Advances in Basic and Applied Sciences 3 (2024) 52-65

Advances in Basic and Applied Sciences

journal homepage: https://abas.journals.ekb.eg/

Modeling of DNA Radiation damage and Biological Response using Monte Carlo Simulation

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ARTICLE INFO

Article history:
Received 19 July 2024
Received in revised form 6 October 2024
Accepted 18 November 2024
Available online 19 November 2024

doi: 10.21608/ABAS.2024.305610.1047

Keywords: Monte Carlo simulation, DNA damage, single break, double break, biological response.

ABSTRACT

The simulation of DNA damage and the subsequent biological response using Monte Carlo simulation techniques is a pivotal area of research in radiation biology and biophysics. Monte Carlo simulations offer a powerful tool for understanding the complex interactions between ionizing radiation and biological systems at a microscopic level. This study aims to develop a comprehensive Monte Carlo simulation model to quantitatively assess DNA damage and predict the biological response of cells exposed to various types and doses of radiation. By modeling the stochastic nature of radiation interactions with biological tissues, we can simulate the generation of primary and secondary ionization events, track the trajectories of ionized particles, and evaluate the resultant DNA damage. The simulation incorporates detailed biological models to account for various types of DNA lesions, including single and double-strand breaks, as well as complex clustered damage sites. Furthermore, the model extends to simulate the cellular response mechanisms, including DNA repair processes, cell cycle arrest, and apoptosis. By integrating these biological responses into the simulation framework, we can predict the probability and extent of cellular damage and survival, providing insights into dose-response relationships and the efficacy of radioprotective agents. The results of this simulation study have significant implications for radiotherapy, radiation protection, and our fundamental understanding of radiation-induced carcinogenesis. By providing a detailed mechanistic understanding of DNA damage and repair, the Monte Carlo simulation model serves as a valuable tool for optimizing radiation treatments and developing strategies to mitigate the adverse effects of radiation exposure. In conclusion, the simulation of DNA damage and biological response using Monte Carlo methods represents a critical advancement in the field of radiation research, offering precise and predictive capabilities that enhance our understanding and management of radiation effects on living organisms.

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1. Introduction

In recent years, there has been a noticeable interest in using biophysical models in radiation therapy of cancer patients to identify the best treatment plans with minimal side effects [1]. This interest is driven by advancements in 3D treatment planning and intensity-modulated radiotherapy, which allow for highly complex dose distributions that were almost unimaginable years ago. Accurate prediction of treatment outcomes provides clinicians with better tools to design more effective treatment plans, achieving improved outcomes while reducing patient side effects [2].

In fact, the primary target of radiation therapy in inducing cell kill is the deoxyribonucleic acid (DNA) within the cells. Ionizing radiation, such as X-rays or gamma rays causes damage to the DNA molecules in cells by directly breaking the DNA strands or indirectly through the generation of free radicals that diffuse and interact with the DNA causing different types of damage [3].

When DNA damage occurs, multiple events can take place including single strand break (SSB), double strand break (DSB), multiple or clustered DNA breaks. In particular, DSBs and its variants can lead to cell death through various mechanisms. Cells have intricate repair mechanisms to fix DNA damage, but if the damage is too severe or if the repair is unsuccessful, the cells may undergo programmed cell death (apoptosis) or mitotic catastrophe [4]. Radiation therapy aims to maximize DNA damage in cancer cells while minimizing damage to surrounding healthy tissues. Monte Carlo simulation, as mentioned earlier, plays a crucial role in understanding the effects of radiation on DNA and therefore can potentially aid in optimizing biophysical models in improving the radiobiological aspects of radiation therapy [5]. Incorporation of iodine (I-125) into DNA served to cause a high incidence of apoptosis in several cell lines provided evidence that DNA is the effective target for inducing cell death [4]. Apoptosis is a phenomenon related to mitosis within interphase, which occurs pre-mitosis during cell cycle. It may happen prior to cell division following radiation by inducing G2 block or following division. Apoptotic factors can originate from the nucleus or the cell membrane, where the hydrolysis of sphingomyelin to create ceramide starts the sphingomyelin pathway [6].

2. SSB and DSB

As outlines earlier, Both SSB and DSB can be brought on by radiation, and the induction of DSBs is typically regarded as a fatal event [7]. SSB occurs when one of the two strands of the DNA double helix is broken, leaving the other intact, leading to a break in the sugar-phosphate backbone of the DNA molecule. SSBs can be repaired through processes such as base excision repair and nucleotide excision repair [8-10]. DSBs are more severe forms of DNA damage where both strands of the DNA molecule are broken. DSBs can be challenging to repair and can result in chromosomal rearrangements if not properly addressed [11, 12]. DSBs are considered one of the most cytotoxic types of DNA damage and can lead to chromosomal rearrangements if not properly repaired. The repair of DSBs can occur through pathways such as non-homologous end joining (NHEJ) or homologous recombination [13]. Figure 1 shows the change of SSB and DSB per electron as function of electron energy. The maximum yield of SSB and DSB was found to cluster around the energy range 0.3- 0.6 keV, which gradually decreases as the energy of the incident electron increases. Our input in Monte Carlo simulation technique is the type of radiation with several number of incidents and choose the single or spectrum of energy as keV then the simulated tool can count the damage which occur in DNA as SSB & DSB and can calculate the energy deposition.

Clustered DNA damage refers to the occurrence of multiple DNA lesions in proximity within a small region of the DNA molecule. This can include the clustering of SSBs, DSBs, or a combination of both. Clustered DNA damage is particularly challenging for repair mechanisms as it can hinder the accurate repair of individual lesions and increase the likelihood of mutations or chromosomal abnormalities [14]. In the context of DNA damage in the framework of radiobiology, a higher number of DSBs is typically associated with more severe biological consequences. Clustering of DSBs, which impairs the repair process and increases the risk of mutations and chromosomal instability is a significant factor contributing to DNA damage [15].

In addition to DSB clustering, other factors that could contribute to DNA damage include the type and energy of ionizing radiation, exposure duration, individual genetic susceptibility, cellular repair mechanisms, and the presence of reactive oxygen species. These factors can influence the extent and complexity of DNA damage, affecting the biological response to radiation exposure [16]. Furthermore, the presence of complex DNA lesions, delayed repair processes, and the potential for carcinogenesis due to gene mutations and chromosomal abnormalities further underscore the importance of understanding the mechanisms of DNA damage and repair. Advanced techniques such as the comet assay and γ-H2AX detection can aid in analyzing DNA damage and assessing the effectiveness of repair mechanisms [17].

Overall, a comprehensive understanding of these factors and the application of Monte Carlo simulation techniques can enhance our knowledge of DNA damage and its implications on biological systems, providing valuable insights for optimizing radiation therapy and minimizing risks associated with radiation exposure [18]. Simulation techniques like Monte Carlo simulation can indeed provide valuable predictions and insights into the effects of radiation on cells and tissues during irradiation. By simulating the physical interactions of ionizing radiation with biological materials at the atomic or DNA level, researchers can better understand the mechanisms of DNA damage and repair, as well as the biological response to radiation exposure [19].

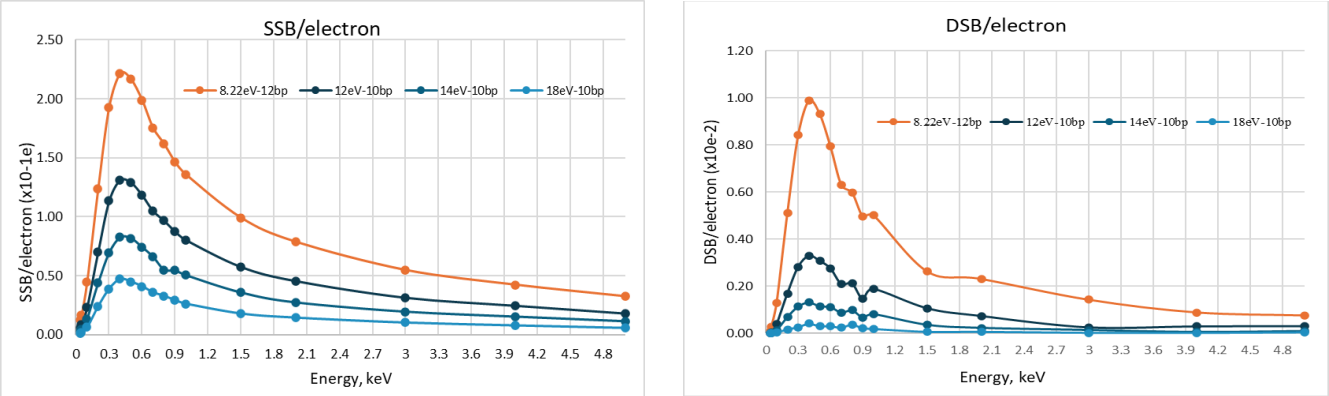

Fig. (1): Spectrum of the SSB (left) and DSB (right) per electron measured for wide range of electron and base pair cut-off values for the energy range 0.04 to 5 keV. Notice that SSB is a multiplication of the factor $x10^{-1}$ and DSB is a multiplication of the factor $x10^{-2}$.

These simulations can help in predicting the outcomes of radiation therapy treatments, optimizing treatment plans, and minimizing potential side effects. Additionally, studying the effects of radiation through simulation can aid in identifying potential risks associated with radiation exposure, such as DNA damage, mutations, and chromosomal instability. Overall, simulations play a crucial role in advancing our understanding of the complex processes involved in radiation biology and can contribute to improving cancer treatment strategies and patient outcomes [20]. Computational method based on Monte Carlo Simulation which is the most valuable technique helpful to simulate track structures in a biological media to calculate the effect of ionizing radiation on DNA. Geant4-DNA Monte Carlo toolkit can simulate physical, physico-chemical, and chemical stages of water radiolysis.

3. Monte Carlo simulation

Monte Carlo models are a type of numerical computer simulation technology that employs statistical resampling to solve complicated systems that are difficult to analyze. Since their conception, MC approaches have been effectively employed in a wide range of fields, including quantum physics, electrical and telecommunication engineering, computational biology, weather forecasting, and, most recently, computer board games [21]. Monte Carlo techniques have been modified to increase their use in radiation therapy with applications in treatment source modeling, imaging process simulations, and patient dose calculations for treatment planning or to get a more optimal estimate of the delivered dose and calculation acceleration techniques for radiation doses [22-24].

4. Different codes are used in DNA damage simulation.

In the context of DNA damage simulation, there are several codes and software programs used to model and study the effects of radiation on DNA. Some of the notable codes are summarized as follows.

4.1. MCNP

The Monte Carlo N-Particle Transport Code (MCNP) is a general-purpose Monte Carlo radiation transport code that can be used for simulating the transport of photons, electrons, and neutrons in complex geometries [25]. It is widely used in radiation physics and dosimetry studies, including the simulation of radiation effects on biological systems such as DNA [26].

4.2. FLUKA

FLUKA is another Monte Carlo simulation code that is used for simulating the transport of particles and radiation through matter. It is commonly used in radiation physics, medical physics, and radiation protection studies to model the interaction of radiation with biological tissues, including DNA damage [26].

4.3. PENELOPE

PENELOPE is a code for the simulation of electron and photon transport in arbitrary materials. It is often used in medical physics and radiation therapy research to study the effects of radiation on biological tissues, including the induction of DNA damage and the development of treatment plans [27].

4.4. PARTRAC simulations

PARTRAC is a Monte Carlo simulation software specifically designed for simulating the physical, physico-chemical, and chemical processes involved in the interaction of ionizing radiation with biological systems. Like Geant4-DNA, PARTRAC is capable of tracking particles in liquid

water and simulating the direct damage to biological sub-units such as DNA [28]. It allows for the detailed study of radiation-induced DNA damage, SSBs, DSBs and clustered DNA lesions [29, 30]. By utilizing PARTRAC simulations, researchers can gain insights into the complex mechanisms of DNA damage and repair following exposure to ionizing radiation. This software can provide valuable information on the biological response to radiation-induced DNA damage, helping to improve our understanding of the effects of radiation therapy and optimize treatment strategies. In summary, PARTRAC simulations serve as a powerful tool for studying the interactions between ionizing radiation and biological systems, particularly in the context of DNA damage. Its capabilities in simulating radiation-induced biological effects make it an asset in the field of radiation biology and radiation therapy research.

4.5. Geant4-DNA

Geant4-DNA is a Monte Carlo simulation code specifically designed to simulate the physical, physico-chemical, and chemical stages of water radiolysis. It can track particles in liquid water and simulate direct damage to small biological sub-units, including the induction of DNA damage such as double-strand breaks (DSBs) and clustered DNA damage [31, 32]. Geant4-DNA is the only available source simulation model which aims to extend GEANT4 to model the effects of radiation on biological systems at cellular and DNA [33]. The GEANT4-DNA code is actively being extended to include physical, chemical, and biological models to simulate cellular and subcellular damage induced by ionizing radiation [34]. It has effectively included a new set of electromagnetic processes and can now track particles in liquid water including low-energy electrons (2 eV^{-1} MeV), protons (10 eV–100 MeV), alpha particles (1 keV–400 MeV), light atoms (H, He, C, O, N, Fe), and ions [35]. The detector construction class in Geant4 enables the development of precise DNA and cellular shapes. It is modeled as a B-DNA arrangement of 30 nm chromatin fibers totaling $5.4x10^8$ base pairs bombarded by varied strengths of protons and alpha particles. By physically tracking particles, Geant4-DNA allows for the simulation of direct damage to small biological sub-units [36].

These codes, among others, play a crucial role in understanding the effects of radiation on DNA and optimizing radiation therapy treatment plans by simulating DNA damage, repair mechanisms, and biological responses to radiation-induced damage.

5. Different types of radiations

In the context of radiation and its effects on DNA, it's important to understand the different types of radiation and their qualities [37].

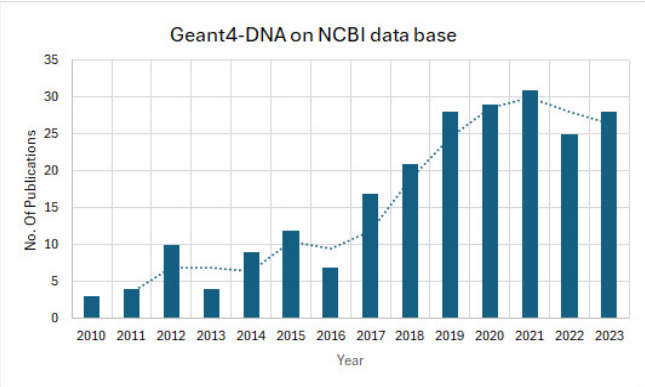

Fig. (2): Shows the number of published journal articles using Geant4-DNA as an investigation tool between 2010 and 2023.

5.1. Photons (X-rays and Gamma rays)

Photons are electromagnetic radiation with no mass or charge. They are commonly used in medical imaging (X-rays) and radiation therapy (X-ray therapy or Gamma Knife)[38]. Photons interact with biological materials primarily through indirect ionization, where they transfer their energy to atoms in the tissue, leading to the creation of free radicals. These free radicals can then cause damage to DNA molecules [37]. The different types of interaction used in Geant4 DNA classified into photons, electron and protons if possible as the three radiations are used in radiation therapy. In simulating DNA damage using Monte Carlo simulation techniques, several physical types of interactions are considered to model the effects of radiation on DNA. They are summarized as follows [39].

5.2. Photon Interactions

5.2.1. Ionization

Ionization is the process by which an atom or molecule acquires a positive or negative charge by gaining or losing electrons [40]. In the context of simulating DNA damage, ionizing radiation (such as X-rays, gamma rays, and charged particles) can directly ionize the DNA molecule, leading to the formation of charged particles and free radicals that can cause damage [40].

5.2.2. Excitation

Excitation occurs when an electron in an atom or molecule is raised to a higher energy state without being completely removed from the atom. This process can result in the formation of excited molecules that can react with DNA and cause damage [40].

5.2.3. Compton Scattering

Compton scattering is a process in which a photon interacts with an outer-shell electron, resulting in the

scattering of the photon and the ejection of the electron [41]. The scattered photon can deposit energy in the DNA molecule, leading to damage [42].

5.2.4. Photoelectric Effect

The photoelectric effect is a process in which a photon is absorbed by an atom, ejecting an electron, and causing the atom to become ionized [43]. This interaction can result in the production of photoelectrons that can cause damage to DNA [44].

5.2.5. Pair Production

Pair production is a process in which a high-energy photon interacts with the electromagnetic field near a nucleus, producing an electron-positron pair. The resulting particles can deposit energy in the DNA molecule, leading to damage [45].

5.2.6. Auger Effect

The Auger effect occurs when an inner-shell electron is ejected from an atom, causing the emission of an Auger electron. This electron can interact with the DNA molecule and induce damage [46]. By considering these physical types of interactions in Monte Carlo simulations, researchers can model the effects of radiation on DNA and gain insights into the mechanisms of DNA damage and repair in response to radiation exposure [47].

6. Charged Particles

6.1. Proton interactions

Elastic scattering occurs when protons collide with atomic nuclei, transferring energy but not affecting the particles' identities. Otherwise, in inelastic scattering, protons send energy to atomic nuclei, which causes atoms to be excited or ionized. Protons ionize atoms by removing electrons and generating ion pairs. It may break DNA strands, leading to mutations or cell death, causing direct DNA damage. Ionization of water molecules generates reactive oxygen species (ROS), which can damage biological components such as DNA, proteins, and membranes, resulting in indirect DNA damage [48]. Nuclear reactions involve high-energy protons that can produce secondary electrons or free radicals, causing DNA strand breakage. High doses of proton radiation can kill cells and are used in proton therapy to treat cancer [45].

The Bragg peak curve displays the energy deposition of charged particles, such as protons or heavy ions, as they pass through DNA [49]. This curve is significant in the field of radiation therapy, namely proton therapy, for cancer treatment [50]. As the particles near at the end of their passage, they lose energy more quickly, producing a sharp peak known as the Bragg peak [51] as shown in fig. 3. The Bragg peak is the point at which the most energy is deposited, causing the most damage to the target cells. Beyond the peak, the energy deposition decreases rapidly, resulting in minimal harm to surrounding healthy tissues [52]. In radiation therapy, the Bragg peak is used to deliver high doses of radiation directly to a tumor while minimizing exposure to healthy tissue. This makes proton therapy an accurate and successful treatment for certain types of cancer [53].

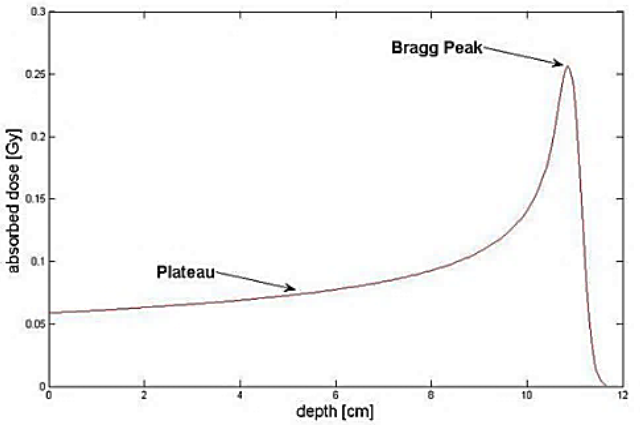

Fig. (3): The Bragg curve represents the absorbed dosage of a monoenergetic proton pencil beam as a function of penetration depth. The dose is low in the plateau region and highest near the end of the proton track, resulting in the so-called Bragg peak.

6.2. Electron interactions

Currently, much is known about how low-energy electrons (LEEs) interact with biomolecules, such as DNA. Providing an insight into the mechanics of electrons created by ionizing radiation is important for determining the radiobiological damage and how it might be modified by DNA changes. These changes lead to increased DNA strand breakage and various lesions. Increased transient anions in DNA can lead to damaging pathways such dissociative electron attachment. Understanding the role of LEEs in radiosensitisation can provide suggestions for developing new radiosensitizers and improving treatments for cancer patients receiving radiotherapy alone or in combination with chemotherapy [54]. Grasping how low energy electrons (LEEs, 0-30 eV) engage with basic molecules and weak biomolecules like O2 and H2O is important for cancer radiation therapy [55].

Experiments on LEE interactions with huge macromolecules have only been conducted in the past two decades, despite their importance to life [56]. Investigations and theoretical studies on electron interactions with basic DNA units, short strands, and bacterial DNA have mainly contributed to our perception of how LEEs mingle with big macromolecules [57]. The experimental results were often achieved by bombarding gaseous solitary targets or clusters of molecules in vacuum, where the molecules might be

vaporized [58]. Biomolecules were introduced from the atmosphere into a vacuum system as multilayer films or self-assembled monolayers [59]. LEEs play a significant role in radiation-induced DNA damage and have potential applications in radiotherapy [60]. Transient anions (TA) are the primary mechanism for breaking chemical bonds with electrons in biomolecules at low energy levels [59]. Quasi-bound states occur when an incident LEE temporarily occupies a previously unoccupied orbital of a molecule. In larger biomolecules, the extra-electron orbital often belongs to a basic unit. The TA can decay by either expelling electrons into a vacuum or dissociating. The final phase, called dissociative electron attachment (DEA), causes bond breakdown [54]. When an anion is autoionized, the electron attachment point becomes dissociative excited, leading to bond scission. Transient anion decay channels can cause DNA damage, such as single and double strand breaks, crosslinks, and other deadly lesions [54].

High-Resolution Electron Energy Loss Spectroscopy (HREELS) is an effective technique for measuring and studying the absolute cross sections of LEEs scattering from biomolecules. These cross sections are used to calculate doses in radiotherapy for cancer treatment. Radiotherapy is an effective and important method for cancer treatment. When high energy ionization radiation (HEIR) (β-rays, ϒ-rays, X-rays) interact with biomolecules like DNA, they deposit energy across the biological medium, resulting in the formation of ions, radicals, and secondary electrons (~10^4 electrons per MeV) [61]. Inelastic processes include low energy secondary electrons collaborate with biomolecules through biological medium. Monte Carlo codes can help predict and explain these damages requiring many variables such as interaction probabilities and cross sections. Determining electron interactions with DNA at low to intermediate energy is complicated due to limited data and the rapid reaction (10^{-18} to 10^{-15} sec) [61]. Elastic scattering occurs when electrons deflect off atomic nuclei or other electrons while retaining their energy. But inelastic Scattering: Electrons lose energy by exciting or ionizing atoms and break DNA strands causing base damage in one strand of DNA. Ionization of water creates reactive oxygen species (ROS), which damage cellular components which causes indirect damage of DNA [62]. Bremsstrahlung is the process by which high-speed electrons decelerate near atomic nuclei and release X-rays. High dosages of electron radiation can cause cell death when applied to electron beam therapy. Uses of electrons as radio therapy cause damage to skin and superficial tissues [63]. Auger Effect: Electrons removed from atoms can result in the emission of secondary electrons which causes cell death or chromosomal abnormalities [46].

6.3. Heavy Ions

Heavy ions are charged particles with high mass, such as carbon ions. They have unique physical and biological properties that make them effective in cancer treatment due to their characteristic energy deposition profile known as the Bragg peak [64]. Each type of radiation interacts with biological tissues differently, leading to varying degrees of DNA damage. Monte Carlo simulations can model these interactions to study the effects of different types of radiation on DNA and help optimize treatment strategies for various medical applications [64]. The interactions of heavy charged particles include elastic scattering occurs when heavy particles scattered from atomic nuclei with minimal energy loss. Inelastic scattering happens when heavy particles transfer large amounts of energy to atomic nuclei, resulting in ionization and excitation [65]. Where ionization occurs when heavy particles ionize atoms as they travel, leaving dense ionization tracks [66]. But nuclear reactions appear when heavy charged particles can cause nuclear reactions, which generate secondary radiation [67]. High Linear Energy Transfer (LET) occurs when heavy particles deposit a lot of energy across short distances, resulting in dense ionization trails [68].

The direct damage of DNA occurs when high LET radiation causes complex, clustered DNA damage, and is difficult for cells to repair but the indirect damage occurs when water ionization produces ROS, which causes oxidative damage [69]. Heavy charged particles are extremely effective in killing cells and are commonly used in cancer therapy. Radiation Sickness and long-term effects occur after exposure causes acute radiation syndrome and increases the risk of cancer and other health disorders [69]. Finally, we can conclude that protons are used in proton treatment because they can precisely target tumors while causing minimum damage to surrounding tissue. Furthermore, electrons which use to treat superficial tumors because of their limited penetration depth. But heavy charged particles are used in heavy ion therapy because of their high LET and efficiency in treating radioresistant malignancies [70]. Understanding the interactions and biological effects of protons, electrons, and heavily charged particles is critical for their use in medical therapies and determining radiation safety. Each type of particle has unique interaction processes and biological effects, making them useful for a variety of therapeutic and diagnostic applications [71].

7. Track Structure versus Condensed History

7.1. Condensed History

Condensed-history MC codes segment a particle travel into discrete stages and use stochastic methods to determine the particle's scattering angle and energy transfer to surrounding materials. Condensed-history MC codes are classified into two types based on their segmentation technique: those with fixed step-sizes (class I) and those with stochastically determined step-sizes (class II). Condensed-history MC codes have limitations due to the step-size and cutoff energy for particle tracking. Condensed-history MC codes were designed for transporting energetic particles,

requiring lengthy step-sizes and minimal cutoff values due to energy resolution and time trade-off. High-energy MC codes have difficulties when used for low-energy interactions in microscale scoring structures [72].

7.2. Track structure simulation.

For many years, track structure codes have been used to simulate the physical interactions of ionizing particles with biological materials on small scales and low energy [36]. Some codes are restricted to physical interaction simulations, whereas others include water radiolysis simulations, realistic geometrical representations of biological targets, and biological repair mechanisms [73]. Individual particle interactions in the traversed medium are simulated using Monte Carlo simulations of main particles and secondary particles [74]. These simulations necessitate knowledge of a variety of categories, including cross-sections for important interaction processes, energy transfer differential, angular deviation, and secondary energy and production angles [75, 76]. In liquid water, the implemented cross sections for electrons, protons, and (He) ions are used as a substitute for biological components [77]. Track structure programs are used to simulate the physical interactions that occur after an incident particle passes through biological materials, resulting in nanometer-scale energy depositions and ionizations in exact cell models. Following these interactions, the generated radical species react with ionized molecules in the physico-chemical stage, followed by the transfer of chemical products on a similar scale [77]. During this stage, the latter react with each other and have different effects on the cell components. The entire procedure culminates in the determination of direct and indirect damage to the cell primary target, genetic molecules [78].

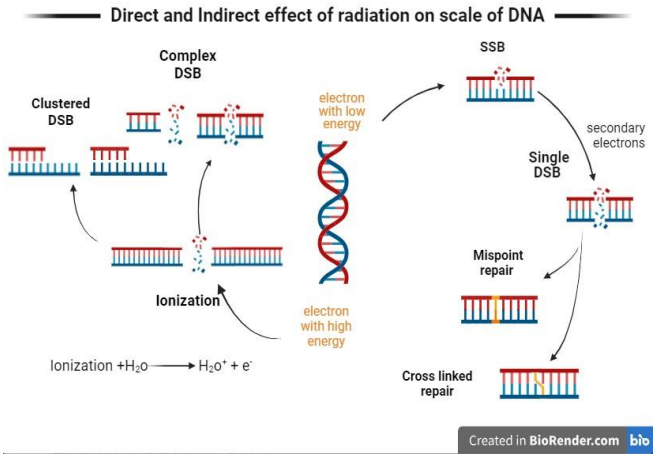

Fig. (4): Shows the difference between direct and indirect effect of radiation on DNA scale with the difference between the track structure simulation and condensed history.

Figure 4 illustrates the direct and indirect effects of radiation on DNA, as well as the difference between the interaction of electrons with low energy with DNA which produced secondary electrons and caused the single DSB, and the interaction of electrons with high energy with DNA, which resulted in ionization and clustered DSB, and the effect of secondary electrons on single DSB.

8. Target Geometry

8.1. Amorphous Geometry

Amorphous geometry refers to DNA that is more disorganized and less structured. This could occur in some situations where the DNA does not have a regular, repeating structure. It lacks a crystalline structure, which means that its atoms are not grouped in a long-range periodic order like the double helix. In some conditions, such as when DNA is denatured (separated into single strands), it may take on an amorphous, random coil configuration. This happens when the hydrogen bonds between base pairs are broken, and the strands no longer maintain the double helical structure. Amorphous DNA can form in a variety of biological situations, including DNA replication, transcription, and when DNA is subjected to physical or chemical stress that disturbs its normal structure [79]. Amorphous models in Monte Carlo simulations are critical for researching disordered systems. They offer realistic simulations of materials that lack long-range order, enabling extensive examination of physical properties and interactions. However, they have a higher complexity and computational cost, needing careful model construction and validation [80].

8.2. Atomistic Geometry

Atomistic geometry is the accurate and precise description of the DNA molecule at the atomic level. This includes the precise places of all atoms in the DNA structure. The double helix, described by Watson and Crick, is the best-known atomistic structure of DNA. This structure consists of a sugar-phosphate backbone and nitrogenous bases (adenine, thymine, cytosine, and guanine), which pair precisely (A-T and C-G). Atomistic models consider a variety of interactions, including hydrogen bonds between base pairs, van der Waals forces, and other molecular forces that maintain the DNA's stability and unique geometry. Crystallography and NMR are commonly employed to identify the atomistic structure of DNA, resulting in highly detailed models that include every atom in the molecule [81].

Atomistic geometry models in Monte Carlo simulations give a highly comprehensive and precise description of materials and biological systems, allowing for accurate analysis of atomic-level interactions and elements. While they provide valuable insights into material behavior, chemical reactions, and biological processes, they are computationally demanding and necessitate meticulous model development and parameterization. Despite these obstacles, their ability to offer thorough and reliable

information makes them indispensable in sectors such as materials science, biology, and pharmaceutical research [82].

9. Radiological Modeling and simulations

9.1. Monte Carlo simulation and DNA damage

MC simulations can reproduce the random phenomena of complex radiation transmission without any large approximation or assumptions [83]. Monte Carlo programs have been created to mimic damage induction at the DNA scale, with a focus on the underlying biological mechanisms of cellular response to radiation [84]. Many theoretical investigations, as well as Monte Carlo track structure computations, have supported understanding and consolidating the differences between different quality radiations, measuring the dynamics of clustered DNA damage, and efforts to create model-guided experiments [85]. MCTS simulates physical interactions that cause "direct" DNA damage, as well as models of chemical species formation and early reactions that cause "indirect" DNA damage. As a result, track structure programs are effective tools for simulating particle tracks in biological matter, and they have a lot of experience calculating radiation effect parameters for radiotherapy and radiation protection [86].

10. Radiation Damage

10.1. Physics of Interactions

The interaction of radiation with living cells contains the transfer of energy from the radioactive materials to atoms and molecules of the irradiated materials [87]. This occurs through various patterns of atomic and nuclear interactions in the form of inelastic and elastic scatterings [87]. A simulation of the Monte Carlo path structure is based either on solving analytic equations that describe the transfer of charged elements in a biological medium or on a numerical solution by sampling the model of the particle interactions with the atoms and molecules of the substance [88].

11. Types of Biological Damage

Biological damage resulting from radiation exposure can manifest in various forms, particularly at the DNA level. Some of the key types of biological damage include:

1. Clustered DNA Damage: Clustered DNA damage refers to the occurrence of multiple DNA lesions, such as SSBs and DSBs, in proximity within a small region of the DNA molecule. This type of damage can be particularly challenging for repair mechanisms and can increase the risk of mutations and chromosomal abnormalities [89].

2. Chromosomal Rearrangements: Chromosomal rearrangements can occur because of DNA damage, particularly DSBs, leading to changes in the structure of chromosomes. If not repaired correctly, these rearrangements can contribute to genetic instability and potential adverse consequences [89].

3. Mutations: DNA damage can lead to mutations in the genetic code, which can affect normal cellular functions and potentially contribute to the development of diseases, including cancer [89].

4. Cell Death: Severe DNA damage can trigger programmed cell death (apoptosis) or result in mitotic catastrophe, where cells undergo catastrophic mitosis due to unrepaired DNA damage [89].

Understanding these types of biological damage is crucial in assessing the impact of radiation exposure on cells and organisms, as well as in developing strategies to mitigate the adverse effects of DNA damage [89].

12. Biological Response

The biological response to DNA damage, particularly clustered DNA damage, is a critical aspect of understanding the effects of radiation on cells. When DNA sustains damage cells activate various mechanisms to repair the lesions and maintain genomic integrity. However, if the damage is severe or not properly repaired, it can lead to a range of biological responses with significant implications [90]. One of the responses to clustered DNA damage is cell death. Cells may undergo programmed cell death known as apoptosis, to eliminate themselves if the damage is too severe to be repaired. This process helps prevent the propagation of damaged cells and maintains tissue homeostasis. In cases where cells with unrepaired DNA damage continue to divide, they may experience mitotic catastrophe, a form of cell death resulting from aberrant mitosis due to damaged DNA [91].

The timing of DNA damage repair is also crucial for the biological response. Delayed repair of DNA damage particularly DSB can increase the likelihood of mutations and chromosomal abnormalities. Persistent DSBs left unrepaired can lead to genomic instability and potentially contribute to the development of cancer [91]. Carcinogenesis, the process of cancer development can be linked to clustered DNA damage. When clustered lesions are not correctly repaired or remain unresolved, they can result in gene mutations and chromosomal instability, providing fertile ground for the initiation and progression of cancer [91].

To evaluate DNA damage and monitor repair processes, researchers utilize techniques such as the comet assay and γ-H2AX detection. The comet assay is effective in quantifying DNA damage in the form of single-strand breaks (SSBs) and double-strand breaks (DSBs), providing insights into the extent of damage within cells. On the other hand, γ-H2AX detection focuses on the phosphorylation of the H2AX protein, a marker closely associated with DSB repair processes [91]. Overall, understanding the biological

response to clustered DNA damage is essential for elucidating the consequences of radiation exposure on cells. By studying how cells react to DNA damage and how repair mechanism's function, researchers can improve radiation therapy strategies, minimize potential risks such as carcinogenesis, and enhance treatment outcomes for patients [91].

13. Biological Response to clustered DNA Damage

13.1. Role of Delayed Repair

Complex DNA lesions, such as DSB and non-DSB clusters, provide a significant challenge to DNA repair processes and cell destiny [92]. The biological relevance of clustered DNA lesions created by repeated ionizations stems from cells failure to process them efficiently when compared to isolated DNA damages, and the consequences of incorrect repair can range from cell death to mutations and chromosomal instability [92]. When DNA damage is repaired by the less accurate non-homologous end-joining (NHEJ) or alternative non-homologous end-joining pathways, chromosomal abnormalities may result [92]. Repair of base damage inside a densely packed damage site is likely to generate further DSBs, either by mistimed endonuclease action at complementary DNA strand base damage or through base damage interaction with the replication machinery [92]. Unrepaired base damage may surround such DSBs formed as repair intermediates, resulting in an unrepairable, complex DSB [92].

Complex DSBs are caused by ionizing radiation or the processing of non-DSB clustered lesions and are either repaired slowly or left unrepaired, causing cell death or mitosis [93]. Large deletions, translocations, and chromosomal abnormalities are found in surviving cells [92]. DNA repair deficits are another mechanism that contributes to the increased mutagenicity of complex DNA damage[92].

Defects in repair enzymes such as DNA and others have been shown to increase the buildup of clustered DNA lesions and genomic instability, as reviewed in [94]. Finally, environmental stress causes DNA damage in cells and tissues through either direct generation of DNA lesions (radiation, chemicals) or epigenetic alterations such as DNA methylation of important repair gene promoters, which reduces repair effectiveness. While delayed or incorrect repair of clustered DNA lesions causes mutations and genetic instability in normal tissue in humans, an "optimistic" theory suggests that it may also assist malignant cells kill themselves [94].

13.2. Double-strand Break Clustering

The existence of additional lesions near a DSB typically determines the degree of damage complexity. DSB clustering is an additional degree of complexity that might prevent lesion processing by creating chromatin instability in the area surrounding a cluster [95]. Exposure of cells to ionizing radiation (especially high-LET radiation) causes the development of DSB clusters. The biological significance of DSB clustering is theoretically validated by substantial mathematical modeling [95]. However, the bulk of experimental approaches used to measure ionizing radiation-induced DNA damage dosage does not provide much information about the precise quantity and spatial arrangement of lesions within one or two helical turns of the DNA, leaving biological responses unknown [95].

13.3. Carcinogenesis Associated with Clustered DNA Damage

DSBs are the most important type of DNA damage caused by ionizing radiation because they can affect cellular fate by causing cell death or carcinogenesis if left unrepaired or incorrectly repaired [95]. Lower accuracy or weaknesses of cellular repair mechanisms, which are responsible for removing or bypassing damaged sites and restoring the initial sequence after exposure to ionizing radiation, are one of the key possible mechanisms in the initiation of mutagenesis and the promotion of carcinogenesis [96]. The creation of gene mutation is thought to be the most important event that could result from DSB processing. Cell death and carcinogenesis are well-known side effects of translocations. Translocations may not be caused directly by ionizing radiation, but they can be generated because of DSB processing in damaged cells by homologous recombination that has evolved to treat this sort of lesion, according to recent research [96].

14. Techniques for DSB Repair analysis

Some tests have been developed to evaluate DNA damage caused by various chemicals, bacteria, radiation or environmental factors. Some of these assays are explained in the following sections [97].

14.1. Comet assay

In the alkaline comet assay, DNA damage in SSB and DSB is measured. This procedure is both quick and inexpensive. It provides crucial information on the dangers of diseases caused by oxidative stress [97]. Cells are placed in a thin layer of agarose on a thin glass slide, then lysed in a solution containing detergent and NaCl, which frees the DNA from the proteins associated to it while leaving DNA fragments connected to the nuclear membrane [97]. The plate is then incubated in an alkaline solution, followed by an electrophoresis and ethidium bromide staining of the DNA. When seen through fluorescence microscopy, DNA fragments move to the anode, generating a comet like picture [97]. The comet's head represents DNA content, whereas the tail represents the frequency of DNA breaks (Figure 5B). DNA content and tail length can be measured using software

intended to analyze comet images. The amount of DNA damage is related to the length of the comet tail [97].

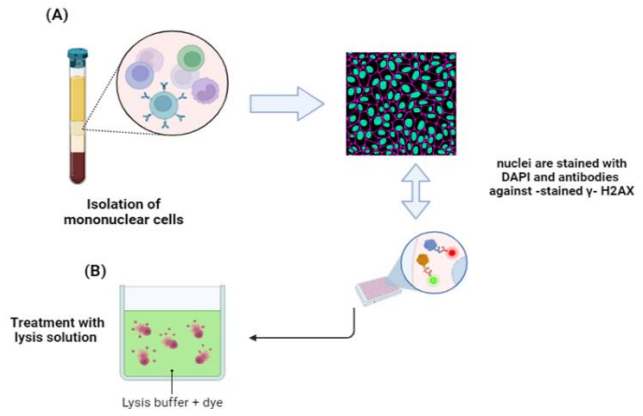

Fig. (5): DNA damage detection assays in general (A) Immunohistochemistry with antibodies against -H2AX: mononuclear cells from peripheral blood are extracted, nuclei are stained with DAPI and antibodies against -stained H2AX, and the cells are seen under fluorescence microscopy. (B) Comet assay: mononuclear cells are also used in the comet assay. On a thin glass slide, the cells are embedded in agarose, lysed, and incubated in an alkaline solution. Electrophoresis is then used to separate the DNA fragments, which are then stained with ethidium bromide. A fluorescent microscope is used to examine the comet-like image. The frequency of DNA breaks is determined by the length of the comet tail.

There is another modified comet assay method in which three different treatments were treated with slides with cells embedded in agarose: 1) Alkaline electrophoresis to detect SSB-induced radiation and alkaline-labile sites; 2) Electrophoresis of cells treated with formamidopyrimidine [Fapy] -DNA glycosylase (Fpg); this releases the damaged purines, leaving apurinic sites (AP sites) that are then cleaved with the cellular AP lyase, producing single strand fragments that can be visualized in the comet assay and 3) Electrophoresis following treatment of the cells with the bacterial endonuclease Endo III, which cleaves the damage strands at oxidized pyrimidine-presenting sites, improving the sensitivity of the comet assay by creating gaps in mutant bases [98].

A disadvantage of the comet assay is its variety through different procedures and laboratories, which makes it difficult to characterize ionizing radiation toxicities. As a result, this issue will need the use of uniform and comparable methods [98]. They considered inter-laboratory differences in comet assay factors like slide brands, alkali treatment duration, and electrophoresis conditions [97]. They discovered that electrophoresis conditions, particularly the temperature during alkaline electrophoresis, affected the rate of conversion of alkali labile sites to single stranded breaks. Furthermore, it has been proposed that comet assay analysis will require the use of standard software.

14.2. γ- H2AX

The histone H2AX variant of the histone H2A is found in small amounts (2 to 25% of total H2A) in nucleosomes and has been linked to DSB repair. The phosphate group in H2AX adopts a location in the protein when it is phosphorylated at serine residue 139 by phosphoinositide-3-kinase-related protein kinases (PIKKs), forming the gamma H2AX (-H2AX) configuration [99]. This phosphoprotein decondenses the chromatin near the DSB in the early stages of DNA repair. H2AX also connects to the DSB ends, generating a "H2AX focus" that extends for several Mb on both sides of the DSB. The detection of -H2AX using antibodies against it is one way for determining DNA damage [99]. Peripheral blood is obtained, and mononuclear cells are isolated and fixed on a glass surface in the -H2AX assays. The data are then evaluated using fluorescence microscopy, which measures fluorescent foci, and immunohistochemistry with anti-H2AX antibody (Figure 5A). Flow cytometry or western blot analysis are alternative options for this test. Measurements of H2AX foci in patients before and after radiotherapies utilizing low and high doses of ionizing radiation revealed a linear association between DNA damage and radiation exposure [99].

The initial number of -H2AX foci in the cells is consistent with DSBs. Due to DNA repair, the H2AX foci fades away after a period. This approach is sensitive for detecting DNA repair in radiotherapy patients, but it can also be used in other sectors, such as DNA damage studies owing to occupational exposure or interaction with environmental toxins, cigarette smoke, medicines, and so on. It's vital to remember that these co-exposures can have an impact on radiotherapy patients' outcomes, therefore they should be considered on a case-by-case basis. Furthermore, phosphorylation of H2AX is seen throughout the replication process, in mitosis, and during DNA fragmentation in apoptosis in the absence of DSB. As a result, the test needs to be able to tell the difference between apoptotic and non-apoptotic cells [99]. The comet assay and -H2AX methods described above are helpful in measuring DNA damage and repair, but they do not identify the types of damage, such as SSB and DSB. To determine whether cells are sensitive or resistant to ionizing radiation, it is also necessary to determine whether the damage is repaired and what type of repair mechanism is in place [99].

15. Engineered proteins to detect spontaneous DSB

To quantify DSBs in bacterial and mammalian cells, researchers created a new synthetic method [100]. The green fluorescent protein (GFP) fused to the GAM protein (GAM-GFP), a viral protein from the bacteriophage Mu that shares

sequence similarity with the eukaryotic proteins KU80 and KU70 involved in NHEJ, is used in this approach. The GAM protein, unlike the KU protein, is not involved in DNA repair [101]. GAM binds to DNA and inhibits a few DNA-repair exonucleases. The analysis and quantification of DNA breaks is now possible thanks to this breakthrough [101]. To produce site specific DSBs, the I-SceI endonuclease is employed, and cells are transfected with a Mu GAM-GFP fusion expression vector. The GAM-GFP protein binds to the DSBs created by the I-SceI treatment, causing fluorescence to appear at the damaged locations, which can be seen using fluorescence microscopy. Because the GAM-GFP protein competes with KU proteins, modest quantities of DNA damage develop, restricting this method to HR DSB repair research [101].

Conclusion

DNA is the blueprint of life, and damage to it can have serious consequences. That's why scientists are interested in understanding how radiation and other factors impact DNA. DNA damage is a result of a series of events, from the initial radiation impact to the final biological response. MC simulations allow researchers to model these events statistically, considering randomness and variation. MC simulations can incorporate various factors affecting DNA damage, such as the type of radiation, the cell's size and environment, and even the presence of oxygen. This helps create a more realistic picture.

MC simulations can estimate the number and complexity of DNA lesions caused by radiation. This includes single-strand breaks (SSBs), double-strand breaks (DSBs), and other oxidative lesions. By simulating the damage, MC paves the way for understanding the cell's response to it. This can include repair mechanisms, cell death, and even mutations. MC simulations are a valuable tool for researchers because they can provide insights into DNA damage and biological response that would be difficult or impossible to obtain through experiments alone. This knowledge is crucial for fields like radiotherapy, where understanding the impact of radiation on healthy and cancerous cells is essential.

References

1. Imani, A., et al., Evaluation of the Radiobiological Models Predicting the Radiation-Induced Hypothyroidism in the Partially Irradiated Thyroid Gland of Patients with Breast Cancer. International Journal of Cancer Management, 2022. 15(4).

2. Fu, D.-R., et al., Retrospective comparison of side effects and outcomes of three-dimensional conformal vs. intensity-modulated radiation therapy in the palliative-intent treatment (4 Gy× 5 daily fractions) of canine intranasal tumors (2010–2017). Frontiers in Veterinary Science, 2023. 10: p. 1011949.

3. Ghosh, S. and A. Ghosh, Activation of DNA damage response signaling in mammalian cells by ionizing radiation. Free Radical Research, 2021. 55(8): p. 814-827.

4. Zhang, Y., X. Song, and K. Herrup, Context-dependent functions of E2F1: cell cycle, cell death, and DNA damage repair in cortical neurons. Molecular Neurobiology, 2020. 57: p. 2377-2390.

5. Hahn, M.B., Accessing radiation damage to biomolecules on the nanoscale by particle-scattering simulations. Journal of Physics Communications, 2023.

6. Sia, J., et al., Molecular mechanisms of radiation-induced cancer cell death: a primer. Frontiers in cell and developmental biology, 2020. 8: p. 41.

7. Dauda, S.E., et al., Actions of a Novel Bacterial Topoisomerase Inhibitor against Neisseria gonorrhoeae Gyrase and Topoisomerase IV: Enhancement of Double-Stranded DNA Breaks. International journal of molecular sciences, 2023. 24(15): p. 12107.

8. Abolfath, R., et al., TH-F-105-02: Molecular Dynamics Simulation of DNA Damage Induction by Ionizing Radiation. Medical Physics, 2013. 40(6Part33): p. 552-552.

9. Wang, Y., et al., Repair of 2′-C-Cyano-2′-Deoxy-1-β-D-arabino-Pentofuranosylcytosine–Induced DNA single-strand breaks by transcription-coupled nucleotide excision repair. Cancer Research, 2008. 68(10): p. 3881-3889.

10. Ribas-Maynou, J. and J. Benet, Single and double strand sperm DNA damage: different reproductive effects on male fertility. Genes, 2019. 10(2): p. 105.

11. Collins, P.L., et al., DNA double-strand breaks induce H2Ax phosphorylation domains in a contact-dependent manner. Nature communications, 2020. 11(1): p. 3158.

12. Kawaguchi, K., et al., Inducible expression of the restriction enzyme uncovered genome-wide distribution and dynamic behavior of histones H4K16ac and H2A. Z at DNA double-strand breaks in Arabidopsis. Plant and Cell Physiology, 2024. 65(1): p. 142-155.

13. Parker, C., et al., Loss of BCL-3 sensitises colorectal cancer cells to DNA damage, revealing a role for BCL-3 in double strand break repair by homologous recombination. bioRxiv, 2021: p. 2021.08. 03.454995.

14. Danforth, J.M., L. Provencher, and A.A. Goodarzi, Chromatin and the cellular response to particle radiation-induced oxidative and clustered DNA damage. Frontiers in Cell and Developmental Biology, 2022. 10: p. 910440.

15. Pessina, F., et al., Functional transcription promoters at DNA double-strand breaks mediate RNA-driven phase separation of damage-response factors. Nature cell biology, 2019. 21(10): p. 1286-1299.

16. Nikitaki, Z., et al., Key biological mechanisms involved in high-LET radiation therapies with a focus on DNA damage and repair. Expert Reviews in Molecular Medicine, 2022. 24: p. e15.

17. Ames, B.N., M.K. Shigenaga, and L.S. Gold, DNA lesions, inducible DNA repair, and cell division: three key factors in mutagenesis and carcinogenesis. Environmental health perspectives, 1993. 101(suppl 5): p. 35-44.

18. Lim, A., et al., A fast Monte Carlo cell-by-cell simulation for radiobiological effects in targeted radionuclide therapy using pre-calculated single-particletrack standard DNA damage data. Frontiers in Nuclear Medicine. 3: p. 1284558.

19. Loan, M., et al., Monte Carlo Simulations of DNA Damage and Cellular Response to Hadron Irradiation. arXiv preprint arXiv:1911.08000, 2019.

20. Zhang, R., et al., Comparison of risk of radiogenic second cancer following photon and proton craniospinal irradiation for a pediatric medulloblastoma patient. Physics in Medicine & Biology, 2013. 58(4): p. 807.

21. Hübler, C., Analysing binding stoichiometries in NMR titration experiments using Monte Carlo simulation and resampling techniques. PeerJ Analytical Chemistry, 2022. 4: p. e23.

22. Seco, J. and F. Verhaegen, Monte Carlo techniques in radiation therapy. 2013: CRC press.

23. Fragoso, M., et al., Dosimetric verification and clinical evaluation of a new commercially available Monte Carlo-based dose algorithm for application in stereotactic body radiation therapy (SBRT) treatment planning. Physics in Medicine & Biology, 2010. 55(16): p. 4445.

24. Huang, J.Y., et al., Accuracy and sources of error of out-of field dose calculations by a commercial treatment planning system for intensity-modulated radiation therapy treatments. Journal of applied clinical medical physics, 2013. 14(2): p. 186-197.

25. Verbeke, J.M., et al. Correlated Production and Analog Transport of Fission Neutrons and Photons using Fission Models FREYA, FIFRELIN and the Monte Carlo Code TRIPOLI-4®. in EPJ Web of Conferences. 2018. EDP Sciences.

26. Elmtalab, S., et al., Determination of the Neutron Contamination During Brain Radiotherapy Using a Moderated-Boron Trifluoride Detector and the MCNP Monte Carlo Code. Radiation Protection Dosimetry, 2022. 198(3): p. 129-138.

27. Mendes, H.R. and A. Tomal. Detailed Monte Carlo simulation of energy integrating and photon counting semiconductor detectors. in Medical Imaging 2022: Physics of Medical Imaging. 2022. SPIE.

28. Sakata, D., et al., Fully integrated Monte Carlo simulation for evaluating radiation induced DNA damage and subsequent repair using Geant4-DNA. Sci Rep. 2020; 10 (1): 20788.

29. Konishi, T., et al., Induction of DNA strand breaks and oxidative base damages in plasmid DNA by ultra-high dose rate proton irradiation. International Journal of Radiation Biology, 2023: p. 1-8.

30. Nickoloff, J.A., N. Sharma, and L. Taylor, Clustered DNA double-strand breaks: biological effects and relevance to cancer radiotherapy. Genes, 2020. 11(1): p. 99.

31. Ali, Y., et al., Monte Carlo simulations of nanodosimetry and radiolytic species production for monoenergetic proton and electron beams: Benchmarking of GEANT4-DNA and LPCHEM codes. Medical Physics, 2022. 49(5): p. 3457-3469.

32. Baba, K., et al., A simulation-based study on water radiolysis species for 1H+, 4He2+, and 12C6+ ion beams with multiple ionization using Geant4-DNA. Journal of Applied Physics, 2021. 129(24).

33. Mirrezaei, E., et al., A simulation approach to predict the calibration curve of low LET radiations for biological dosimetry using the Geant4-DNA toolkit. Journal of Instrumentation, 2022. 17(01): p. P01014.

34. Bayarchimeg, L., et al. Simulation of radiation damage to neural cells with the Geant4-DNA toolkit. in EPJ Web of Conferences. 2018. EDP Sciences.

35. Kurudirek, M., Water and tissue equivalence properties of biological materials for photons, electrons, protons and alpha particles in the energy region 10 keV–1 GeV: a comparative study. International journal of radiation biology, 2016. 92(9): p. 508-520.

36. Bernal, M.A., et al., An atomistic geometrical model of the B-DNA configuration for DNA–radiation interaction simulations. Computer Physics Communications, 2013. 184(12): p. 2840-2847.

37. Nikitaki, Z., et al., Measurement of complex DNA damage induction and repair in human cellular systems after exposure to ionizing radiations of varying linear energy transfer (LET). Free radical research, 2016. 50(sup1): p. S64-S78.

38. Raja, S.M.N., S.A. Othman, and R.M. Roslan, A Short Review on the Imaging Technology in Radiation Therapy. e-Jurnal Penyelidikan dan Inovasi, 2023: p. 108-122.

39. Forster, J.C., et al., Monte Carlo simulation of the oxygen effect in DNA damage induction by ionizing radiation. Radiation research, 2018. 190(3): p. 248-261.

40. Hamer, K.A., et al., Tracking Charge Migration with Frequency-Matched Strobo-Spectroscopy. The Journal of Physical Chemistry A, 2024. 128(1): p. 20-27.

41. Kircher, M., et al., Kinematically complete experimental study of Compton scattering at helium atoms near the threshold. Nature physics, 2020. 16(7): p. 756-760.

42. Seibert, M.M., et al., Single mimivirus particles intercepted and imaged with an X-ray laser. Nature, 2011. 470(7332): p. 78-81.

43. Allison, J., et al., Recent developments in Geant4. Nuclear instruments and methods in physics research section A: Accelerators, Spectrometers, Detectors and Associated Equipment, 2016. 835: p. 186-225.

44. Krausz, F. and M. Ivanov, Attosecond physics. Reviews

of modern physics, 2009. 81(1): p. 163-234.

45. Aricò, G., et al., Developments of the nuclear reaction and fragmentation models in FLUKA for ion collisions at therapeutic energies. CERN Proc., 2019. 1: p. 321-326.

46. Lin, E.-H., et al., Novel cancer therapy approach based on Auger effect mediated by monoenergetic x-ray. Cancer Research, 2019. 79(13_Supplement): p. 3941-3941.

47. Chatzipapas, K.P., et al., Ionizing radiation and complex DNA damage: quantifying the radiobiological damage using Monte Carlo simulations. Cancers, 2020. 12(4): p. 799.

48. Grissi, C., et al., Superparamagnetic iron oxide nanoparticles induce persistent large foci of DNA damage in human melanoma cells post-irradiation. Radiation and Environmental Biophysics, 2023. 62(3): p. 357-369.

49. Gorfinkiel, J.D. and S. Ptasinska, Electron scattering from molecules and molecular aggregates of biological relevance. Journal of Physics B: Atomic, Molecular and Optical Physics, 2017. 50(18): p. 182001.

50. Macchi, A., M. Borghesi, and M. Passoni, Ion acceleration by superintense laser-plasma interaction. Reviews of Modern Physics, 2013. 85(2): p. 751-793.

51. Cronin, A.D., J. Schmiedmayer, and D.E. Pritchard, Optics and interferometry with atoms and molecules. Reviews of Modern Physics, 2009. 81(3): p. 1051-1129.

52. Salari, E. and E.I. Parsai, Advances in Radiotherapy Dosimetry Techniques and Pre-Treatment Verification, in Advances in Dosimetry and New Trends in Radiopharmaceuticals. 2023, IntechOpen.

53. Mladenović, M., D. Arbutina, and S. Milanović, Strengthening nuclear security culture within Public company Nuclear Facilities of Serbia. 29. симпозијум ДЗЗСЦГ: зборник радова, 2017: p. 413-417.

54. Sanche, L., Interaction of low energy electrons with DNA: Applications to cancer radiation therapy. Radiation Physics and Chemistry, 2016. 128: p. 36-43.

55. Illenberger, E. and J. Momigny, Gaseous molecular ions: an introduction to elementary processes induced by ionization. Vol. 2. 1992: Springer Science & Business Media.

56. Klyachko-Gurvich, G.L., et al., Desaturation of fatty acids as an adaptive response to shifts in light intensity 1. Physiologia Plantarum, 1999. 107(2): p. 240-249.

57. Sevilla, M.D. and W.A. Bernhard, Mechanisms of direct radiation damage to DNA. EDP Sciences, Les Ulis, 2008.

58. Neustetter, M., et al., The effect of solvation on electron attachment to pure and hydrated pyrimidine clusters. Angewandte Chemie International Edition, 2015. 54(31): p. 9124-9126.

59. Sanche, L., Role of secondary low energy electrons in radiobiology and chemoradiation therapy of cancer. Chemical Physics Letters, 2009. 474(1-3): p. 1-6.

60. Gentles, A.J., et al., The prognostic landscape of genes and infiltrating immune cells across human cancers. Nature medicine, 2015. 21(8): p. 938-945.

61. Chauhan, D. and C. Limbachiya, Electron interactions with analogous of DNA/RNA nucleobases: 3-hydroxytetrahydroFuran and α-Tetrahydrofurfuryl alcohol. Radiation Physics and Chemistry, 2023. 207: p. 110802.

62. Liu, W., et al., Calculation on spectrum of direct DNA damage induced by low-energy electrons including dissociative electron attachment. Radiation and environmental biophysics, 2017. 56: p. 99-110.

63. Deut, U., et al., Secondary radiation dose modeling in passive scattering and pencil beam scanning very high energy electron (VHEE) radiation therapy. Medical Physics, 2023. 50(7): p. 4491-4504.

64. Tommasino, F. and M. Durante, Proton radiobiology. Cancers, 2015. 7(1): p. 353-381.

65. Men'shikov, L., P. Men'shikov, and M. Faifman, Energy Distribution of Electrons in the Migdal Model of Atomic Ionization. Physics of Atomic Nuclei, 2022. 85(6): p. 577-587.

66. Roberts, B., V. Flambaum, and G. Gribakin, Ionization of atoms by slow heavy particles, including dark matter. Physical Review Letters, 2016. 116(2): p. 023201.

67. Fedotov, S. and V. Kushin, Distributions of energy imparted to a micro-volume by secondary charged fragments of nuclear interactions in space radiation field. Radiation and Environmental Biophysics, 2023. 62(3): p. 307-315.

68. Reindl, J., et al., Dosimetry of heavy ion exposure to human cells using nanoscopic imaging of double strand break repair protein clusters. Scientific Reports, 2022. 12(1): p. 1305.

69. Sotomayor, C.G., et al., Ionizing Radiation-Induced Oxidative Stress in Computed Tomography—Effect of Vitamin C on Prevention of DNA Damage: PREVIR-C Randomized Controlled Trial Study Protocol. Journal of Clinical Medicine, 2024. 13(13): p. 3866.

70. Seidensaal, K., et al., Re-irradiation with protons or heavy ions with focus on head and neck, skull base and brain malignancies. The British Journal of Radiology, 2020. 93(1107): p. 20190516.

71. Lesmana, H., et al., MONTE CARLO NEUTRON DOSE MEASUREMENT IN PROTON THERAPY FOR HEALTHCARE WORKER RADIATION SAFETY. Jurnal Kedokteran Diponegoro (Diponegoro Medical Journal), 2023. 12(3): p. 157-166.

72. Tajik-Mansoury, M., H. Rajabi, and H. Mozdarani, A comparison between track-structure, condensed-history Monte Carlo simulations and MIRD cellular S-values. Physics in Medicine & Biology, 2017. 62(5): p. N90.

73. Shin, W.-G., et al., A Geant4-DNA evaluation of radiation-induced DNA damage on a human fibroblast. Cancers, 2021. 13(19): p. 4940.

74. Shan, J., et al., Virtual particle Monte Carlo: A new concept to avoid simulating secondary particles in proton therapy dose calculation. Medical physics, 2022. 49(10): p.

6666-6683.

75. Strungaru, M., et al., Spin-lattice dynamics model with angular momentum transfer for canonical and microcanonical ensembles. Physical Review B, 2021. 103(2): p. 024429.

76. Li, X. and H. Zou, A molecular dynamics and quantum mechanical investigation of intermolecular interaction and electron-transfer mechanism between copper-containing nitrite reductase and redox partner pseudoazurin. Physical Chemistry Chemical Physics, 2023. 25(11): p. 7783-7793.

77. Bäckström, G., et al., Track structure of protons and other light ions in liquid water: Applications of the LIonTrack code at the nanometer scale. Medical Physics, 2013. 40(6Part1): p. 064101.

78. Wu, S.-H., et al., Bufalin alters gene expressions associated DNA damage, cell cycle, and apoptosis in human lung cancer NCI-H460 cells in vitro. Molecules, 2014. 19(5): p. 6047-6057.

79. Morales, J.C. and E.T. Kool, Minor groove interactions between polymerase and DNA: more essential to replication than Watson–Crick hydrogen bonds? Journal of the American Chemical Society, 1999. 121(10): p. 2323.

80. Zhou, X., et al., Incremental SWAP operator for entanglement entropy: Application for exponential observables in quantum Monte Carlo simulation. Physical Review B, 2024. 109(16): p. 165106.

81. Chou, S.-H. and K.-H. Chin, Solution structure of a DNA double helix incorporating four consecutive non-Watson-Crick base-pairs. Journal of Molecular Biology, 2001. 312(4): p. 769-781.

82. Valencia, N.C., et al., Coarse-Grained Monte Carlo Simulations with Octree Cells for Geopolymer Nucleation at Different pH Values. Materials, 2023. 17(1): p. 95.

83. Farmer, J., Development of a Quasi-Monte Carlo Method for Thermal Radiation. 2019.

84. Han, Y., et al., Calculation of the DNA damage yield and relative biological effectiveness in boron neutron capture therapy via the Monte Carlo track structure simulation. Physics in Medicine & Biology, 2023. 68(17): p. 175028.

85. Rafiepour, P., et al. The Effects of Magnetic Field along with Nanoparticles on DNA Damage Induced by a Carbon Beam: A Monte Carlo Study. in 2021 IEEE Nuclear Science Symposium and Medical Imaging Conference (NSS/MIC). 2021. IEEE.

86. Patin, E.C., et al., Harnessing radiotherapy-induced NK-cell activity by combining DNA damage–response inhibition and immune checkpoint blockade. Journal for ImmunoTherapy of Cancer, 2022. 10(3).

87. Keta, O., et al., DNA double-strand breaks in cancer cells as a function of proton linear energy transfer and its variation in time. International Journal of Radiation Biology, 2021. 97(9): p. 1229-1240.

88. Haj Ismail, A.A.K., Monte Carlo simulation of the cosmic muon charge ratio. Kuwait Journal of Science, 2022. 49(1).

89. Gerelchuluun, A., DNA Damage, Repair Mechanisms, and Chromosomal Aberrations. Proton Beam Radiotherapy: Physics and Biology, 2020: p. 183-208.

90. Abo Shdeed, T., Study of secondary particles resulting along 50–150 MeV accelerated protons in liver tissues using MCNPX and abdomen DICOM images. Arab Gulf Journal of Scientific Research, 2023. 41(1): p. 77-90.

91. Roos, W.P. and B. Kaina, DNA damage-induced cell death by apoptosis. Trends in molecular medicine, 2006. 12(9): p. 440-450.

92. Bukowska, B. and B.T. Karwowski, The clustered DNA lesions–types, pathways of repair and relevance to human health. Current Medicinal Chemistry, 2018. 25(23): p. 2722-2735.

93. Nakano, T., et al., Formation of clustered DNA damage in vivo upon irradiation with ionizing radiation: Visualization and analysis with atomic force microscopy. Proceedings of the National Academy of Sciences, 2022. 119(13): p. e2119132119.

94. Audrey, A., et al., Processing DNA lesions during mitosis to prevent genomic instability. Biochemical Society Transactions, 2022. 50(4): p. 1105-1118.

95. Arnould, C., et al., Chromatin compartmentalization regulates the response to DNA damage. Nature, 2023. 623(7985): p. 183-192.

96. Buchko, G.W., S.S. Wallace, and M.A. Kennedy, Base excision repair: NMR backbone assignments of Escherichia coli formamidopyrimidine-DNA glycosylase. Journal of Biomolecular NMR, 2002. 22(PNNL-SA-35528).

97. Puig, J., et al., DNA damage protection for enhanced bacterial survival under simulated low Earth orbit environmental conditions in Escherichia coli. Frontiers in Microbiology, 2021. 12: p. 789668.

98. Rojas, E., et al., DNA-AP sites generation by etoposide in whole blood cells. BMC cancer, 2009. 9: p. 1-9.

99. Masuda, Y., et al., TRIM29 regulates the assembly of DNA repair proteins into damaged chromatin. Nature communications, 2015. 6(1): p. 7299.

100. Gaudelli, N.M., et al., Programmable base editing of A• T to G• C in genomic DNA without DNA cleavage. Nature, 2017. 551(7681): p. 464-471.

101. Paix, A., et al., Precision genome editing using synthesis-dependent repair of Cas9-induced DNA breaks. Proceedings of the National Academy of Sciences, 2017. 114(50): p. E10745-E10754.