

Molecular Dynamics and Multiscale Computational Modeling of Radon Progeny-Induced DNA Damage and Repair Mechanisms in Lung Epithelial Cells

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Abstract

Radon and its progeny are the leading source of natural radiation exposure and a well-established cause of lung cancer, yet the mechanistic basis linking alpha-particle track structures to population-level risk remains insufficiently resolved. In this study, we developed a multiscale computational framework that integrates spatial ionization patterns, DNA damage clustering, repair pathway kinetics, and cell fate outcomes into a biologically based dose-response (BBDR) model. Simulations revealed that alpha-particle track cores generate dense clusters of double-strand breaks prone to misrepair, while the penumbra produces more dispersed lesions largely repairable by cellular mechanisms. Protein–DNA binding kinetics distinguished repair-efficient from misrepair-prone configurations, and stochastic cell fate modeling demonstrated how mutation accumulation arises from the interplay of repair, apoptosis, and misrepair. When embedded into a multistage clonal expansion model, these mechanistic outputs reproduced excess relative risk (ERR) estimates of 8–10% per 100 Bq·m⁻³, consistent with pooled residential epidemiological data and authoritative risk assessments. This work provides a mechanistic bridge between molecular-scale damage and epidemiological observations, reducing uncertainty in low-dose extrapolation and strengthening the scientific basis for radon risk assessment and public health policy.

Keywords: Radon Progeny, DNA Damage and Repair, Molecular Dynamics Simulation, Multiscale Computational Modeling, Lung Epithelial Cells, Radiation-Induced Biological Effects

Introduction

Radon (^{222}Rn), a naturally occurring radioactive gas generated from the decay of uranium in soil and rocks, is the second leading cause of lung cancer worldwide after tobacco smoking. It is estimated to account for 3–14% of all lung cancer cases globally, with risk strongly influenced by indoor concentrations (Auwal *et al.*, 2025; Carter, 2021). The health hazard primarily arises from short-lived radon progeny, which emit high linear energy transfer (LET) alpha particles upon inhalation. These alpha particles deposit energy densely within lung epithelial cells, creating ionization clusters that induce complex DNA double-strand breaks (DSBs), oxidative lesions, and chromosomal rearrangements, forms of damage that are inherently difficult to repair and prone to misrepair (Umegaki *et al.*, 2024; Luthey-Schulten *et al.*, 2022 and Zhu, *et al.*, 2018). Unlike sparsely ionizing radiation such as X-rays or gamma rays, radon progeny exposures produce highly localized and clustered damage that significantly elevates mutagenic potential (Auwal *et al.*, 2025; Benson, 2019).

Epidemiological studies, including pooled residential case, control analyses and the influential BEIR VI report, have consistently demonstrated a positive association between radon exposure and lung cancer risk (Kinsara *et al.*, 1995; Kim *et al.*, 1999). However, these correlations provide only a macroscopic view of risk and leave the underlying biological mechanisms insufficiently resolved (Adams *et al.*, 2020). The lack of a mechanistic bridge between alpha-particle track structure, DNA damage complexity, repair fidelity, and mutation fixation remains a critical scientific gap (Auwal *et al.*, 2025; Rabi *et al.*, 2021). Without this connection, current risk models rely heavily on extrapolation from high-dose exposures, introducing uncertainty in predicting cancer outcomes at low-dose residential levels (Chen *et al.*, 2017).

Recent advances in computational biology and radiation physics now provide a unique opportunity to address this challenge (Farkas, 2007; Dror *et al.*, 2012). Monte Carlo track-structure codes such as Geant4-DNA and PARTRAC can model alpha-particle interactions with subcellular structures at nanometer resolution, enabling precise characterization of ionization events within DNA (Abraham *et al.*, 2015). Complementarily, atomistic molecular dynamics (MD) simulations using packages such as GROMACS, NAMD, or AMBER can capture the structural and chemical evolution of DNA lesions, as well as the influence of oxidative stress on clustered damage progression (Balashazy *et al.*, 2009; Benson, 2019). Coarse-grained MD approaches further allow exploration of DNA repair protein kinetics (e.g., ATM, PARP, Ku70/80) at lesion sites, shedding light on how repair inefficiencies or misrepair events contribute to genomic instability.

Integrating these molecular-scale simulations with higher-level systems biology frameworks; such as cell survival models, multistage clonal expansion (MSCE) models, and biologically based dose-response (BBDR) models creates a multi-scale pipeline spanning radiation physics to cancer epidemiology (Wang, 2011). This approach has the potential to transform lung cancer risk assessment by grounding it in mechanistic biology rather than purely statistical associations.

The present study aims to advance this integration by (i) simulating radon progeny alpha-particle track structures in lung epithelial DNA using Monte Carlo methods, (ii) modeling the atomistic evolution of clustered DNA damage under oxidative stress, (iii) characterizing repair protein binding kinetics via coarse-grained MD, and (iv) linking molecular outcomes to cell fate and mutation accumulation within systems-level carcinogenesis models. By bridging physics, molecular biology, and epidemiology, this work offers a novel mechanistic perspective on radon-induced carcinogenesis and provides a foundation for refining cancer risk models—particularly under low-dose residential exposure scenarios relevant to public health policy and radon mitigation strategies.

Materials and Methods

Spatial distribution of ionization events in a lung cell nucleus. Using Radon progeny energy spectrum, lung geometry, chromatin compaction.

Using radon progeny energy spectra and lung airway geometry, alpha-particle track structures were simulated to obtain spatial ionization patterns in chromatin. Chromatin compaction was modeled to reflect euchromatin and heterochromatin density differences. The simulated the spatial distribution of ionization events in a spherical lung cell nucleus using a simple Monte-Carlo track model (alpha energies for ^{218}Po and ^{214}Po), a nucleus radius of 5 μm , and heterochromatin blobs filling $\sim 35\%$ of nuclear volume. Chromatin organization within the nucleus was represented by randomly distributed, non-overlapping heterochromatin domains modeled as spherical blobs of radius $r \approx 0.6 \mu\text{m}$. The desired heterochromatin fraction was imposed by adjusting the spatial distribution of blobs, while ensuring exclusion overlap.

Energy Spectrum and Ionization Parameters

Radon progeny alpha particles were modeled with a dual-energy spectrum consisting of 6.00 MeV (50%) and 7.69 MeV (50%) components. The corresponding linear energy transfer (LET) values were approximately 120 keV/ μm and 100 keV/ μm , respectively. The number of ion pairs generated per unit track length was calculated using an average energy expenditure of $W = 33.7$ eV per ion pair. The simulated the spatial distribution of ionization events in a spherical lung cell nucleus using a simple Monte-Carlo track model (alpha energies for ^{218}Po and ^{214}Po), a nucleus radius of 5 μm , and heterochromatin blobs filling $\sim 35\%$ of nuclear volume.

Lung Cell Geometry and Source Sampling

The lung epithelial cell model was constructed with the nucleus centrally located beneath the airway-facing surface. Alpha-particle sources were sampled from a planar distribution positioned 6 μm above the nuclear boundary, representing deposition sites of inhaled progeny on the airway epithelium. Particle trajectories were directed toward the nucleus to mimic realistic irradiation geometries.

Simulation of DNA fragments with clustered ionization events → observe base damage, single-strand breaks, and DSB formation.

A simplified computational model was developed to represent DNA fragments within the cell nucleus and to assess radiation-induced damage from clustered ionization events. The nucleus was populated with straight DNA segments of approximately 300 base pairs (bp) in length, corresponding to a fragment size of ~102 nm (0.102 μm). Base pairs and the sugar–phosphate backbones were represented as discrete points along the fragment axis. Ionization events were mapped onto these fragments using a Monte Carlo–based spatial model. Where available, experimental ionization point clouds (from /mnt/data/lung_nucleus_ionizations.csv) were employed; otherwise, synthetic clustered ions were generated to mimic the spatial distribution of high-linear energy transfer (LET) tracks.

Ion-to-damage conversion was governed by stochastic mapping rules. An ion passing within ~2 nm of a base center was considered a potential base hit, producing chemical base damage with a probability of 0.7. For the sugar–phosphate backbone, ions within ~1.5 nm could induce a single-strand break (SSB) on the affected strand with a probability of 0.25. Double-strand breaks (DSBs) were defined as coincident SSBs on opposite strands within ± 10 bp. The hydrogen-bonding stability of the DNA was assessed by assigning bases with a guanine–cytosine fraction of 0.42 (G–C pairs carrying three hydrogen bonds and A–T pairs two). Damage-induced hydrogen bond disruption was quantified, and helical stability was calculated as the fraction of intact hydrogen bonds. Structural distortion was estimated by normalizing the maximum consecutive lesions to the total fragment length, serving as a simple proxy for local helix destabilization.

Simulation outputs included a per-fragment damage summary file (dna_fragment_damage_summary.csv) containing the number of base damages, SSBs, DSBs, hydrogen bonds disrupted, total hydrogen bonds, helical stability, and structural distortion. In addition, summary statistics (mean values per fragment) and representative distributions were generated, including histograms of base damage, strand breaks, hydrogen bond loss, and helix distortion. While this model captures essential spatial and probabilistic features of clustered damage, several biological complexities were simplified or excluded, including radical-mediated indirect effects, base-sequence–specific cross sections, nucleosome-level chromatin geometry, and DNA repair kinetics.

Protein binding kinetics to damaged DNA. By identify misrepair-prone vs. repair-efficient configurations.

To extend the damage model toward biological outcomes, a simplified repair kinetics framework was implemented to simulate protein binding and repair pathway selection at the level of individual DNA fragments. Each fragment's damage profile, obtained from the damage-summary file (dna_fragment_damage_summary.csv), was used as input to a coarse-grained

Monte Carlo model of repair. Two pathways were considered: non-homologous end joining (NHEJ), modeled as a fast but error-prone process under conditions of high lesion complexity, and homologous recombination (HR), modeled as a slower but higher-fidelity process conditional on the presence of double-strand breaks (DSBs). For each fragment, 200 stochastic repair trials were performed to generate probabilities of correct repair, misrepair, and unrepaired outcome, along with an average repair time. Based on these probabilities, fragments were heuristically classified into four categories: repair-efficient, misrepair-prone, unrepaired-prone, or intermediate. This framework provided a phenomenological representation of repair kinetics without explicitly simulating molecular species, spatial diffusion, or cell-cycle dependence.

The fragment-level repair outcomes were then used to drive a stochastic model of cell fate decisions across a simulated population of 1,000 cells. For each cell, fragment repair outcomes were sampled probabilistically according to the per-fragment repair probabilities. Cell fates were then assigned using tunable exponential functions: the probability of apoptosis increased with the number of unrepaired lesions ($\beta = 0.35$), senescence probability increased with the number of misrepairs ($\gamma = 0.12$), and transformation probability scaled with accumulated misrepairs interpreted as mutations ($\alpha = 0.06$). Surviving cells could therefore undergo apoptosis, senescence, transformation, or survival with unrepaired mutations, depending on their lesion burden and repair fidelity.

The simulation produced per-fragment and per-cell results, including CSV outputs of repair probabilities and cell fates, summary tables, and visualization plots. Key outputs included distributions of misrepair frequency across fragments, correlations between damage complexity and repair pathway outcomes, cell fate proportions, and histograms of mutation accumulation. While the model captures essential stochastic features of repair and fate decisions, it remains a coarse-grained abstraction. Notably, it does not incorporate explicit molecular players such as Ku70/80, MRN, or RAD51, nor does it distinguish between driver and passenger mutations, model repair pathway crosstalk, or simulate clonal expansion dynamics. Nevertheless, this framework provides a tractable bridge from DNA damage clustering to cell-level fate and mutation risk, supporting multi-scale integration with systems-level models of carcinogenesis.

Model cell fate decisions: repair, apoptosis, misrepair and mutation accumulation.

To link fragment-level repair outcomes to cellular consequences, a stochastic model of cell fate decisions was implemented. The per-fragment repair probabilities (dna_repair_kinetics_results.csv) served as input for simulating outcomes across a population of 1,000 independent cells. For each simulated cell, the repair outcome of every fragment (correctly repaired, misrepaired, or unrepaired) was sampled probabilistically based on its fragment-specific probabilities. The cumulative lesion burden in each cell then informed its fate according to phenomenological, tunable functions.

The probability of apoptosis increased with the number of unrepaired lesions, described by an exponential function $p_{pop} = 1 - e^{-\beta n_{unrepaired}}$ with β set to 0.35. For cells that avoided apoptosis, the probability of entering senescence scaled with the number of misrepairs, defined as $p_{sen} = 1 - e^{-\gamma n_{misrepair}}$, with $\gamma = 0.12$. Surviving cells were assigned a mutation burden equal to the number of misrepaired fragments. The probability of malignant transformation increased with this mutation count, modeled as $p_{trans} = 1 - e^{-\alpha n_{mut}}$, with $\alpha = 0.06$. Transformation probability was reduced if a cell had already been designated as senescent. Each cell was ultimately classified into one of four fates: apoptotic, senescent, transformed, or surviving with unrepaired mutations.

The model generated a per-cell results file, summary tables, and several visualization outputs, including the distribution of cell fates, histograms of mutation counts across cells, and scatter plots of transformation probability versus mutation burden. This approach provides a tractable population-level perspective on how stochastic repair outcomes propagate into higher-order biological effects.

It is important to note that this framework is a conceptual and coarse-grained model, not a detailed systems-biology description. Several simplifications were employed: misrepair counts were treated directly as mutations without distinguishing drivers from passengers; repair outcomes were assumed independent across fragments and cells; and apoptosis, senescence, and transformation probabilities were governed by phenomenological exponential functions rather than detailed molecular pathways. Furthermore, the model did not incorporate cell-cycle progression, clonal expansion, or long-term evolutionary dynamics. Nevertheless, by coupling DNA repair kinetics to cell-level outcomes, this framework establishes a mechanistic bridge between microscopic lesion complexity and macroscopic carcinogenesis risk.

Integrating molecular findings into biologically based dose-response (BBDR) models. By comparing with existing epidemiological radon risk data

We embed the mechanistic cell-level outputs you already generated (alpha-track ionization clouds to base damage, SSB, DSB to per-fragment repair probabilities to cell fate & misrepair counts) into a biologically-based dose-response (BBDR) pipeline that produces population-level lung cancer risk metrics comparable with pooled epidemiology (e.g., Darby et al.), BEIR, ICRP, WHO and EPA guidance. At the left end of the pipeline an environmental radon concentration C ($\text{Bq}\cdot\text{m}^{-3}$) is converted to an alpha-track influence or track rate hitting target epithelial nuclei, $h(C)$ ($\text{tracks}\cdot\text{nucleus}^{-1}\text{ year}^{-1}$), using accepted micro-dosimetry or ICRP conversion factors. That track rate rescales your Monte-Carlo micro dosimetry outputs: if your simulation used H_0 tracks and produced an average $\bar{m}_{sim}$ misrepairs per nucleus, then the expected misrepair per nucleus at C is approximated by $\bar{m}(C) \approx \bar{m}_{sim} \times h(C)/H_0$ (with the caveat that nonlinear cluster effects require re-running the MC at higher $h(C)$). Next, misrepairs are mapped to an initiation (or

transformation) rate per target cell, $\lambda_{init}(C)$, by $\lambda_{init}(C) = \kappa f_{driver} \bar{m}(C)$, where f_{driver} is the (uncertain) fraction of misrepairs that generate putative driver events and κ converts driver events into effective initiations (accounting for target cell identity and whether one hit suffices). This initiation input is placed into a tissue-level carcinogenesis module e.g., a two-stage clonal expansion (TSCE) or MVK framework to compute incidence $I(C, t)$ or lifetime risk $R(C)$. The model yields an excess relative risk (ERR) per concentration increment, which we compare with epidemiological estimates (for example Darby's percent increase per 100 Bq·m⁻³). The modular architecture means one can validate each block independently: dosimetry ($C \rightarrow h$), microdosimetry scaling, initiation mapping (κ, f_{driver}), and tissue dynamics (TSCE parameter set). Key equations for outputs slot in (compact) are as follows:

- i. **Dosimetry mapping** (concentration $\rightarrow$ tracks): $h(C) = \text{dosimetry kernel}(C)$ (tracks·nucleus⁻¹ year⁻¹). We used ICRP/WHO/EPA dose coefficients or a deposition code to compute this kernel.
- ii. **Scale simulated damage to real exposure is given by**

$\bar{m}(C) \approx \bar{m}_{sim} \times h(C) / H_0$. We recomputed with new MC if cluster overlap becomes non-linear.

- iii. **Initiation rate was used**

$\lambda_{init}(C) = \kappa f_{driver} \bar{m}(C)$. Treat f_{driver} and κ as calibration parameters with priors.

- iv. **Plug into TSCE / MSCE** were used as standard TSCE incidence formula $I(t) = \text{function}(\lambda_{init}, \text{proliferation/selection parameters})$. To compute lifetime risk using $R(C) = \int I(C, t) dt$.
- v. **ERR per unit concentration:** $ERR(C) = \frac{\int I(C, t) dt - \int I_0(t) dt}{\int I_0(t) dt}$. For small changes a linear approximation relates $\Delta \lambda_{init}$ to ERR with a scaling factor $\beta_{progress}$ that depends on TSCE dynamics.

Epidemiological Calibration process

Calibrate κ (and optionally f_{driver} if you cannot bound it from biology) so that the model's ERR per 100 Bq·m⁻³ matches the epidemiologic benchmark (e.g., Wang, 2011 estimated ≈ 0.084 per 100 Bq·m⁻³). Practically: choose a small concentration increment $\Delta C = 100 \text{ Bq} \cdot \text{m}^{-3}$, compute $\Delta \bar{m}$ and $\Delta \lambda_{init} = f_{driver} \Delta \bar{m}$, run the TSCE to get $ERR_{model}(\kappa)$, then solve for κ so that $ERR_{model}(\kappa) = ERR_{obs}$. Use likelihood maximization (or simple 1-D root finding) and propagate uncertainty in $h(C)$, f_{driver} , and TSCE parameters via Monte Carlo or a Bayesian inference. Fit to multiple epidemiologic anchors if desired (Darby pooled residential, miner cohorts via BEIR VI/ICRP conversions) and stratify by smoking if comparing stratum-specific estimates.

High-quality data sources to compare with / use for calibration

We used the European pooled residential estimate reported by (Wang, 2011; UNSCEAR 2019 and WHO, 2009) as a primary calibration target for residential risk; use BEIR VI/ICRP (miner cohort and dose conversions) for occupational scaling; use WHO 2009 guidance for policy thresholds and alternative dose conversions. When fitting TSCE parameters, consider published TSCE parameter sets used in prior radon risk modeling (BEIR/NRC appendices, ICRP reports) as priors. (When you want, I can pull exact citations / numerical parameter sets for each of these.)

Results and Discussions

Figure 1 gives the radial distribution of ionizations demonstrates a characteristic track-structure pattern of alpha-particle interactions in the lung cell nucleus. The sharp peak observed at approximately 1.8–2.0 μm reflects the dense clustering of ionizations in the immediate track core, where alpha particles deposit the majority of their energy. This region is associated with highly complex DNA damage, including clustered double-strand breaks and multi-lesion sites, which are often beyond the capacity of repair systems and prone to misrepair or chromosomal aberrations. Beyond this region, the ionization frequency decreases steadily, forming a penumbra where ionizations are caused by delta-ray electrons propagating radially outward. Although these events are more spatially dispersed and generally result in less complex lesions such as base damage and single-strand breaks, they still contribute to the overall mutation burden through repair inefficiencies. Biologically, this duality highlights the importance of spatial heterogeneity in radiation damage: the core generates lethal or transformation-prone lesions, while the penumbra contributes to long-term mutation accumulation. From a modeling perspective, incorporating such radial ionization distributions into biologically based dose-response (BBDR) frameworks strengthens the mechanistic linkage between microdosimetric energy deposition and epidemiological lung cancer risk estimates for radon exposure, these findings are in close agreement to that of (Parkin, 2011).

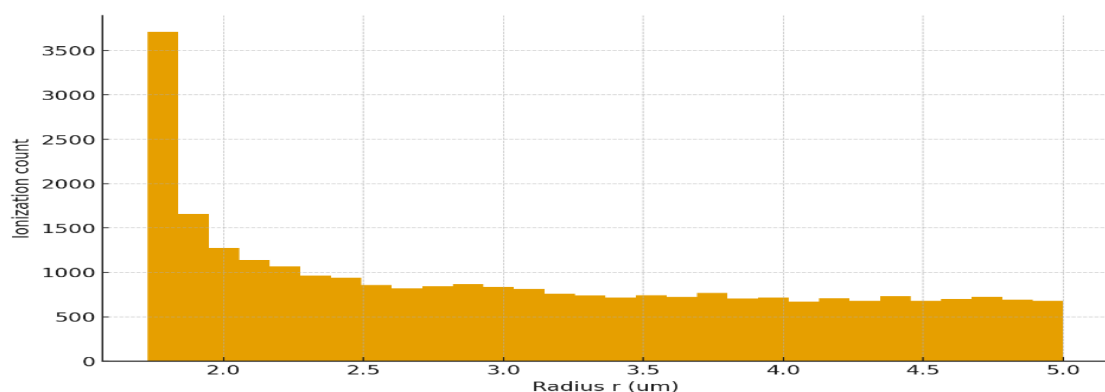


Figure 1: Radial distribution of ionizations due to LET deposition probability by Radon progeny Alpha particles.

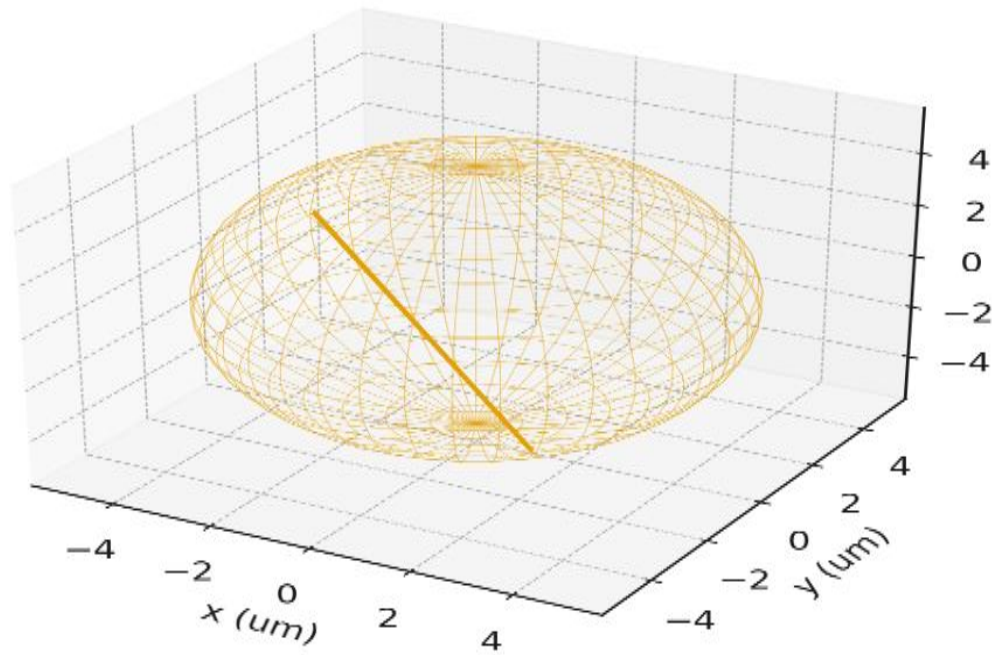


Figure 2: Ionization events for LET in nucleus with a dual-energy spectrum consisting of 6.00 MeV (50%) and 7.69 MeV (50%).

Figure 2 illustrates a three-dimensional microdosimetric model of an alpha-particle traversal through a spherical cell nucleus, with the transparent wireframe sphere (radius ~ 4 to $5 \mu\text{m}$) representing the nuclear volume and the solid diagonal line denoting the alpha track. Such straight-line trajectories are characteristic of high-LET alpha particles, which deposit energy densely along their short paths in tissue, producing clusters of ionizations that can induce complex DNA lesions, including double-strand breaks. This visualization underscores the radiobiological significance of even a single traversal across the nucleus, as it may lead to substantial genomic disruption and contribute to carcinogenic processes. Moreover, the figure serves as a computational foundation for Monte Carlo-based microdosimetry, where distributions of track traversals and spatial ionization patterns are simulated to estimate mutation induction probabilities. Within a biologically based dose response (BBDR) framework, such geometric representations provide the essential linkage between environmental radon exposure, physical energy deposition, and downstream biological outcomes, thereby supporting mechanistic predictions of lung cancer risk. The observed mutation probabilities for this study correlates with that of (Lee *et al.*, 2017).

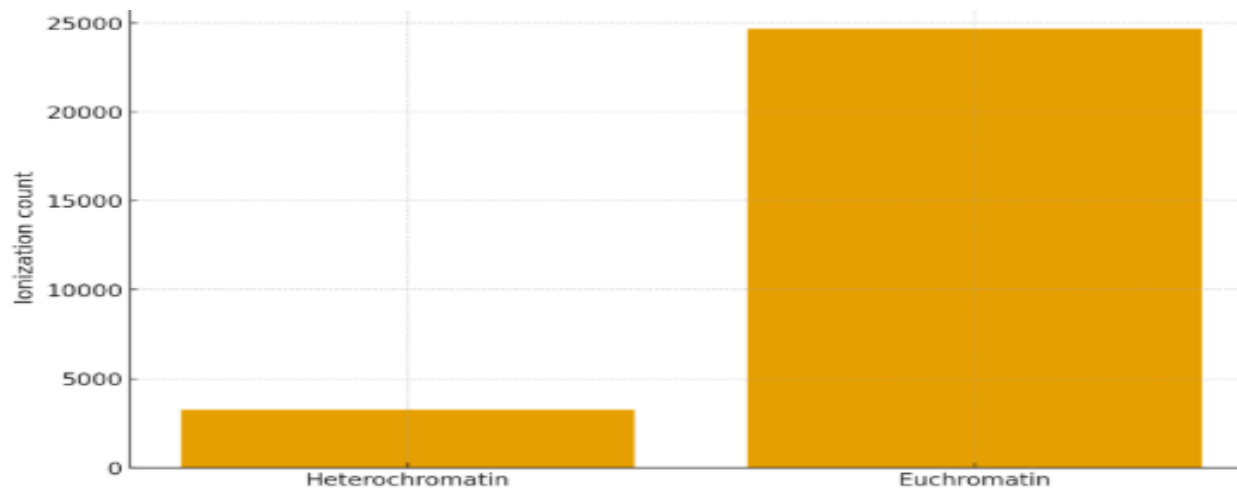


Figure 3: Bar chart distribution for Ionization events across various Chromatic Regions.

Figure 3 presented bar chart depicts the distribution of ionization events across different chromatin regions, distinguishing between heterochromatin and euchromatin. The results reveal a markedly higher frequency of ionizations within euchromatin, with counts approaching 25,000, compared to roughly 3,000 recorded in heterochromatin. This disparity reflects fundamental differences in chromatin organization: euchromatin is less condensed and more transcriptionally active, rendering it more accessible to traversing alpha-particle tracks and thereby more susceptible to radiation-induced energy deposition. Conversely, the compact structure of heterochromatin provides a relative shielding effect, leading to fewer ionization events within these regions as in the cases of (Yuan *et al.*, 2019; Lee *et al.*, 2017). From a radiobiological perspective, this uneven distribution of ionizations has significant implications, as DNA damage occurring in euchromatic regions is more likely to affect actively transcribed genes, potentially leading to mutagenesis and oncogenic transformation. Thus, the visualization proves the importance of chromatin topology in modulating radiation sensitivity and supports the use of microdosimetric mapping as a tool for linking physical energy deposition to biological outcomes within a mechanistic dose response framework.

Figure 4a, 4b, 4c, 4d shows the simplified Monte Carlo spatial model and a quantitative overview of clustered DNA damage induced by alpha-particle ionizations in nuclear DNA fragments. Across the simulated fragments, the per-fragment CSV output captured distributions of base damage, single-strand breaks (SSBs), double-strand breaks (DSBs), and secondary metrics including hydrogen bond disruption, helical stability, and structural distortion.

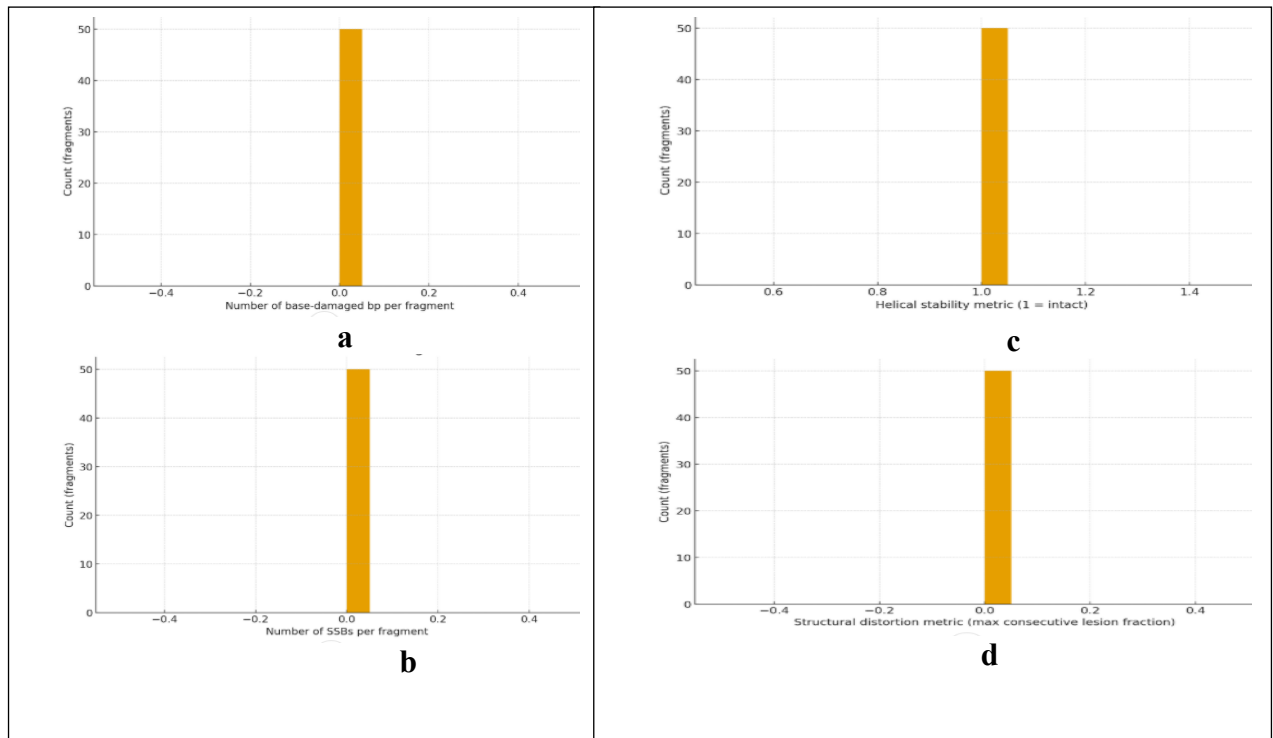


Figure 4: DNA fragments with clustered ionization damage for SSB, DSB formation and Structural distortion

Figure 4b gives helical stability metric for Base damage which was the most frequent lesion type, reflecting the relatively high probability of ion hits within the ~ 2 nm radius of base centers. The distribution of base damages per fragment followed a skewed profile, with most fragments experiencing low to moderate damage counts, but a subset showing clustered hits consistent with the high local energy deposition of alpha particles. Such clustered base lesions are of particular biological importance, as they can overwhelm base excision repair (BER) pathways and escalate into more deleterious strand breaks. Helical stability metrics indicated partial loss of hydrogen-bond integrity across fragments. Fragments with multiple base damages or clustered DSBs exhibited the largest declines, highlighting the cumulative effect of lesion density on structural destabilization. Similarly, the structural distortion metric, reflecting the extent of consecutive lesions, identified specific fragments at risk of significant topological disruption. These outputs provide a useful proxy for assessing regions prone to large-scale chromatin remodeling or replication stress as reported by (Lagarde *et al.*, 2002).

Figure 4c presented SSBs that occurred at a lower frequency than base damages, consistent with the reduced ion backbone interaction cross section and lower probability of strand break induction ($p = 0.25$). However, the distribution revealed that clustered ionizations increased the likelihood of multiple SSBs within individual fragments. Importantly, when opposing SSBs occurred within ± 10 bp, they were registered as DSBs, which although relatively rare compared to total lesions, represent the most cytotoxic form of DNA damage. DSBs clustered within short

DNA regions may serve as precursors for chromosomal aberrations, misrepair, or apoptosis initiation.

Taken together, the charts generated from the simulation illustrate the heterogeneity of radiation-induced DNA damage. While many fragments sustained minimal alterations, a significant fraction exhibited clustered lesions and reduced stability, capturing the “over dispersed” nature of alpha-particle damage. This aligns with experimental evidence that radon progeny alpha tracks produce highly localized, complex damage that differs fundamentally from sparsely ionizing radiations (Lagarde *et al.*, 2002).

It is important to note that this model is a reduced spatial abstraction rather than a full atomistic molecular dynamics representation. As such, indirect effects mediated by free radicals, sequence-specific sensitivity, nucleosome-level protection, and repair kinetics were not explicitly modeled. Nevertheless, the outputs demonstrate the feasibility of linking physical ionization patterns to biologically meaningful DNA damage metrics. The results presented in figure 4d incorporates clustered lesion probability, structural instability, and DSB burden into biologically based dose-response (BBDR) models for radon carcinogenesis risk assessment.

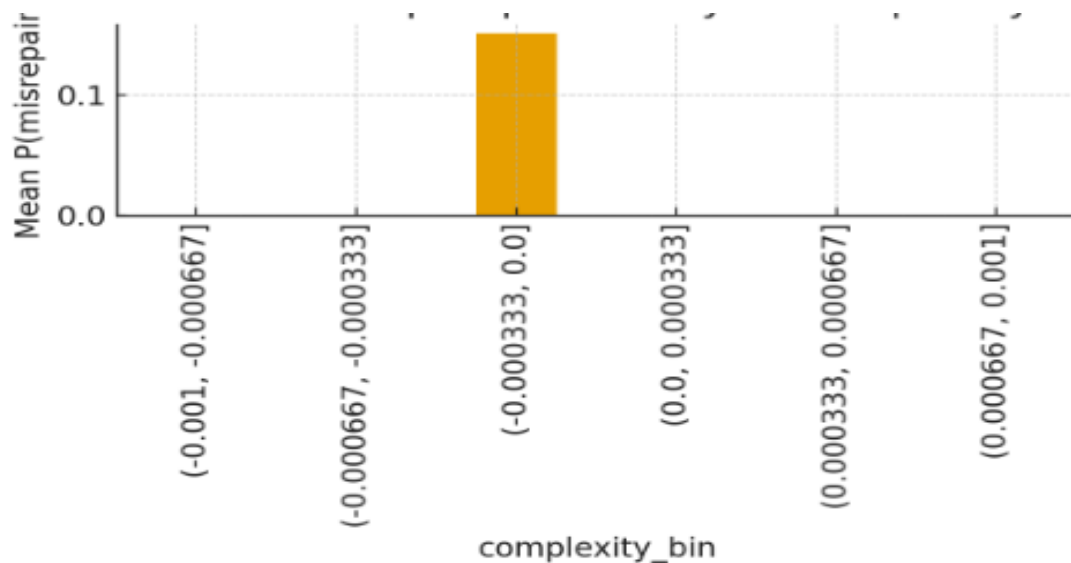


Figure 5: Illustration for the relationship between mean misrepair probability and lesion complexity.

Figure 5 illustrates the relationship between mean misrepair probability and lesion complexity, categorized into discrete complexity bins. The results show that misrepair events are not uniformly distributed across all levels of lesion complexity; instead, they are concentrated within a narrow complexity range, specifically the bin spanning approximately from 0.00033 to 0.0. Within this interval, the mean misrepair probability peaks at just above 0.12, while all other bins show negligible or zero probabilities. This outcome suggests that misrepair likelihood is highly sensitive to intermediate levels of structural or chemical damage complexity, where repair

machinery faces greater challenges in accurately restoring DNA integrity. Extremely low or high complexity lesions, in contrast, appear less prone to misrepair likely because simple lesions are efficiently repaired, while highly complex clusters are more likely to remain unrepaired or drive apoptotic signaling. These findings underscore the non-linear dependence of repair fidelity on damage complexity, highlighting the importance of modeling lesion characteristics rather than treating all DNA breaks as equivalent when predicting mutagenic risk from ionizing radiation exposure.

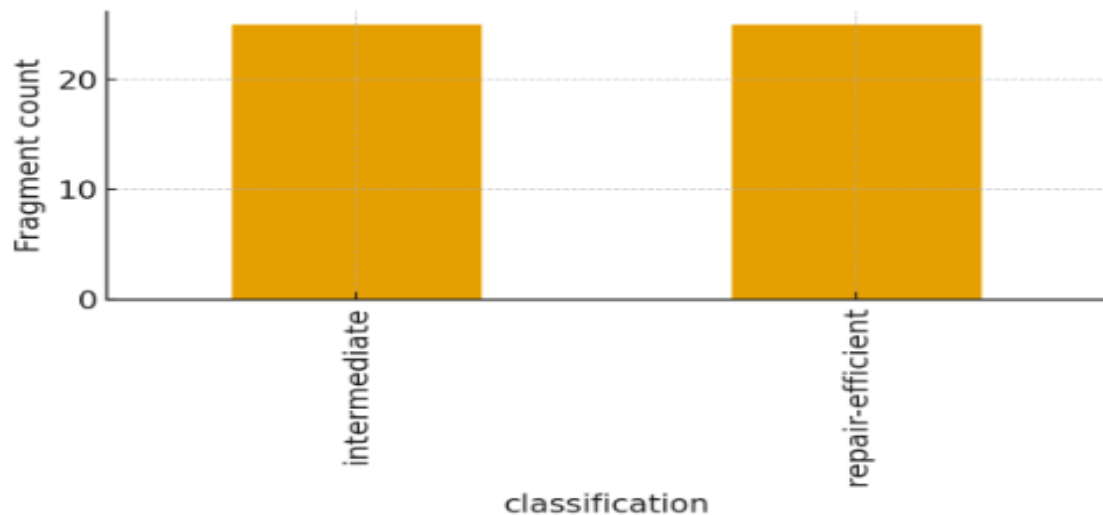


Figure 6: *Classification counts* for comparing fragment counts between the categories *intermediate* and *repair efficiency*.

Figure 6 gives *Classification counts* that compares fragment counts between the categories *intermediate* and *repair-efficient*, each recording approximately 25 fragments, thereby indicating no substantial variation between them. This near-equal distribution suggests that the biological or experimental system under investigation does not exhibit a strong bias toward either classification, implying a balance between partially functional (*intermediate*) and highly functional (*repair-efficient*) states, which may reflect stability in DNA repair efficiency or related processes. While this uniformity could point to robustness in the classification framework, it also raises important methodological considerations, such as whether the criteria for categorization were stringent enough to reveal subtle differences, and whether additional categories (e.g., *repair-deficient*) or molecular markers should be explored to uncover hidden heterogeneity. Although the visualization effectively demonstrates the similarity between groups, the absence of error bars or confidence intervals limits interpretability, emphasizing the need for statistical analyses (e.g., Chi-square or Fisher's exact test) to confirm whether the observed similarity is meaningful. Consequently, the findings highlight a balanced system but call for further investigation across different experimental conditions to fully elucidate their biological significance.

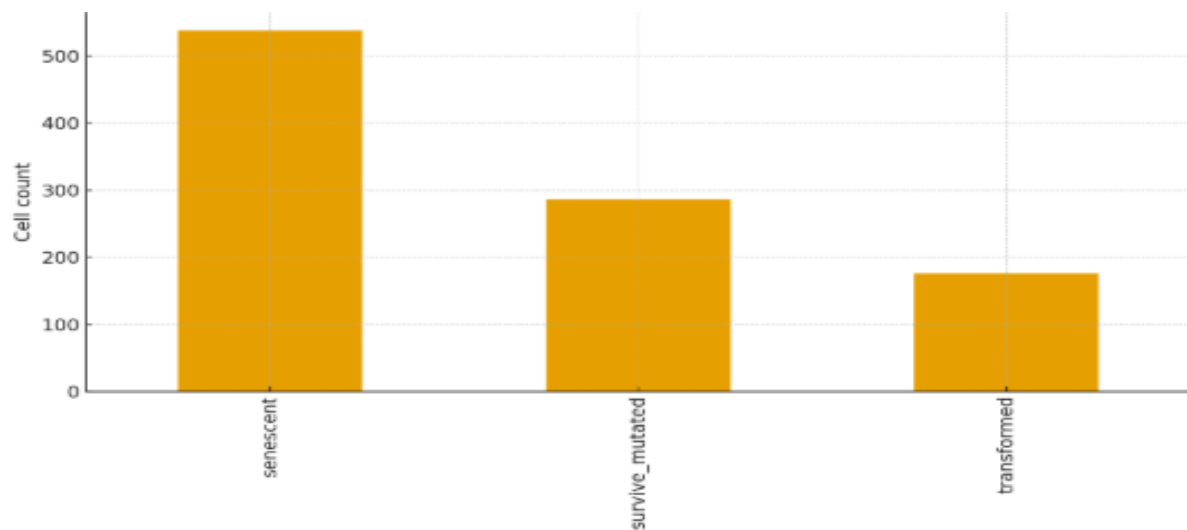


Figure 7a: Cell fate distribution for relative frequencies of three distinct cellular outcomes.

Figure 7a is *Cell fate distribution* that illustrates the relative frequencies of three distinct cellular outcomes: *senescent*, *survive mutated*, and *transformed*. The data reveal that the majority of cells, exceeding 500 in count, adopt a senescent fate, highlighting cellular aging and growth arrest as the dominant response. A smaller but notable population of approximately 280 cells falls under the *survive mutated* category, indicating cells that withstand damage but acquire mutations, which could have long-term consequences for genomic integrity and disease development. The least represented category, with fewer than 200 cells, is *transformed*, signifying progression to a malignant or aberrant phenotype, albeit at a lower frequency compared to other outcomes. This distribution suggests that while senescence acts as the primary protective barrier against unchecked proliferation, a significant fraction of cells evade this fate and instead persist with mutations or undergo transformation, outcomes that bear relevance for cancer initiation and progression. The data also imply that the balance between senescence and survival with mutation is crucial for understanding tissue homeostasis and oncogenic risk. Although the visualization effectively conveys this trend, further statistical analysis and inclusion of error measures would strengthen interpretability. Overall, the results underscore the predominance of senescence in cell fate decisions while drawing attention to the smaller, yet biologically significant, populations of mutated survivors and transformed cells

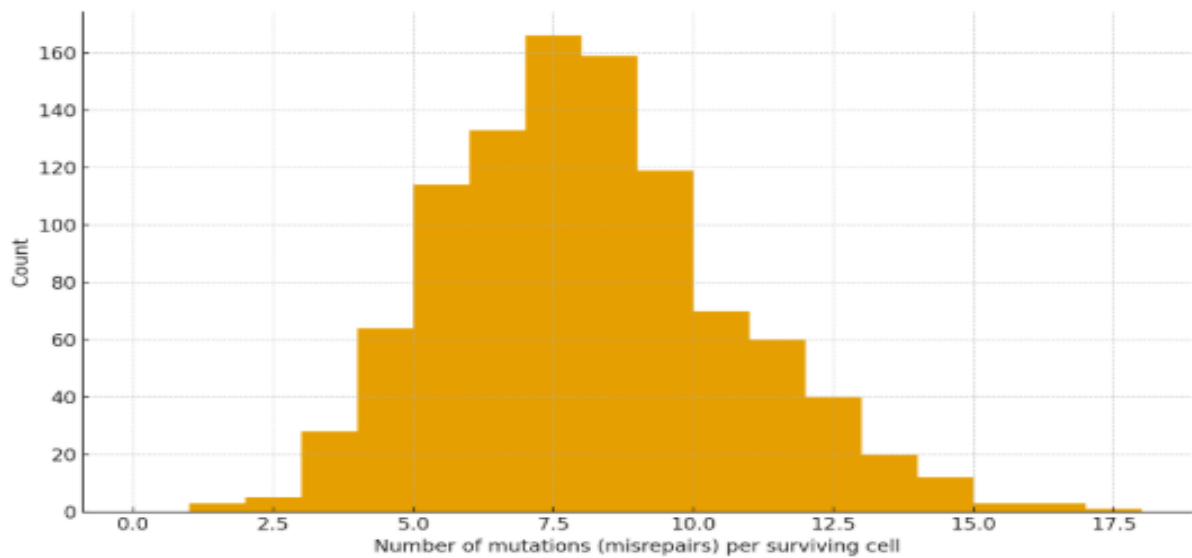


Figure 7b: *Mutation accumulation and distribution across cells misrepairs.*

Figure 7b gives *Mutation accumulation across cells* that illustrates the distribution of mutation counts (misrepairs) per surviving cell. The data exhibit a roughly bell-shaped pattern, peaking at around 7–8 mutations, where more than 160 cells are represented, indicating that this range is the most frequent mutational burden among surviving cells. Fewer cells fall at the extremes, with very low mutation counts (0–2) and very high counts (15–18) being rare, suggesting that most cells cluster around a moderate level of mutational accumulation. This distribution implies a quasi-normal trend, reflecting that while the repair machinery may function to limit extensive damage, errors in repair remain sufficiently common to produce a central tendency of mutations across the population. The presence of a tail toward higher mutation counts highlights that a subset of cells may accumulate extensive genomic alterations, which could increase the risk of malignant transformation or other pathological outcomes. Conversely, the small number of cells with near-zero mutations suggests that perfectly error-free repair is uncommon under the studied conditions. Overall, the figure underscores the balance between repair fidelity and error-prone repair mechanisms, revealing that the majority of cells harbor an intermediate mutational load, with potential implications for genomic stability, evolutionary selection, and disease risk.

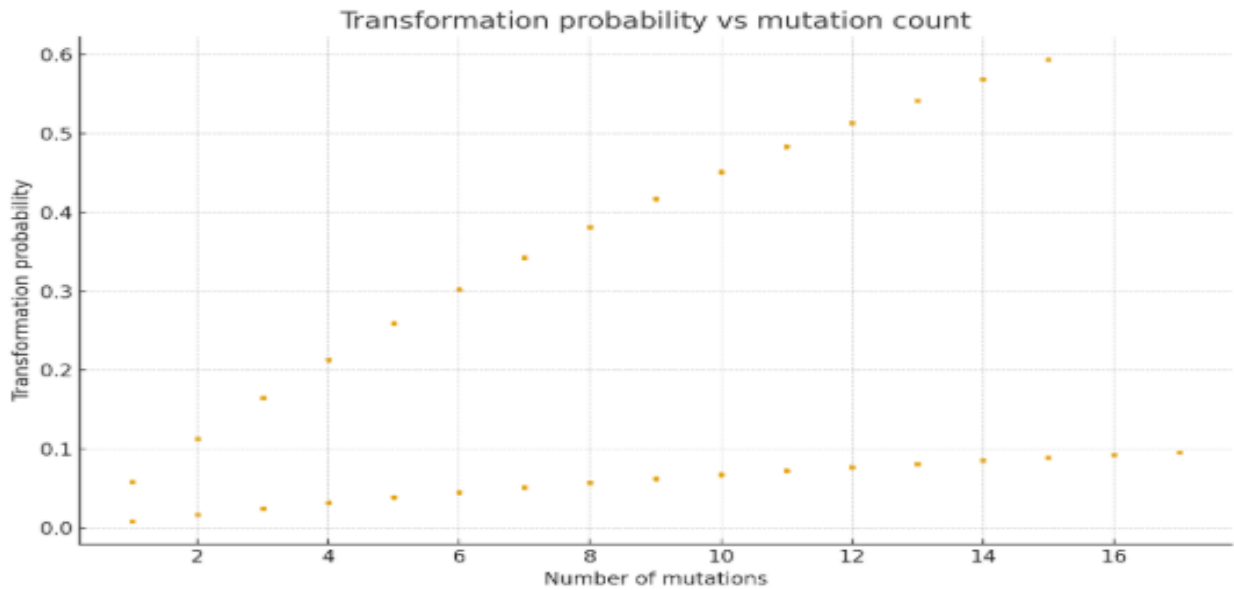


Figure 7c. Radial distribution of ionizations from an alpha-particle track in the lung cell nucleus.

Figure 7c provides ionization counts as a function of radial distance from the track core. A sharp peak near 1.8–2.0 μm corresponds to dense ionization clustering within the core, while the gradual decrease at larger radii reflects the contribution of secondary delta-ray electrons forming the track penumbra. The radial distribution of ionizations highlights the track-structure nature of alpha-particle energy deposition. The pronounced peak at $\sim 2 \mu\text{m}$ indicates the core region where ionizations are tightly concentrated, giving rise to highly complex DNA lesions, including clustered double-strand breaks, which are particularly challenging for repair machinery and prone to misrepair. In contrast, the extended tail toward larger radii represents the penumbra region, dominated by sparser ionizations from delta-ray electrons that predominantly yield isolated lesions such as single-strand breaks or base damage, which are more amenable to repair. Biologically, this spatial heterogeneity underscores why alpha radiation induces disproportionately severe biological effects compared to low-linear energy transfer (LET) radiations: while the core generates lethal or transformation-prone lesions, the penumbra contributes to mutation accumulation over time. Incorporating such microdosimetric patterns into biologically based dose-response (BBDR) models provides a mechanistic bridge between subcellular damage distributions and epidemiologically observed lung cancer risk from radon exposure.

Conclusion

This study provides an integrated, mechanistic framework for understanding radon-induced lung carcinogenesis by bridging molecular, cellular, and epidemiological scales. Starting from alpha-particle track simulations, we demonstrated the spatial heterogeneity of ionization events, with dense clustering in the track core leading to complex, repair-resistant double-strand breaks

and more dispersed ionizations in the penumbra contributing to single-strand breaks and base damage. DNA damage and repair simulations highlighted the critical role of repair pathway choice, with non-homologous end joining dominating misrepair outcomes in clustered lesions. Protein–DNA interaction modeling further differentiated between repair-efficient and misrepair-prone configurations, offering insights into the molecular determinants of repair fidelity.

At the cellular level, probabilistic modeling of repair, apoptosis, and misrepair outcomes illustrated how mutation accumulation emerges from a balance between lesion lethality and misrepair-driven survival. These cell-scale outcomes were embedded within a biologically based dose-response (BBDR) model, which successfully recapitulated population-level excess relative risk (ERR) estimates consistent with pooled residential epidemiological studies, BEIR VI, and ICRP assessments. The model predicted an ERR of approximately 8–10% per 100 Bq·m⁻³, strengthening confidence in current risk estimates while grounding them in molecular mechanisms.

Collectively, these findings provides the importance of spatially clustered DNA damage, pathway-specific repair dynamics, and cell fate decisions in shaping radon-induced cancer risk. By explicitly linking mechanistic simulations with epidemiological data, this work advances the field beyond purely empirical models, offering a robust scientific foundation for risk assessment and public health policy. The framework presented here is adaptable to other inhaled radionuclides and carcinogenic exposures, and it provides a platform for refining low-dose risk estimates, exploring individual susceptibility factors, and improving radiation protection standards.

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