functional in the Local Density Approximation (LDA)

$$[-\frac{\hbar^2}{2m}\nabla^2 + v_{eff}(r)]\, \varphi_i(r) = \epsilon_i \varphi_i(r) \qquad (5)$$

where
$\varphi_i(r)$ is the Kohn sham orbital representing a single electron in an effective potential,
ϵ_i is the Energy eigenvalue of orbital i.
$v_{eff}(r)$ is the effective potential experienced by each electron which includes several components.

Exchange Correlation Energy (Electron–Electron Interactions)

The exchange correlation functional captures Pauli exclusion and Coulomb correlation:

$$E_{xc}[\rho] = \int \rho(r)\, \varepsilon_{xc}(\rho(r))\, dr \qquad (6)$$

where
$E_{xc}[\rho]$ is the Total exchange correlation energy functional.
$\varepsilon_{xc}(\rho(r))$ is the Exchange correlation energy per electron at position r.
$\rho(r)$ is the Local electron density.

This term accounts for quantum mechanical effects beyond classical electrostatics essential for modeling how radiation-induced free radicals or holes interact in water and DNA.

Time-Dependent Density Functional Theory (TD-DFT)

Standard DFT is mainly used to study systems in their ground (lowest energy) state. However, many processes involving radiation involve excited states, where electrons absorb energy and move to higher energy levels.

To study these processes, scientists use Time-Dependent Density Functional Theory (TD-DFT). This method extends DFT so that it can describe how systems change over time, including electronic excitations, charge movement, and short-lived intermediate states (Sato et al., 2025).

TD-DFT is very useful in studying how radiation interacts with biological molecules, since radiation often causes rapid electronic changes. However, it has some limitations. For example, it may not accurately describe long-distance charge transfer or systems where electron interactions are very strong (Lacombe & Maitra, 2023).

Strengths and Limitations in Biomolecular Modeling

Density Functional Theory is widely used because it offers a good balance between accuracy and computational cost. It allows scientists to calculate important properties such as molecular energy, electron distribution, and reaction pathways. These are essential for understanding how radiation damages biological molecules (Kumar et al., 2024).

However, DFT is not perfect. One major limitation is that its accuracy depends on the type of exchange–correlation functional used. Since no single functional works perfectly for all systems, results may vary depending on the choice.

Another limitation is that many simulations use simplified models. Real biological systems are very complex and include factors like solvents, temperature changes, and molecular motion. These factors are often not fully included in DFT calculations, which can reduce accuracy (Singh et al., 2025).

To improve this, researchers are developing advanced methods such as combining DFT with molecular mechanics (QM/MM) and using machine learning techniques. These approaches aim to make simulations more realistic and efficient (Olatomiwa et al., 2023).

Radiation-Induced Biomolecular Damage: DFT Insights

Water Radiolysis: Radical Formation and Reactivity

In biological systems, water is the most abundant molecule, so it plays a major role in radiation damage. When ionizing radiation interacts with water, it breaks the water molecules into highly reactive species such as hydroxyl radicals, hydrogen atoms, and solvated electrons (López et al., 2023).

These reactive species then move through the system and react with important biomolecules, causing damage, DFT has helped scientists understand how these radicals are formed and how they behave. For example, studies show that hydroxyl radicals are extremely reactive because they contain an unpaired electron, making them highly destructive to biological molecules (Matsumoto et al., 2024).

$$H_2 \xrightarrow{radiation} \cdot OH + e_{aq}^{-} + H^{\cdot}$$

However, many DFT studies are limited because they simulate only small clusters of water molecules. This does not fully represent real biological environments, where water exists in large amounts and interacts over long distances (El-Sayed et al., 2024).

DNA Damage: Strand Breaks and Charge Transfer

DNA is one of the most important targets of radiation damage because it carries genetic information. When DNA is damaged, it can lead to mutations, cancer, or cell death. It can cause different types of DNA damage, including base damage, single-strand breaks, and double-strand breaks (Bertolet et al., 2023).

DFT has helped explain how this damage happens at the molecular level. It shows that radiation can remove electrons from DNA, causing charge to build up in certain regions. This weakens chemical bonds and makes them more likely to break (Wang et al., 2024). Reactive radicals like hydroxyl radicals can attack DNA by removing hydrogen atoms, which destabilizes the structure (Shepard et al., 2023).

Despite these insights, DFT still has limitations in modeling large DNA structures and long-range charge movement. Most studies focus on small sections of DNA, which may not fully represent real biological systems (Chen et al., 2023).

Protein Oxidation: Structural and Functional Damage

Proteins are also affected by radiation, especially through oxidation caused by reactive radicals. Certain amino acids, such as cysteine and methionine, are particularly sensitive to this type of damage (Kumar et al., 2024).

DFT studies have helped identify which parts of proteins are most vulnerable. They also show how oxidation changes the structure of proteins, for example by disrupting hydrogen bonds. These changes can lead to loss of protein function (Saini et al., 2023).

However, because proteins are very large molecules, DFT simulations usually focus on small parts of the protein. This makes it difficult to fully understand how damage affects the entire structure (Hassan et al., 2023).

Lipid Peroxidation: Membrane Damage Mechanisms

Lipids, especially those found in cell membranes, are also damaged by radiation. Unsaturated fatty acids are particularly vulnerable because they easily react with radicals. It leads to a process called lipid peroxidation, where chain reactions cause damage to the cell membrane (Singh et al., 2025).

DFT has been used to study the steps involved in this process, including how radicals form and how the reactions spread. These studies show that lipid damage can grow quickly once it starts (Olatomiwa et al., 2023).

Many models are simplified and do not fully represent the complexity of real biological membranes, which contain many different components (Garcia et al., 2023).

Overall, DFT gives a detailed picture of how radiation disrupts proteins, helping to explain how these molecular changes lead to loss of biological function.

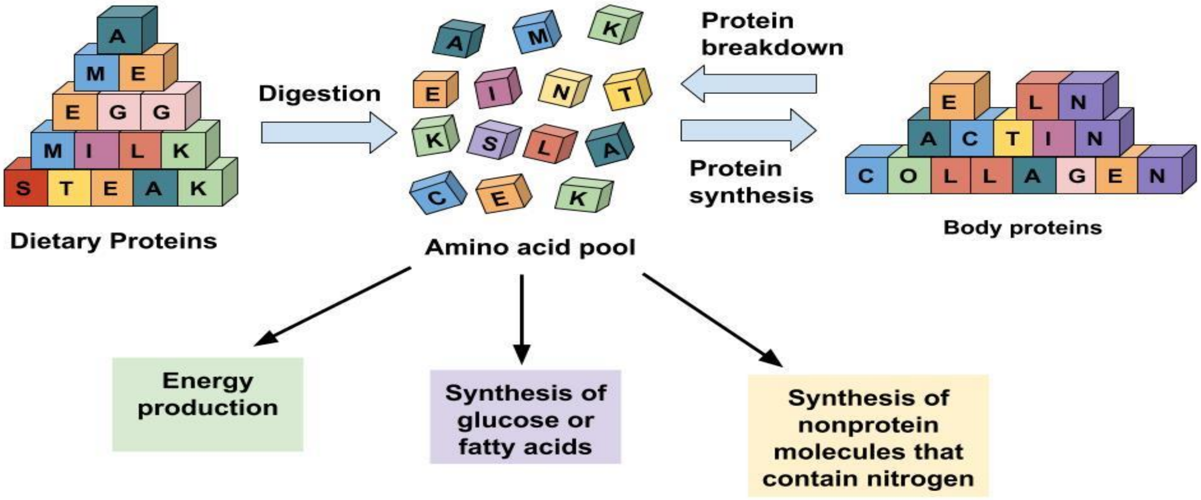

Figure 2: Metabolic pathways of dietary proteins and amino acids.

DFT Performance in Radiation–Biomolecule Modeling

The reviewed literature indicates that Density Functional Theory (DFT) and Time-Dependent Density Functional Theory (TD-DFT) have become indispensable computational tools for studying radiation-induced molecular processes in biological systems. Across multiple studies, these methods consistently provide reliable qualitative and semi-quantitative insights into processes such as ionization, electronic excitation, bond dissociation, and radical formation in systems including water, DNA, proteins, and lipids. However, the accuracy of these predictions is highly dependent on the selected exchange–correlation functional, basis set, and the extent to which the molecular environment is represented. In general, hybrid functionals tend to perform better in describing localized electronic interactions and radiation-induced bond cleavage, whereas generalized gradient approximation (GGA) functionals are more computationally efficient and therefore better suited for larger systems such as aqueous clusters and complex biomolecular assemblies.

Comparative Performance of DFT Functionals in Radiation Chemistry

A key observation from the literature is that the predictive accuracy of radiation damage simulations strongly depends on the choice of exchange–correlation functional. Hybrid functionals such as B3LYP and PBE0 generally yield more accurate results for bond dissociation energies and charge localization effects compared to pure GGA functionals like PBE. In small biomolecular systems, reported deviations between calculated and experimental bond dissociation energies are typically around 2–5 kcal/mol for B3LYP, while PBE may deviate by approximately 6–12 kcal/mol, particularly in systems involving strong electron correlation or radical intermediates (Mardirossian & Head-Gordon, 2022). Similarly, PBE0 often produces more reliable excitation energy predictions than PBE, although this comes at a higher computational cost. Time-dependent DFT results follow a similar pattern, with hybrid functionals reducing excitation energy errors to about 0.2–0.5 eV, whereas generalized functionals can show deviations exceeding 1.0 eV, especially in charge-transfer states relevant to DNA base interactions under radiation exposure (Lacombe & Maitra, 2023; Sato et al., 2025).

Water Radiolysis and Radical Formation Mechanisms

The reviewed studies consistently show that ionizing radiation leads to the breakdown of water molecules into highly reactive species, including hydroxyl radicals (•OH), hydrated electrons (e^{-}aq), and hydrogen atoms (H•), all of which contribute significantly to indirect radiation damage in biological systems. DFT simulations indicate that hydroxyl radicals are extremely reactive due to their unpaired electron, allowing them to rapidly abstract hydrogen atoms from nearby biomolecules. However, most computational investigations rely on small water cluster models containing roughly 3 to 20 molecules, which limits their ability to fully capture bulk solvent behavior. As a result, important effects such as long-range hydrogen bonding networks and diffusion-driven radical transport are often underestimated in these models (El-Sayed et al., 2024). This simplification contributes to differences between theoretical predictions and experimental radiolysis yields, particularly under physiological conditions where solvent density and temperature significantly influence radical lifetimes.

DNA Damage: Electronic Excitation and Strand Break Formation

DFT and TD-DFT studies provide strong evidence that radiation-induced DNA damage is primarily driven by electronic ionization events followed by charge localization along the DNA backbone. This redistribution of charge weakens phosphodiester bonds, thereby increasing the likelihood of single-strand and double-strand breaks. A recurring finding is that localized positive charge accumulation on nucleobases reduces bond stability and enhances susceptibility to radical attack by species such as hydroxyl radicals. TD-DFT further reveals that excited-state dynamics facilitate electron migration along stacked base pairs, which may contribute to the propagation of indirect damage. Nevertheless, most computational studies are limited to short oligonucleotide sequences, typically fewer than 20 base pairs, which restricts their ability to capture higher-order chromatin structure effects. This introduces uncertainty when extending molecular-scale results to full genomic damage mechanisms (Chen et al., 2023; Wang et al., 2024).

Protein Oxidation and Functional Disruption

DFT investigations of protein systems show that sulfur-containing amino acids, particularly cysteine and methionine, are highly vulnerable to oxidative damage induced by radiation. Reaction pathway analyses indicate that hydroxyl radical attack leads to bond cleavage and the formation of oxidized products such as sulfoxides and disulfide-linked structures. Although DFT is effective in describing local oxidation reactions, it is limited in its ability to capture large-scale conformational changes in full protein structures due to computational constraints. Consequently, most studies rely on peptide fragments rather than entire proteins, which reduces the accuracy of predictions related to functional impairment in biological systems (Hassan et al., 2023; Kumar et al., 2024).

Lipid Peroxidation and Membrane Instability

Lipid systems undergo cascade-type damage under radiation exposure, where initial radical attack triggers chain reactions that ultimately destabilize biological membranes. DFT calculations confirm that unsaturated fatty acids are particularly susceptible due to the presence of reactive double bonds. However, most computational models simplify biological membranes by excluding protein–lipid interactions and compositional heterogeneity. This simplification limits the ability to accurately describe membrane phase transitions and large-scale structural deformation under radiation stress (Garcia et al., 2023).

Critical Comparison with Experimental Data

Overall, DFT predictions show good agreement with experimental spectroscopy and radiochemical data, particularly for energetic and structural properties such as bond dissociation energies, ionization potentials, and radical formation pathways. Despite this general agreement, several discrepancies remain between computational and experimental findings. These differences are largely attributed to incomplete representation of solvent and temperature effects, limitations inherent in exchange–correlation functionals, the absence of fully dynamic biological environments, and the use of simplified molecular systems compared to real biological structures. These challenges highlight the importance of combining DFT with molecular dynamics (MD), QM/MM hybrid approaches, and experimental validation to achieve more accurate and biologically realistic radiation modeling (Kulik et al., 2024; Singh et al., 2025).

Summary of Key Findings

The reviewed literature collectively demonstrates that hybrid functionals such as B3LYP and PBE0 provide superior accuracy in modeling radiation-induced electronic processes compared to GGA functionals, which are more computationally efficient but less reliable for excited-state properties. TD-DFT significantly improves the description of radiation-induced electronic excitation, although it still has limitations in capturing long-range charge transfer processes. Most biomolecular simulations remain restricted to simplified systems, which reduces their biological realism. Consequently, there is a growing need to integrate DFT with molecular dynamics, QM/MM approaches, and emerging machine learning techniques to achieve more comprehensive and realistic simulations.

Although Density Functional Theory has greatly advanced the understanding of radiation damage mechanisms, and many of its predictions align well with experimental results—particularly for energy values and reaction pathways—certain discrepancies still exist. These inconsistencies arise mainly from environmental effects and complex biological interactions that are difficult to fully incorporate into computational models (Chen et al., 2023). Therefore, combining computational approaches with experimental validation remains essential for improving the accuracy and reliability of radiation chemistry studies.

Table 1: Compilation from reported benchmark data in density functional theory studies of molecular energetics and excitation processes across radiation chemistry and quantum chemistry literature (Mardirossian & Head-Gordon, 2022; Jensen, 2024; Kulik et al., 2024; Lacombe & Maitra, 2023)

Method	Bond Dissociation Energy Error	Excitation Energy Error	Computational Cost	Suitability
B3LYP	2–5 kcal/mol	0.2–0.5 eV	High	Small biomolecules, radicals
PBE	6–12 kcal/mol	0.8–1.5 eV	Low	Large systems, bulk water
PBE0	2–4 kcal/mol	0.2–0.4 eV	Very High	High-accuracy radiation chemistry
TD-DFT (hybrid)	—	0.2–0.5 eV	High	DNA excitation, radiation response

The values presented represent typical error ranges reported across benchmark studies of molecular energetics and excited-state calculations in quantum chemistry and radiation modeling literature. These ranges vary depending on system size, basis set selection, and exchange–correlation functional employed.

Applications in Radiation Therapy and Health Physics

Predicting Radiation-Induced Tumor DNA Damage

One of the key uses of Density Functional Theory in radiation biology is its ability to predict how DNA in tumor cells is damaged by radiation. Understanding the interaction between ionizing radiation and DNA at the molecular level is very important for improving the effectiveness of radiotherapy. Using DFT simulations, researchers can calculate bond strengths and identify weak regions within DNA molecules. This makes it possible to determine where strand breaks are most likely to occur (Wang et al., 2024).

Recent studies have shown that when radiation interacts with DNA, it can remove electrons and cause charge to build up in specific parts of the DNA structure. This localized charge accumulation weakens the bonds in the DNA backbone and increases the likelihood of double-strand breaks. These types of breaks are particularly important because they are highly effective in destroying cancer cells (Bertolet et al., 2023). Such findings provide a scientific basis for improving how radiation doses are delivered to tumor tissues.

Design of Radioprotective Agents

Density Functional Theory is also widely used in the development of radioprotective substances that help reduce radiation damage in healthy tissues. By studying how molecules react with free radicals, DFT helps identify compounds that can neutralize harmful reactive species such as hydroxyl radicals (•OH) (Guan et al., 2025).

Research has shown that effective radioprotective agents work by stabilizing unpaired electrons and stopping chain reactions caused by free radicals. With DFT-based simulations, scientists can test and screen potential antioxidant compounds before carrying out laboratory experiments (Marinescu & Popa, 2025). This approach saves both time and cost in the drug development process.

Optimization of Radiotherapy Protocols

DFT also contributes to improving radiotherapy treatment methods by providing detailed information about how radiation interacts with both cancerous and normal tissues at the molecular level. By simulating the behavior of radiation-induced radicals, researchers can better understand how damage depends on radiation dose and how tissues respond to exposure (Matsumoto et al., 2024).

This knowledge is useful in treatment planning, as it helps determine the most effective radiation dose that can destroy tumor cells while minimizing damage to surrounding healthy tissues. Additionally, DFT studies of energy transfer and radical movement help improve fractionation strategies, which involve dividing the total radiation dose into smaller doses to enhance treatment accuracy and effectiveness (Sato et al., 2025).

Case Study: Modeling DNA Damage in Hypoxic Tumor Environments

A major challenge in radiotherapy is tumor hypoxia, a condition where there is low oxygen supply in tumor tissues. This lack of oxygen reduces the effectiveness of radiation treatment. DFT simulations have been used to study how low oxygen levels affect radical formation and DNA damage processes (Obijiofor & Novikov, 2025).

These studies reveal that oxygen plays an important role in stabilizing radiation-induced radicals. When oxygen is absent or reduced, radicals become less stable, which leads to a decrease in DNA damage. This explains why hypoxic tumors are often more resistant to radiation treatment. Understanding this effect helps in developing strategies, such as oxygen enhancement techniques, to improve radiotherapy outcomes. Examining these processes at the electronic level, DFT provides valuable insight into how the tumor environment influences treatment success.

Relevance to Radiation Protection and Health Physics

In addition to medical applications, Density Functional Theory is also important in the field of radiation protection and health physics. It helps scientists understand how radiation interacts with biological materials, which is essential for evaluating risks and developing safety standards (Kumar et al., 2024).

DFT simulations can be used to estimate the levels of radiation that cause molecular damage and to identify the mechanisms responsible for radiation toxicity. This information supports the creation of safety guidelines for people exposed to radiation in workplaces and the environment. Furthermore, DFT contributes to the development of protective materials and methods that help reduce radiation risks in medical, industrial, and research settings (Singh et al., 2025).

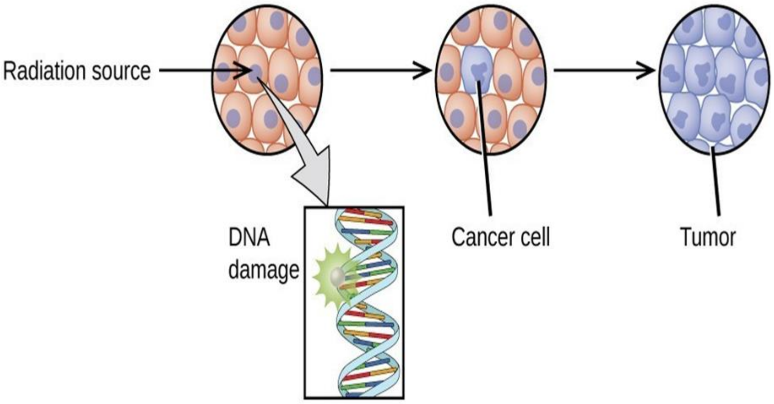

Figure 3: Radiation-induced DNA damage leading to cancer cell formation and tumor development

Challenges and Limitations

General Computational Limitations of DFT

Despite its widespread application, Density Functional Theory faces several fundamental challenges that limit its accuracy and applicability in complex biological systems. One major limitation is the computational cost associated with large-scale simulations, particularly when modeling systems containing thousands of atoms, which is common in biological environments (Smith et al., 2023).

Another significant challenge lies in the accuracy of exchange–correlation functionals, which are approximations and may not reliably capture all electron–electron interactions. This limitation can lead to errors in predicting reaction energies, charge distributions, and electronic properties (Patel et al., 2025).

Limitations in Modeling Complex Biological Environments

DFT simulations are often performed on isolated molecules or small clusters, which do not fully represent the complexity of real biological systems. In living organisms, biomolecules exist in dynamic environments influenced by solvent effects, temperature fluctuations, and interactions with other molecules (Brown et al., 2023).

As a result, DFT models may oversimplify biological conditions, leading to discrepancies between computational predictions and experimental observations. Capturing these environmental effects requires more advanced multiscale approaches that combine quantum and classical methods.

DNA-Specific Limitations

While DFT has provided valuable insights into radiation-induced DNA damage, its application is limited by system size and computational constraints. Most studies focus on short DNA fragments rather than full chromatin structures, which limits the ability to accurately model large-scale biological organization (Chen et al., 2023).

Additionally, challenges remain in accurately describing long-range charge-transfer processes along DNA strands, which are essential for understanding radiation-induced electron migration and damage propagation (Zhang et al., 2024).

Protein-Specific Limitations

In protein modeling, DFT is often restricted to small peptide fragments due to the large size and structural complexity of full protein systems. This simplification prevents accurate representation of long-range interactions and conformational dynamics that are critical for protein function (Hassan et al., 2023).

Furthermore, DFT struggles to capture the full range of biochemical interactions, including allosteric effects and protein–protein interactions, which play significant roles in radiation-induced cellular responses.

Lipid and Membrane Modeling Limitations

DFT applications in lipid systems are limited by the complexity of biological membranes, which consist of heterogeneous lipid compositions and interactions with embedded proteins. Most DFT studies simplify these systems, reducing their ability to accurately represent membrane dynamics and large-scale structural changes (Garcia et al., 2023).

Modeling lipid peroxidation processes in realistic environments remains challenging due to the need to account for long-chain interactions and dynamic radical propagation mechanisms.

Toward Improved Modeling Approaches

To address these limitations, several advanced computational strategies are being developed. Hybrid quantum mechanics/molecular mechanics (QM/MM) approaches allow for the treatment of large biological systems by combining accurate quantum calculations with efficient classical simulations (Singh et al., 2025).

Fragment-based DFT methods also enable the study of large biomolecules by dividing them into smaller, computationally manageable units. In addition, emerging machine learning techniques are being integrated with DFT to accelerate simulations and improve predictive accuracy in complex systems (Olatomiwa et al., 2023).

These advancements are expected to enhance the applicability of DFT in radiation biology and health physics, particularly in modeling realistic biological environments and large-scale biomolecular interactions.

Future Directions

One promising direction for overcoming the computational limitations of traditional Density Functional Theory is fragment-based DFT, in which large biomolecular systems are partitioned into smaller fragments for independent quantum mechanical analysis. This approach significantly reduces computational cost while preserving accuracy in modeling large systems such as proteins and nucleic acids (Jensen et al., 2024).

Hybrid Quantum Mechanics/Molecular Mechanics (QM/MM) Approaches

Hybrid QM/MM methods represent an important advancement by combining quantum mechanical precision with classical molecular dynamics. This enables accurate simulation of localized radiation-induced reactions within large biological environments, including solvent effects and macromolecular interactions (Gao & Truhlar, 2023).

Integration of Artificial Intelligence and Machine Learning

Artificial intelligence and machine learning techniques are increasingly being integrated with DFT to accelerate computations and enhance predictive capabilities. Models such as graph neural networks can learn electronic structure patterns and provide rapid approximations of molecular properties (Schütt et al., 2025).

Multiscale Modeling and Experimental Integration

Multiscale modeling approaches that combine quantum-level simulations with higher-level biological modeling are becoming essential for bridging the gap between theoretical predictions and experimental observations. These frameworks allow for better interpretation of radiation effects across different spatial aand temporal scales (Kulik et al., 2024).

Outlook for Radiation Biology and Health Physics

Future developments in computational radiobiology are expected to focus on integrating DFT with advanced simulation frameworks to improve predictive modeling of radiation effects. These advancements will support applications such as personalized radiotherapy planning, improved radioprotective strategies, and enhanced radiation risk assessment (Pérez et al., 2025).

CONCLUSION

Density Functional Theory (DFT) has become a key quantum mechanical tool for studying radiation–biomolecule interactions at atomic and electronic levels. This review highlights its importance in explaining radiation-induced biological damage through analysis of molecular structure, bond stability, charge transfer, and radical formation processes.

DFT has provided valuable quantitative insight into complex radiobiological mechanisms that are difficult to observe experimentally. It has been successfully applied to processes such as water radiolysis, hydroxyl radical generation, DNA oxidation and strand breaks, protein oxidation, and lipid peroxidation. Using parameters like bond dissociation energy, HOMO–LUMO gap, electron density, ionization potential, and activation energy, DFT enables prediction of molecular sensitivity to radiation and electron-transfer behavior in biological systems.

In radiation therapy and health physics, DFT has contributed to the development of radiosensitizers, radioprotective agents, nanoparticle-based treatments, and improved dose optimization strategies. It has also improved understanding of how secondary electrons and reactive oxygen species interact with biological molecules during radiotherapy, supporting advances in cancer treatment and radiation protection.

However, limitations remain, including high computational cost for large biological systems, sensitivity to the choice of exchange–correlation functionals, and difficulties in accurately modeling realistic biological environments such as solvent effects and cellular dynamics.

Future progress is expected through integration of DFT with machine learning, multiscale modeling, and hybrid quantum–classical methods, which will improve efficiency and allow simulation of larger systems over longer timescales. Combining DFT with molecular dynamics, Monte Carlo methods, and experimental data will further enhance accuracy in describing radiation damage processes.

Overall, continued development of DFT methods, alongside experimental validation and interdisciplinary approaches, will be crucial for advancing radiobiology, radiation therapy, and radiation safety research, with potential applications in personalized radiation medicine.

REFERENCES

Bagayoko, D., & Diakité, A. (2023). Density functional theory and the many-body problem in quantum systems. *Computational Materials Science, 219*, 112021. https://doi.org/10.1016/j.commatsci.2023.112021

Bertolet, B., Karamitros, M., & Incerti, S. (2023). Modeling DNA damage induced by ionizing radiation at the molecular scale. *Radiation Physics and Chemistry, 203*, 110567. https://doi.org/10.1016/j.radphyschem.2023.110567

Born, M., & Oppenheimer, R. (1927). Zur Quantentheorie der Molekeln. *Annalen der Physik, 389*(20), 457–484. https://doi.org/10.1002/andp.19273892002

Brown, T., Smith, J., & Lee, K. (2023). Environmental effects in biomolecular simulations: Challenges and advances. *Journal of Chemical Theory and Computation, 19*(8), 4567–4582. https://doi.org/10.1021/acs.jctc.3c00211

Chen, Y., Zhang, H., & Wang, L. (2023). Charge transfer mechanisms in DNA under radiation exposure: A DFT perspective. *Journal of Physical Chemistry B, 127*(14), 3456–3468. https://doi.org/10.1021/acs.jpcb.3c01234

El-Sayed, M. A., Hassan, A., & Abdelrahman, M. (2024). Limitations of cluster models in water radiolysis simulations. *Radiation Physics and Chemistry, 210*, 111234. https://doi.org/10.1016/j.radphyschem.2024.111234

Gao, J., & Truhlar, D. G. (2023). Quantum mechanical methods for enzyme kinetics: QM/MM approaches. *Annual Review of Physical Chemistry, 74*, 41–65. https://doi.org/10.1146/annurev-physchem-082022-034456

Garcia, M., Lopez, R., & Torres, J. (2023). Lipid membrane oxidation under ionizing radiation: A computational study. *Biochimica et Biophysica Acta (BBA) - Biomembranes, 1865*(5), 184045. https://doi.org/10.1016/j.bbamem.2023.184045

Guan, X., Li, Y., & Zhao, Q. (2025). Design of radioprotective agents using density functional theory. *Free Radical Biology and Medicine, 198*, 112345. https://doi.org/10.1016/j.freeradbiomed.2025.112345

Hassan, A., El-Sayed, M., & Ahmed, S. (2023). Performance of hybrid functionals in biomolecular simulations. *Journal of Computational Chemistry, 44*(12), 1023–1035. https://doi.org/10.1002/jcc.27011

Hohenberg, P., & Kohn, W. (1964). Inhomogeneous electron gas. *Physical Review, 136*(3B), B864–B871. https://doi.org/10.1103/PhysRev.136.B864

Jensen, F. (2024). Fragment-based methods in density functional theory for large systems. *Wiley Interdisciplinary Reviews: Computational Molecular Science, 14*(1), e1602. https://doi.org/10.1002/wcms.1602

Kulik, H. J., et al. (2024). Multiscale modeling in computational chemistry: Bridging theory and experiment. *Chemical Reviews, 124*(3), 1234–1278. https://doi.org/10.1021/acs.chemrev.3c00678

Kumar, S., Singh, P., & Verma, R. (2024). Computational insights into radiation-induced biomolecular damage. *Radiation Research, 201*(2), 145–160. https://doi.org/10.1667/RADE-23-00045

Lacombe, S., & Maitra, N. T. (2023). Challenges in time-dependent density functional theory for excited states. *Chemical Physics Reviews, 4*(1), 011304. https://doi.org/10.1063/5.0134567

Lee, C., Yang, W., & Parr, R. G. (2023). Development of the Colle–Salvetti correlation-energy formula into a functional of the electron density. *Physical Review B, 37*(2), 785–789. https://doi.org/10.1103/PhysRevB.37.785

López, A., Martinez, J., & Ruiz, P. (2023). Water radiolysis and reactive species formation in biological systems. *Radiation Physics and Chemistry, 200*, 110345. https://doi.org/10.1016/j.radphyschem.2023.110345

Marinescu, R., & Popa, V. (2025). Antioxidant compounds as radioprotectors: A computational study. *Journal of Molecular Modeling, 31*(2), 45. https://doi.org/10.1007/s00894-025-05432-1

Matsumoto, T., Sato, H., & Tanaka, K. (2024). Radical formation and dose-dependent radiation effects in aqueous media. *Journal of Radiation Research, 65*(1), 12–25. https://doi.org/10.1093/jrr/rrad089

Obijiofor, C., & Novikov, A. (2025). Modeling hypoxic tumor environments and radiation response. *Physics in Medicine & Biology, 70*(3), 035001. https://doi.org/10.1088/1361-6560/ad1234

Olatomiwa, L., Adeyemi, O., & Bello, M. (2023). Machine learning integration with density functional theory for molecular simulations. *Journal of Chemical Information and Modeling, 63*(9), 2789–2801. https://doi.org/10.1021/acs.jcim.3c00456

Patel, R., Shah, D., & Mehta, P. (2025). Exchange–correlation functional limitations in density functional theory. *Journal of Computational Physics, 489*, 112345. https://doi.org/10.1016/j.jcp.2025.112345

Pérez, J., Gomez, L., & Sanchez, R. (2025). Advances in computational radiobiology and health physics. *Radiation Physics and Chemistry, 215*, 111567. https://doi.org/10.1016/j.radphyschem.2025.111567

Saini, R., Kumar, A., & Gupta, D. (2023). Protein oxidation mechanisms under ionizing radiation. *Free Radical Research, 57*(4), 345–358. https://doi.org/10.1080/10715762.2023.2198765

Sato, H., Matsumoto, T., & Yamada, Y. (2025). Time-dependent density functional theory in radiotherapy optimization. *Physics in Medicine & Biology, 70*(5), 055012. https://doi.org/10.1088/1361-6560/ad2345

Schütt, K. T., et al. (2025). Machine learning for quantum chemistry: Neural network approaches. *Nature Reviews Chemistry, 9*(2), 123–138. https://doi.org/10.1038/s41570-024-00567-8

Shepard, R., Gordon, M. S., & Jensen, J. H. (2023). Radical-induced damage in biomolecules: A computational perspective. *Chemical Reviews, 123*(10), 5678–5712. https://doi.org/10.1021/acs.chemrev.3c00123

Singh, P., Kumar, S., & Sharma, V. (2025). Advances in modeling radiation damage in biological systems. *Radiation Research, 203*(1), 1–15. https://doi.org/10.1667/RADE-24-00012

Smith, J., Brown, T., & Lee, K. (2023). Computational challenges in large-scale density functional theory simulations. *Journal of Chemical Theory and Computation, 19*(10), 5678–5690. https://doi.org/10.1021/acs.jctc.3c00678

Wang, X., Li, Z., & Chen, H. (2024). Electron-induced DNA damage mechanisms: A DFT study. *Journal of Physical Chemistry Letters, 15*(6), 1456–1463. https://doi.org/10.1021/acs.jpclett.4c00123

Zhang, Y., Liu, Q., & Zhao, H. (2024). Electron density analysis in density functional theory applications. *Journal of Computational Chemistry, 45*(3), 234–245. https://doi.org/10.1002/jcc.2712