Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

A Process-Based Model of LET- and Oxygen-Dependent Survival in Carbon-Ion Irradiation

Ladan Rezaee

Ladan.Rezaee@iau.ac.ir

Islamic Azad University

Research Article

Keywords: Heavy-ion irradiation, LET, Hypoxia, RBE, DNA fixation, Radiobiological modeling

Posted Date: November 18th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-11596463/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

Additional Declarations: No competing interests reported.

A Process-Based Model of LET- and Oxygen-Dependent Survival in Carbon-Ion Irradiation

Ladan Rezaee

Department of Physics, Shi.C., Islamic Azad University, Shiraz, Iran

E-mail address: Ladan.Rezaee@iau.ac.ir

ORCID ID: 0000-0003-0260-5276

Abstract

Biological effectiveness of carbon-ion irradiation is influenced mainly by linear energy transfer (LET) and oxygenation. Models accounting for the combined effects of these factors are commonly formulated using simple oxygen-scaling relationships, which limit the ability to separately assess the effects of fixation kinetics and LET. In this study, a process-based fixation-kinetics model was used to investigate model parameters and sensitivity for LET- and oxygen-dependent survival in carbon-ion irradiation. The model combines oxygen-mediated damage fixation, oxygen-independent damage stabilization, and LET-dependent saturation within a common analytical formulation. Model parameters were estimated using experimental data for clonogenic survival and relative biological effectiveness (RBE). The model captured the main trends in survival and RBE using a small number of bounded parameters. Sensitivity analysis indicated that the effective fixation time window had limited influence under normoxic conditions but became increasingly important under hypoxic conditions, whereas oxygen-independent stabilization contributed more strongly at intermediate and high LET. The LET-dependent saturation term captured the increase and subsequent turnover of RBE at high LET without introducing additional oxygen-scaling factors. These results demonstrate that the fixation-kinetics framework provides a compact analytical approach for examining the coupled effects of LET and oxygenation on biological response to carbon-ion irradiation.

Keywords: Heavy-ion irradiation; LET; Hypoxia; RBE; DNA fixation; Radiobiological modeling.

1.Introduction

Heavy-ion radiotherapy has been employed in radiation oncology for a long time because of its advantageous depth dose distribution and biological efficacy over photons (Durante and Loeffler 2010; Schardt et al. 2010). The high linear energy transfer (LET) of charged particles leads to densely ionizing tracks and clusters of DNA damage, especially complex double-strand breaks (DSBs), which are closely associated with clonogenic cell killing (Goodhead 1994; Ward 1994; Prise et al. 2001). Nevertheless, the biological effect is not only a function of LET but also of the biochemical microenvironment, particularly oxygenation.

Tumor hypoxia is a major factor of radioresistance in solid tumors (Gray et al. 1953; Vaupel et al. 2001; Horsman and Overgaard 2016). According to the oxygen fixation theory (Roots and Okada 1972; Ward 1988; Grimes and Partridge 2015; Brown and Wilson 2004; Wenzl and Wilkens 2011), molecular oxygen increases the stability of radiation-induced radical damage, leading to the formation of stable DNA lesions. Under hypoxic conditions, decreased fixation efficacy results in the decreased radiosensitivity and alteration of the relationship between LET and RBE. The oxygen enhancement ratio is usually used as a way to define this process, but it is a phenomenological model based on the lack of time dependence and consideration of radical diffusion kinetics coupled with LET.

Many LET-based RBE models treat oxygenation and radiation quality as separable or only weakly coupled factors (Kellerer and Rossi 1972; Scholz and Kraft 1996; Scholz et al. 2020). Although these models are able to average trends, they do not contain explicit physico-chemical descriptions of radical recombination, oxygen reactions, and DSB stabilization on appropriate time and length scales (Buxton et al. 1988; Mozumder 1999; Sonntag 2006). This is particularly important in hypoxic environments, in which reaction-diffusion competition determines fixation probability.

The other type of models, which consider factors related to track structure, oxygen chemistry, and post-irradiation phenomena, is also a possible way of modeling DSBs (Chadwick and Leenhouts 1973; Curtis 1986; Grimes et al. 2016). One such time-resolved models was developed earlier (Rezaee 2026a), in which DSB formation was described as a result of lesion production and fixation processes occurring both in the presence and absence of oxygen. However, the problem of robustness and sensitivity of parameters of the model has not been considered yet.

For practical use of fixation-based survival models, parameter stability and sensitivity characteristics are as important as the underlying biological assumptions. Parameters such as the effective fixation time window, oxygen-independent rate of stabilization, LET-dependent overkill attenuation, and lethal conversion efficiency are biologically plausible but not universal constants. The problems of identifiability of parameters and consistency across different data sets should be considered as it could be problematic due to uncertainty of parameters which would affect the reliability and applicability of the results of simulations obtained in various experimental settings (Goodhead 1994; Wardman 2016).

Building on the fixation-kinetics formulation of LET- and oxygen-dependent cell survival, the present study aims to investigate parameter sensitivity, model structural identifiability, and plausible parameter ranges across different LET and oxygenation levels. Model behavior is evaluated using published datasets from in vitro experiments on cell survival and relative biological effectiveness (RBE) under oxic and hypoxic conditions (Furusawa et al. 2000; Tinganelli et al. 2013; Belli et al. 2008). The study examines the individual contributions of fixation kinetics, oxygen-independent stabilization, and LET-dependent saturation to the radiobiological response.

2. Materials and Methods

2.1 Overview of the Fixation-Kinetics Framework

A fixation-kinetics analytical model describing the stabilization of radiation-induced DNA double-strand breaks (DSBs) as a coupled function of oxygen availability, radiation quality (LET), and post-irradiation chemical dynamics was applied. The model, previously developed and described by Rezaee (2026a), is based on radiation chemistry and track-structure physics and includes oxygen-dependent and oxygen-independent fixation pathways (Ward 1988, 1994; Grimes and Partridge 2015).

After the energy deposition event by charged particles, DSBs are modeled as unstable lesions that undergo competing physico-chemical reactions on timescales ranging from nanoseconds to microseconds. In the oxygen-dependent fixation pathway, DNA damage caused by radicals reacts with molecular oxygen to produce a chemically stable lesion. The probability of fixation is a function of oxygen concentration and an effective fixation time window, Δt, rather than enzymatic repair (Buxton et al. 1988; Sonntag 2006; Wardman 2016).

An oxygen-independent pathway contributes to the stabilization of DSBs under hypoxic conditions through the ionization clusters and saturated radical environments produced by high-LET tracks (Wenzl and Wilkens 2011; Scholz et al. 2020; Nikjoo et al. 2001). The mechanism is described by an effective fixation rate constant, k_0, which depends on LET because of the increasing spatial correlations and complexity of damage (Kellerer and Rossi 1972; Nikjoo 2003).

The combined processes support the reproduction of survival under oxic and hypoxic conditions, including scenarios where traditional OER concepts fail (Furusawa 2000; Tinganelli et al. 2013). Stabilized DSBs are associated with clonogenic survival based on a repair-misrepair approach (Chadwick and Leenhouts 1973; Curtis 1983).

To account for the non-monotonic dependence of RBE on LET, the framework includes two additional terms inherited from the original formulation (Rezaee 2026a): (i) an LET-dependent overkill attenuation factor, $\psi(\mathrm{LET})$, representing saturation at high ionization densities (Ward 1994; Friedrich 2013; Surdutovich and Solov'yov 2019), and (ii) a lethal efficiency factor, η, describing incomplete conversion of fixed DSBs into clonogenic cell killing (Curtis 1986; Wang 2018).

The structural form of the original model was preserved. In this study, parameter sensitivity, structural identifiability, boundedness of the parameter space, and robustness across LET and oxygenation regimes relevant to heavy-ion radiation are explored.

2.2 Experimental Datasets and Data Selection

2.2.1 Survival and RBE Datasets

Parameter estimation and sensitivity analysis depended on survival and RBE values that covered wide ranges of LET and oxygenation. The published survival and RBE in vitro datasets for carbon ion irradiation have been chosen due to their frequent involvement in modeling radiobiological systems (Durante and Loeffler 2010; Schardt et al. 2010).

The basic survival data were taken from (Furusawa et al. 2000) and (Tinganelli et al 2013), and included normoxic and hypoxic survival curves for various LET values. Additional RBE datasets from (Weyrather et al. 1999) and (Belli et al. 2008) was used to evaluate LET-dependent trends. The analyzed datasets include V79 Chinese hamster fibroblasts, HSG human salivary gland tumor cells, and additional cell systems commonly used in radiobiological investigations.

Because DSB fixation cannot be observed directly in routine radiobiological experiments, parameter estimation was based on macroscopic biological endpoints. The conceptual basis of the fixation approach (Rezaee 2026a) utilizes clonogenic survival and RBE as an intermediary between microscopic damage stabilization and the effect on biological outcomes (Ward 1994; Chadwick and Leenhouts 1973; Curtis 1986).

The normoxic datasets correspond to oxygen partial pressures of approximately 70-80 mmHg, while the hypoxic datasets (≈5-10 mmHg) represent tumor-relevant conditions (Gray et al. 1953; Vaupel et al. 2001; Horsman and Overgaard 2016). The inclusion of both conditions allows the distinction of oxygen-dependent and oxygen-independent effects.

2.2.2 Oxygenation Conditions and LET Coverage

The chosen data sets cover a wide range of LET values for carbon ions, from the area of highest biological effectiveness (≈100-150 keV/µm) to the high-LET overkill region (>300 keV/µm). This LET coverage facilitates assessment of the relative contributions of oxygen-dependent fixation, oxygen-independent stabilization, and LET-dependent saturation processes (Goodhead 1994; Friedrich 2013).

Normoxic data sets are mainly used to constrain saturation and lethal efficiency as a function of LET, while hypoxic data sets allow a higher sensitivity to the time window of effective fixation and the oxygen-independent rate constant, increasing sensitivity to parameters associated with alternative stabilization pathways (Furusawa et al. 2000; Tinganelli et al. 2013).

A list of all in vitro data sets employed for parameter fitting and validation is given in Table 1. Only studies with clearly specified irradiation conditions and well-documented clonogenic assay data were considered.

Table 1. Summary of in vitro datasets used for parameter estimation and validation, including cell line, oxygenation status, ion species, LET range, dose range, and biological end-point.

Reference	Cell line	Ion species	Oxygen condition	LET range (keV/µm)	Biological endpoint	Use in this study
Furusawa et al. 2000	V79, HSG	Carbon	Normoxic (~76 mmHg) Hypoxic (~7.6 mmHg)	~13 – 400 keV/µm	Survival fraction, RBE_{10}	Parameter estimation and hypoxia analysis
Tinganelli et al. 2013	V79	Carbon	Acute hypoxia vs normoxia	~30 – 200 keV/µm	Survival fraction	Oxygenation-dependent comparison
Belli et al. 2008	multiple human normal & tumor	Carbon	Normoxic	~30–100 keV/µm	RBE	Cross-cell-line comparison
Weyrather et al. 1999	multiple repair capacities	Carbon	Normoxic	~20 – 200 keV/µm	RBE	Assessment of LET-dependent trends

2.3 Parameter Estimation and Sensitivity Framework

2.3.1 Estimation of the Oxygen-Independent Fixation Rate k_0

One of the main objectives was to estimate the oxygen-independent fixation rate k_0, which represents the stabilization of radiation-induced DSBs not mediated by oxygen, related to track-structure effects (Goodhead 1994; Ward 1988; Nikjoo 2001), within the fixation model (Rezaee 2026a).

The estimation of k_0 was based on the differences between oxic and hypoxic survival curves after carbon-ion irradiation. The linear coefficients α of the linear quadratic model for oxic and anoxic conditions (Tinganelli et al. 2013) were applied for all LET values. As α is proportional to the number of fixed lethal lesions per dose (Chadwick and Leenhouts 1973; Curtis 1986), the experimental ratio $\alpha_{\mathrm{anoxic}}/\alpha_{\mathrm{oxic}}$ is a quantitative estimate of oxygen-independent fixation.

In the time-dependent model, the total probability of stabilization after an effective time interval Δt is

$$P_{\mathrm{fix}}^{\mathrm{tot}} = 1 - \exp[-(k_{O_2} + k_0)\Delta t] \tag{1}$$

where k_{O_2} represents oxygen-dependent fixation. In hypoxic environments, k_{O_2} is significantly lowered, and the fixation process relies mainly on k_0. By equating the experimental α-ratio to the ratio of the theoretical fixation probabilities in oxic and hypoxic environments, the value of k_0 can be estimated without introducing additional adjustable parameters, thereby reducing parameter redundancy.

The values $k_0(\mathrm{LET}, \Delta t)$ were calculated numerically for fixation times ranging from microseconds to minutes. For low LET values (<100 keV/µm), k_0 remained constant, suggesting limited oxygen-independent contributions to fixation in sparsely ionizing tracks. For intermediate LET values (≈100-150 keV/µm), k_0 increased, reflecting the presence of ionization clusters and complex DNA damage (Goodhead 1994; Prise et al. 2001). In the overkill domain at high LET values, k_0 decreased (Nikjoo 2003; Friedrich 2013).

A clear dependence on Δt was found, with larger fixation windows corresponding to smaller values of inferred k_0, consistent with the exponential form of Eq. (1) and the interplay between k_0 and Δt, especially in hypoxic high-LET environments.

For the purpose of sensitivity analysis, k_0 values were parameterized using a continuous cluster-saturation function. Analysis of fixation probability indicated that oxygen-independent stabilization is more important for hypoxic environments on short to medium timescales, while oxygen-dependent fixation is much more rapid in normoxic environments. These results suggest that k_0 can be inferred from experimentally accessible survival data and may contribute to improved descriptions of LET- and oxygen-dependent survival.

2.3.2 Effective Fixation Time Window Δt

The fixation window Δt is the time frame after irradiation during which the radiation-induced DSBs are chemically accessible to oxygen fixation. It is treated not as a fundamental constant but as an effective timescale that emerges from the competition between radiation chemistry, oxygen diffusion, and the initiation of enzymatic repair in fixation theory (Rezaee 2026a).

The reaction times for primary radicals in the vicinity of charged particle tracks are microsecond to millisecond timescales (Roots and Okada, 1972; Ward, 1988; Buxton et al., 1988). Oxygen fixation by diffusion-limited reactions between molecular oxygen and damage-related radicals takes seconds to minutes (Goodhead 1994; Nikjoo et al. 2001; Blakely and Kronenberg 1998). In contrast, enzymatic recognition and repair of DSBs are initiated minutes after irradiation (Jeggo and Löbrich 2007; Kinner et al. 2008; Lomax et al. 2013), after which no further oxygen fixation is possible.

In the model, oxygen fixation during Δt is

$$P_{O_2} = 1 - \exp[-k_{O_2}\Delta t] \tag{2}$$

where k_{O_2} is a function of oxygen concentration and diffusion characteristics for diffusion-limited conditions (Mozumder 1999; Collins and Kimball 1949).

On the basis of radiochemical and radiobiological arguments, Δt was set to vary between 1 and 600 s. The lower limit excludes ultrafast radical reactions that occur before significant oxygen diffusion, while the upper limit estimates the beginning of early DSB repair, beyond which oxygen fixation becomes biologically unlikely (Ward 1988; Lomax et al. 2013).

High-LET radiation produces clustered damage and localized oxygen depletion, potentially extending the period during which damage remains chemical accessible (Prise et al. 2001; Nikjoo et al. 2006), and thus Δt was varied over this range. Sensitivity analysis showed that Δt had a small effect on normoxic conditions, consistent with efficient oxygen fixation, but a strong dependence on hypoxic conditions, where the availability of oxygen directly affects the fraction of DSBs fixed before the start of repair (Ward 1988; Blakely and Kronenberg 1998). The analysis therefore treats Δt as a bounded but variable parameter whose influence can be assessed across different LET and oxygenation conditions.

2.3.3 Overkill Attenuation Function ψ(LET)

At high LET, biological effectiveness typically reaches a plateau and may subsequently decrease, overkill effect (Goodhead 1994; Scholz and Kraft 1996; Friedrich et al. 2013; Surdutovich and Solov'yov 2019), due to the high ionization density causing overlapping damage that does not scale with lethal events.

In addition, there have been suggestions of a statistical-mechanical approach to LET-dependent attenuation, which has been described recently by Rezaee 2026b. This approach suggests that overkill results from the saturation of a finite population of radiation sensitive chromatin domains. In this approach, an equation describing an LET-dependent attenuation is deduced from the percentage of chromatin domains left over as targets for formation of further independent lethal lesions. It can be said that the statistical-mechanical approach provides a possible explanation of the reduction of the effective yield of lethal lesions with increasing LET and also the occurrence of an RBE maximum. While the current approach to LET-dependent attenuation focuses on the conversion of fixed double strand breaks into lethal lesions, the statistical-mechanical approach gives another way to explain LET-dependent saturation.

In the present fixation-based framework, the LET-dependent attenuation factor introduced by Rezaee (2026a) accounts for this effect by modifying the efficiency of conversion of chemically fixed DSBs into clonogenic cell killing, independently of the fixation probability. If $N_{\mathrm{fix}}(\mathrm{LET})$ is the number of fixed DSBs and $N_{\mathrm{lethal}}(\mathrm{LET})$ is the number of lethal lesions, then

$$N_{\mathrm{lethal}}(\mathrm{LET}) = \psi(\mathrm{LET}) N_{\mathrm{fix}}(\mathrm{LET}) \tag{3}$$

with $0 < \psi(\mathrm{LET}) \leq 1$. At low LET, $\psi(\mathrm{LET}) \to 1$; at high LET, $\psi(\mathrm{LET}) < 1$, indicating decreased marginal lethality at high lesion densities. Fixation kinetics and LET-dependent saturation are again structurally decoupled.

The attenuation was parameterized using a logistic-type function (Rezaee 2026a):

$$\psi(\mathrm{LET}) = \frac{1}{1 + z_1 . \exp[z_2 . (\mathrm{LET} - \mathrm{LET}_{\mathrm{peak}})]} \tag{4}$$

with $\mathrm{LET}_{\mathrm{peak}} \approx 150\ \mathrm{keV/\mu m}$ for carbon ions. The parameters z_1 and z_2 control the magnitude and steepness of the post-peak decline, and were set to physically realistic bounds ($0.05 \leq z_1 \leq 0.2$ and $0.005 \leq z_2 \leq 0.02$), consistent with a smooth transition to $\psi \approx 0.4 - 0.6$ at $\mathrm{LET} \geq 300\ \mathrm{keV/\mu m}$, as reported for survival flattening (Furusawa et al. 2000; Belli et al. 2008, Weyrather et al. 1999; Aoki et al. 2000).The set $(z_1, z_2) = (0.1, 0.01)$ was chosen to model RBE turnover without dataset-specific tuning.

The constraints were informed by (i) consistency with published RBE-LET dependencies (Furusawa et al. 2000; Belli et al. 2008, Weyrather et al. 1999), (ii) microdosimetric evidence for saturation above ~150 keV/µm (Nikjoo 2003; Friedland et al. 2017), and (iii) experimental survival flattening at LET > 300 keV/µm. The total reduction in attenuation was constrained to a 40-60% reduction in effective survival in the extreme overkill domain. Consequently, $\psi(\mathrm{LET})$ is interpreted as a

phenomenological representation of LET-dependent saturation rather than a repair process, maintaining a process-based distinction between chemical fixation and track-structure-induced saturation.

2.3.4 Lethal Efficiency Scaling Factor η

Chemical fixation alone does not necessarily result in clonogenic lethality. The transfer of stabilized DSBs to lethal lesions is a function of repair pathway choice, chromatin structure, lesion complexity, and cell-specific differences (Goodhead 1994; Ward 1988; Scholz et al. 2020).

The number of stabilized DSBs expected at LET and dose D is

$$N_{\mathrm{fix}}(\mathrm{LET}, D) = P_{\mathrm{fix}}^{\mathrm{tot}} . N_{\mathrm{DSB}}(\mathrm{LET}, D) \tag{5}$$

with total fixation probability $P_{\mathrm{fix}}^{\mathrm{tot}}$ (Eq. 1). The initial DSB number is assumed to be linear in dose (Wang 2018):

$$N_{\mathrm{DSB}}(\mathrm{LET}, D) = \phi(\mathrm{LET}) . D \tag{6}$$

where $\phi(\mathrm{LET})$ is the DSB number per unit dose. Only a fraction $\psi(\mathrm{LET}) \leq 1$ of the fixed lesions leads to lethality (Eq. 3), and using Poisson statistics, the intrinsic survival is given by

$$S = \exp(-N_{\mathrm{lethal}}) \tag{7}$$

To account for biological and experimental variability not explicitly represented in the model (e.g., plating efficiency or normalization), a global scaling factor for the lethal efficiency η, was introduced to account for biological and experimental variability not explicitly represented in the model:

$$S_{\mathrm{eff}} = \eta . S \tag{8}$$

In this case, η serves as an empirical normalization factor between the model's survival and the experimental clonogenic survival.

This approach maintains a distinction between (i) damage fixation and stabilization, N_{fix}, (ii) LET-dependent saturation, $\psi(\mathrm{LET})$, and (iii) biological scaling, η. Experimental observations suggest that fixation alone is insufficient to explain observed survival slopes; only a fraction of the fixed DSBs is clonogenically lethal (Ward 1988; Curtis 1986; Lomax et al. 2013).

In the current study, η was set using reference data for photons and low-LET ions, where the effect of overkill is small, and η was assumed to be LET-independent, such that the dependence on radiation quality is solely due to $\psi(\mathrm{LET})$. Sensitivity analysis showed that η primarily influences the absolute survival level but does not affect LET-dependent RBE or oxygen enhancement, which supports the idea that η can be considered as a normalization constant and not a radiation quality parameter.

In summary, the hierarchical separation of fixation kinetics (Δt), LET-dependent saturation (ψ), and biological conversion efficiency (η) facilitates interpretation and reduces parameter coupling in LET- and oxygen-dependent survival modeling.

2.4 Sensitivity Analysis

Parameter robustness and sensitivity characteristics were assessed using the fixation-based framework developed by Rezaee (2026a). Sensitivity analysis provides a quantitative measure of how parameter uncertainty influences model predictions (Saltelli et al. 2008; Paganetti 2014; Inaniwa et al. 2015). The parameters examined in the sensitivity analysis were k_0, Δt, $\psi(\mathrm{LET})$, and η.

One-at-a-time (OAT) sensitivity analysis was performed, where each parameter was varied over biologically plausible and physically reasonable ranges while fixing other parameters at their baseline values (Saltelli et al. 2008; Helton e al. 2006). For model output Y, the normalized sensitivity coefficient with respect to parameter z was

$$\sigma_z = \frac{\partial \ln Y}{\partial \ln z} \approx \frac{Y(z+\Delta z) - Y(z-\Delta z)}{2\,Y(z)} \cdot \frac{z}{\Delta z} \tag{9}$$

This dimensionless quantity allows for comparison across parameters with different scales.

Parameter values were set within biologically plausible and experimentally supported bounds: k_0 varied within ranges consistent with oxic-hypoxic survival differences (Ward 1988; Blakely and Kronenberg 1998); Δt varied between 1-600 s, encompassing post-irradiation chemistry and the onset of early repair (Jeggo and Löbrich 2007; Lomax et al. 2013); ψ(LET) parameters were constrained to reproduce observed RBE saturation (Furusawa et al. 2000; Curtis 1986; Weyrather et al. 1999); and η was varied within empirically supported ranges from low-LET reference data (Goodhead 1994; Scholz et al. 2020).

Sensitivity was evaluated using (i) clonogenic survival in the low-dose domain and (ii) relative biological effectiveness at 10% survival,

$$\mathrm{RBE}_{10} = \frac{D_{10}^{\mathrm{ref}}}{D_{10}^{\mathrm{ion}}} \tag{10}$$

where D_{10}^{ref} and D_{10}^{ion} are the doses corresponding to 10% survival for reference radiation and carbon ions, respectively.

Finite-difference perturbations prevented numerical instability and ensured that the results remained physical, i.e., that fixation probabilities and survival were non-negative (Paganetti 2014; Inaniwa et al. 2015). A schematic diagram of the analysis is shown in Figure 1.

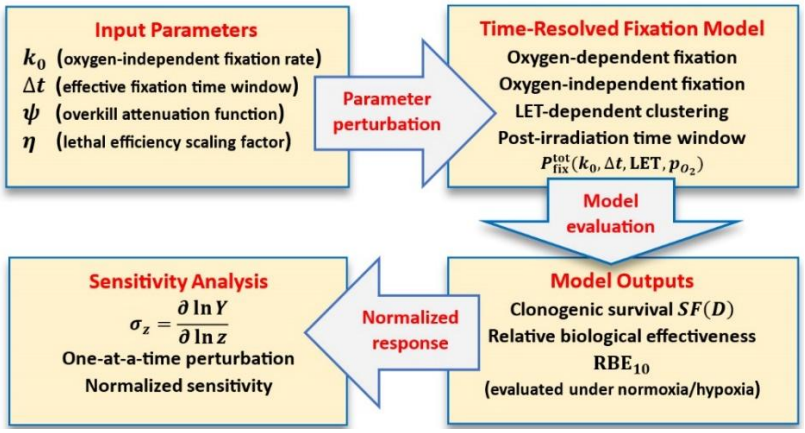


Figure 1. Schematic representation of the sensitivity analysis procedure. Model parameters (k_0, Δt, ψ(LET), and η) are varied independently and used as input to the fixation-kinetics model to calculate clonogenic survival and RBE. Normalized sensitivity coefficients are obtained for each parameter at defined LET and oxygenation levels.

3. Results

3.1 Landscapes of the Oxygen-Independent Fixation Rate k_0

Figure 2 illustrates k_0 maps as a function of LET and the effective fixation time window Δt, obtained by direct inversion of the experimental oxic and anoxic survival curves (Section 2.3.1). This approach provides estimates of oxygen-independent DSB fixation rates that are constrained by the analyzed survival datasets.

A clear LET dependence is observed: k_0 rises from low to intermediate LET values and saturates at higher LET, consistent with increased ionization clustering and complex DNA damage formation, which becomes stable independently of oxygen (Goodhead 1994; Nikjoo et al. 2001; Friedrich et al. 2013).

For a fixed LET, k_0 is lower for larger Δt, since a larger fixation time window corresponds to a smaller instantaneous rate of fixation to produce the same oxygen-independent contribution as inferred from experiments. The $k_0(\mathrm{LET}, \Delta t)$ surfaces are smooth and continuous over several orders of magnitude in time, suggesting stable parameter behavior over the investigated LET and Δt ranges.

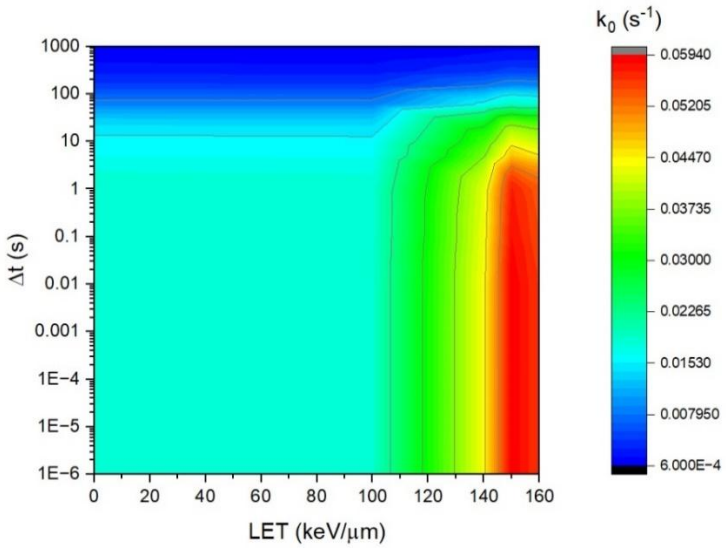


Figure 2. Oxygen-independent fixation rate k_0 as a function of LET and effective fixation time window Δt, derived from the inversion of oxic and anoxic survival curves. The surfaces illustrate the variation of k_0 across LET and Δt values inferred from the analyzed survival datasets.

Typical numerical values of k_0 for chosen pairs of LET and Δt are presented in Table 2. The values remain within biologically plausible ranges and exhibit similar trends across the analyzed datasets.

These k_0 landscapes indicate that oxygen-independent fixation may contribute increasingly to the predicted response at intermediate and high LET values, where hypoxic protection is reduced. The observed LET dependence would not be captured by a constant k_0. These $k_0(\mathrm{LET}, \Delta t)$ surfaces provide a reference for the subsequent sensitivity analyses presented below.

Table 2. Typical numerical values of the oxygen-independent fixation rate k_0 for various pairs of LET and Δt, calculated from experimental oxic-anoxic survival ratios.

Δt (s)	k_0 (s^{-1})				
	LET = 0	LET = 100 keV/μm	LET = 140 keV/μm	LET = 150 keV/μm	LET = 160 keV/μm
0.01	0.01876	0.01858	0.04399	0.05924	0.05549
5	0.01642	0.01630	0.03690	0.04744	0.04481
60	0.0086	0.00863	0.01596	0.01919	0.01845
150	0.0045	0.00447	0.00788	0.00931	0.00899
300	0.0026	0.00235	0.00408	0.00481	0.00465
600	0.00118	0.00117	0.00205	0.00241	0.00233

3.2 Sensitivity to the Fixation Time Window (Δt)

Figure 3 illustrates the survival sensitivity to changes in Δt for normoxic and hypoxic conditions, showing distinct trends for the two oxygenation states. For normoxic conditions, the sensitivity of survival to Δt remains relatively low for the LET values, with variations of less than 10-20% over the biologically relevant time scale of 1-600 s. With an abundance of oxygen, the

radical fixation process is rapid compared to enzymatic repair, and thus variations in Δt make little difference (Roots and Okada 1972; Ward 1988; Lomax et al. 2013). Under hypoxic conditions, survival predictions show substantially greater sensitivity to Δt, with variations of up to ~40% (Ward 1988; Blakely and Kronenberg 1998; Kinner et al. 2008).

Sensitivity generally increases with LET, as higher ionization densities lead to clustering and hypoxic regions, which enhance the role of Δt, particularly in hypoxic conditions (Prise et al. 2001; Nikjoo et al 2006). This trend is consistent with the increasing influence of fixation kinetics under conditions of limited oxygen availability. The relatively low sensitivity observed under normoxic conditions suggests limited dependence of the model predictions on Δt within the investigated range, whereas the larger sensitivities observed under hypoxia highlight the influence of fixation timescales on predicted survival in simulating the effect of oxygen-modified RBE. These results indicate that Δt has a limited influence under normoxic conditions but becomes an important source of variability in model predictions under hypoxia.

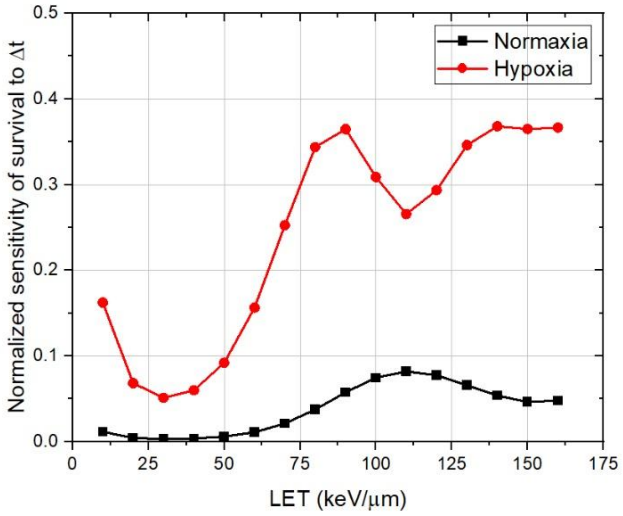


Figure 3. Normalized sensitivity of calculated clonogenic survival with respect to variations of the fixation time window Δt as a function of LET for normoxic and hypoxic conditions. The sensitivity coefficients were calculated by perturbing Δt around its nominal value while keeping all other variables constant.

3.3 Sensitivity to Overkill Attenuation ψ(LET) and Lethal Efficiency Scaling η

Figure 4 summarizes the sensitivity of predictions to variations in the overkill attenuation function ψ(LET) and the scaling factor η for lethal efficiency. The two parameters influence different components of the model formulation: ψ(LET) controls saturation of damage effectiveness at high LET values, while η controls the global mapping between chemically stabilized lesions (CSL) and clonogenic survival.

Sensitivity analysis indicates that ψ(LET) becomes increasingly influential beyond the RBE maximum. In the absence of an LET-dependent saturation term, the model would predict a more pronounced increase in effectiveness with LET than generally observed experimentally (Furusawa et al. 2000; Belli et al. 2008; Weyrather et al. 1999). As shown in Figure 4, sensitivity is low at low LET but increases abruptly above 150 keV/µm, corresponding approximately to the LET region where RBE reaches its maximum. At high ionization densities, energy contributes increasingly to overlapping or redundant lesions, making marginal lethality less probable (Scholz et al. 1996; Nikjoo 2003; Friedrich et al. 2013). In contrast, η-sensitivity is flat with respect to LET, translating the survival curves in the vertical direction without changing the position of the RBE peak or its dependence on LET. η represents an effective conversion factor between stabilized damage and clonogenic cell death, irrespective of radiation quality.

These sensitivity patterns suggest that ψ(LET) and η influence different aspects of model behavior, where the saturation as a function of LET is completely described by ψ(LET), and the absolute survival scaling is determined by η. The adopted formulation reduces potential parameter coupling between LET-dependent saturation and overall survival normalization and

facilitates parameter interpretation, since the variation of both parameters with LET would make the physical rationale of the RBE turn-over ambiguous.

Overall, the sensitivity analysis indicates that $\psi(\mathrm{LET})$ primarily affects LET-dependent saturation behavior, whereas η mainly influences the overall survival level. Their distinct sensitivity profiles support the use of separate parameters for LET-dependent saturation and survival normalization within the present framework.

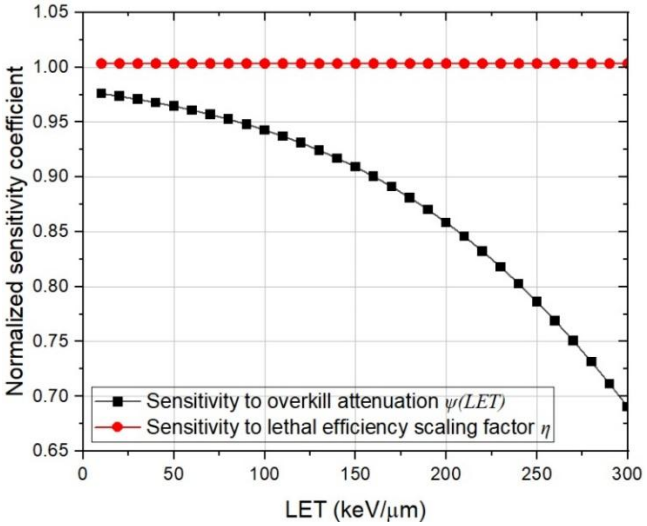


Figure 4. Normalized sensitivity of predicted survival with respect to the overkill attenuation function $\psi(\mathrm{LET})$ (black curve) and the lethal efficiency scaling factor η as a function of LET (red curve). Sensitivities were calculated by perturbing each parameter around its nominal value while keeping all other parameters fixed. Absolute values of sensitivity coefficients are plotted.

3.4 Quantitative Validation at Fixed LET Under Oxic and Hypoxic Conditions

Figure 5 compares model predictions with experimental clonogenic survival data for V79 cells irradiated with carbon ions at $\mathrm{LET} = 50\ \mathrm{keV/\mu m}$ under oxic and hypoxic conditions. In this case, the radiation quality is held fixed, and allowing the influence of oxygenation to be examined at fixed radiation quality.

In the model, lethal lesions obey Eq. (3), and survival is calculated using Poisson statistics. At this LET, $\psi(\mathrm{LET})$ is constant, and differences between oxic and hypoxic survival are solely due to differences in total fixation probability $P_{\mathrm{fix}}^{\mathrm{tot}}$.

Parameter values were constrained within the ranges defined in Section 2 and were not adjusted specifically for this dataset. Effective lethal yield $\phi(\mathrm{LET})$ was bounded by DSB induction rates for similar LET values, and fixation probabilities were bounded by reaction-diffusion kinetics and oxygen modification ratios. The attenuation function $\psi(\mathrm{LET})$ employed its independently specified LET-dependent form.

The shaded regions represent survival envelopes obtained by propagating the allowed parameter ranges through the model. The experimental observations fall within or close to the predicted survival envelopes for both oxygenation conditions.

The predicted uncertainty bands remain relatively narrow, and indicating limited variation in model predictions within the investigated parameter ranges once the radiation quality and the mechanistically justified parameters are specified. No oxygen-specific modification of the model structure was introduced.

These results are consistent with the representation of oxygen effects through changes in fixation probability within the present framework, without changing the damage profile with LET. The corresponding parameter values remained within the predefined parameter bounds.

The agreement between model predictions and the experimental survival data supports the ability of the framework to reproduce major oxygen-dependent trends at fixed LET. The relatively narrow prediction envelopes further suggest that model outputs remain reasonably stable within the investigated parameter ranges.

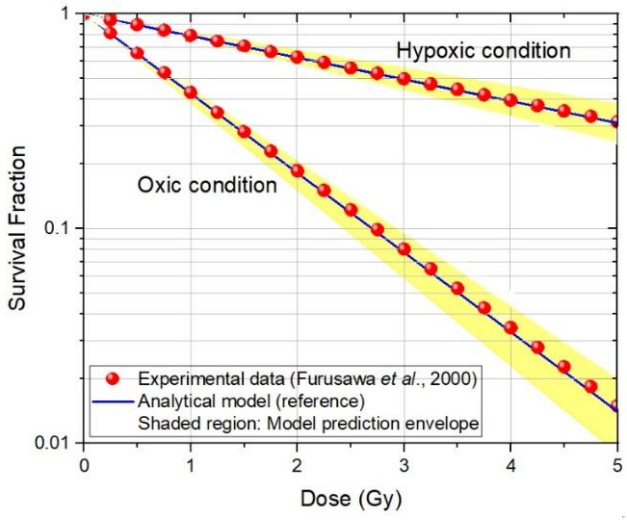


Figure 5. Dose-response survival curves for carbon ion irradiation at LET $= 50$ keV/μm in V79 cells under oxic and hypoxic conditions. The symbols are experimental data. The solid lines are model predictions, and the shaded areas are survival envelopes obtained from predefined parameter ranges.

3.5 Parameter Domain Consistent with Available Experimental Data

Table 3 summarizes the parameter ranges that were found to be consistent with the analyzed survival and RBE datasets and that produced stable model behavior over the investigated LET and oxygenation ranges. These ranges were identified through consistency with published experimental observations, model assumptions, and local sensitivity analysis rather than through unconstrained optimization.

The oxygen-independent fixation rate, k_0, was found to lie within $(1.2 - 4.8) \times 10^{-3}\ s^{-1}$ over the LET range considered in this study. Within this interval, the model reproduced the observed differences between oxic and hypoxic survival while preserving physically realistic fixation probabilities. Outside this interval, model predictions tended either toward negligible oxygen-independent stabilization or toward hypoxic responses that were less consistent with the analyzed datasets.

The effective fixation time window, Δt, was constrained to 1–600 s. This interval reflects the period during which oxygen-mediated chemical stabilization may compete with radical recombination and the initiation of biological repair processes. Sensitivity analysis indicated that variations within this range primarily affected hypoxic predictions while having a comparatively limited influence under normoxic conditions.

The LET-dependent attenuation factor, $\psi(\mathrm{LET})$, remained within the interval 0.72–1.00 for the LET values considered. Within this range, the model reproduced the observed saturation and turnover behavior of RBE at high LET while maintaining smooth LET-dependent behavior.

The lethal-efficiency scaling factor, η, was constrained to 0.111–0.125. Variations of η mainly affected the absolute normalization of survival predictions and exhibited little influence on LET-dependent or oxygen-dependent trends.

Local sensitivity analysis indicated that the principal model parameters affect different aspects of the predicted response. The fixation parameters (k_0 and Δt) primarily influence oxygen-dependent behavior, whereas $\psi(\mathrm{LET})$ governs high-LET saturation effects and η acts mainly as a normalization factor. These sensitivity patterns suggest that the parameters predominantly influence different aspects of model behavior, thereby reducing potential parameter compensation during model calibration.

The parameter intervals summarized in Table 3 define a bounded region of parameter space that remains consistent with the datasets analyzed in this study and provides a reference domain for subsequent model evaluation and comparison.

Table 3. Experimentally supported parameter ranges of the fixation-based survival model.

Parameter	Physical meaning	Units	Investigated range	Primary determinants	Primary influence in the model
k_0	Oxygen-independent fixation rate	s^{-1}	$(1.2–4.8) \times 10^{-3}$	LET, local track structure, radical density	Influences hypoxic stabilization
Δt	Effective fixation time window	s	1–600	Radical chemistry, oxygen diffusion kinetics	Influences oxygen-dependent fixation
$\psi(\mathrm{LET})$	LET-dependent attenuation factor	dimensionless	0.72–1.00 (10–300 keV/μm)	Ionization density, track saturation	Describes saturation behavior at high LET
η	Lethal efficiency scaling factor	dimensionless	0.111–0.125	Low-LET reference survival calibration	Controls overall survival normalization

4. Discussion

The present study examines the behavior of a fixation-kinetics framework for describing LET- and oxygen-dependent survival in heavy-ion irradiation. The analyses presented in Section 3 indicate that the framework remains numerically stable over the investigated LET and oxygenation ranges and allows closed-form evaluation without the need for stochastic track-structure simulations. Particular emphasis was placed on parameter sensitivity, parameter-domain characterization, and the respective roles of oxygen-dependent fixation, oxygen-independent stabilization, and LET-dependent saturation within the model formulation. The results provide insight into how these processes contribute to predicted survival and RBE trends across different irradiation conditions.

4.1 Parameter Separation and Sensitivity Structure

The results indicate a compact parameter space (Table 3) together with distinct sensitivity patterns for the principal model parameters (Figures 3–4). Within the investigated parameter ranges, the framework separates LET-dependent effects, represented primarily by k_0, Δt, and $\psi(\mathrm{LET})$, from overall survival normalization represented by η. As shown in Section 3.3, variations in $\psi(\mathrm{LET})$ mainly affect the high-LET region, whereas variations in η primarily influence the overall magnitude of survival predictions. These differing sensitivity profiles suggest a reduced likelihood of strong parameter compensation within the investigated parameter ranges.

The $k_0(\mathrm{LET}, \Delta t)$ surfaces presented in Section 3.1 exhibit smooth and continuous behavior over the investigated LET and fixation-time ranges. Within the framework, oxygen-independent stabilization is represented by k_0, while LET-dependent saturation is represented separately through $\psi(\mathrm{LET})$. This separation allows the respective influences of fixation-related processes and saturation-related processes to be examined independently. The selected $\psi(\mathrm{LET})$ parameterization was chosen to remain consistent with reported RBE turnover behavior at high LET and was applied uniformly throughout the analyses presented here.

4.2 Hypoxic Robustness and Oxygen-Dependent Fixation

Hypoxic conditions provide a particularly sensitive setting for evaluating fixation-based survival models because oxygen-dependent stabilization becomes an important determinant of the predicted biological response. The sensitivity analysis presented in Section 3.2 indicates that the effective fixation time window, Δt, has limited influence under normoxic conditions but becomes increasingly important under hypoxia, where oxygen availability constrains fixation efficiency and competes with early damage-processing pathways. As LET increases, the oxygen-independent stabilization rate, k_0, contributes progressively

to the predicted response under hypoxic conditions, consistent with reported reductions in oxygen dependence at intermediate and high LET values.

An important feature of the framework is that both k_0 and the attenuation function $\psi(\mathrm{LET})$ are independent of oxygen concentration. Consequently, LET-dependent saturation behavior is retained across different oxygenation conditions, while oxygen effects enter the model through fixation kinetics. This separation enables the respective influences of oxygen availability and radiation quality to be examined independently and facilitates sensitivity analyses across a broad range of oxygenation conditions.

4.3 Implications for Process-Based Radiobiological Modeling

The present analysis provides insight into the respective contributions of oxygen-dependent fixation, oxygen-independent stabilization, and LET-dependent saturation within a unified analytical framework. Examination of the parameter sensitivities indicates that different components of the model predominantly influence different regions of the LET–oxygenation space.

The results suggest that the fixation-related parameters, particularly k_0 and Δt, exert their strongest influence under hypoxic conditions, whereas the attenuation function $\psi(\mathrm{LET})$ primarily affects model behavior in the high-LET region where saturation effects become important. The normalization factor η mainly influences the overall magnitude of survival predictions and exhibits limited impact on LET-dependent or oxygen-dependent trends. These distinct sensitivity patterns facilitate interpretation of model behavior and suggest a reduced likelihood of strong parameter compensation within the investigated parameter ranges.

Another physical explanation of LET-dependent attenuation and the overkill effect is offered by the corresponding statistical mechanics model using chromatin domain occupation (Rezaee 2026b).

The parameter ranges identified in this study were found to be consistent with the analyzed experimental datasets while maintaining stable model behavior. Within the investigated conditions, the framework reproduced observed survival and RBE trends without requiring large adjustments of individual parameters. This behavior may be useful for comparing alternative descriptions of oxygen effects, damage stabilization, and LET-dependent saturation.

More broadly, the results highlight the value of treating fixation kinetics and LET-dependent effectiveness as separate components within analytical radiobiological models. Such separation allows the relative influence of different physical and chemical processes on predicted survival behavior to be examined within a compact parameter framework.

The present study therefore provides a basis for future comparisons with other radiobiological modeling approaches, including oxygen-modified RBE formulations, track-structure-based models, and reaction-kinetics descriptions of radiation-induced damage stabilization.

4.4 Limitations and Outlook

Several limitations of the present study should be acknowledged.

First, model evaluation was performed primarily using published in vitro clonogenic survival and RBE datasets. Although these datasets provide controlled conditions for investigating LET and oxygenation effects, they do not capture the full biological complexity of in vivo systems, including spatial oxygen heterogeneity, vascular dynamics, and tissue-specific responses.

Second, the parameters Δt and η should be interpreted as effective model quantities rather than direct measurements of individual biological processes. The current formulation does not explicitly resolve oxygen transport, radical diffusion fields, or detailed DNA repair pathway kinetics. Future developments may incorporate more detailed reaction–diffusion descriptions while preserving the analytical structure of the framework.

Third, the model focuses on early damage stabilization and subsequent survival response. Processes occurring at later times, including pathway-specific DNA repair and cell-cycle-dependent effects, are not explicitly represented and may contribute to biological response under some irradiation conditions.

Although parameter characterization was performed using carbon-ion datasets, the mathematical structure of the framework is not restricted to a particular ion species. Extension to other charged particles would require appropriate LET-dependent input data and validation against corresponding experimental measurements.

Future work may include broader validation using additional cell lines, oxygenation conditions, and irradiation modalities, as well as systematic comparisons with established radiobiological models. Such studies would help clarify the applicability and limitations of fixation-based approaches for describing LET- and oxygen-dependent biological effects.

5. Conclusion

The present study examined a fixation-kinetics framework for describing LET- and oxygen-dependent survival based on oxygen fixation chemistry and LET-dependent energy deposition. The analyses showed that oxygen-dependent fixation, oxygen-independent stabilization, and LET-dependent saturation contribute to model behavior in distinct ways across the investigated LET and oxygenation ranges. The results indicate that the framework reproduces reported survival and RBE trends under oxic and hypoxic conditions while maintaining stable behavior within bounded parameter ranges. Sensitivity analyses identified the effective fixation time window as an important determinant of hypoxic response, whereas LET-dependent saturation primarily influenced model predictions at high LET. The oxygen-independent stabilization rate contributed increasingly under hypoxic conditions and at intermediate-to-high LET values. By separating fixation-related processes from LET-dependent saturation and overall survival normalization, the framework enables systematic examination of the respective roles of these model components. Within the conditions investigated in this study, the analytical formulation provided a compact description of LET- and oxygen-dependent radiobiological response without requiring additional oxygen-scaling correction factors. The findings provide a basis for future evaluation and comparison of fixation-based approaches alongside other radiobiological modeling frameworks that account for oxygen effects and radiation quality in heavy-ion irradiation.

Funding statement

No Funding.

Declaration of competing interest

The author declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

References

Aoki M, Furusawa Y, Yamada T (2000) LET dependency of heavy-ion induced apoptosis in V79 cells. J Radiat Res 41:163–175.

Belli M, Bettega D, Calzolari P et al (2008) Effectiveness of monoenergetic and spread-out Bragg peak carbon ions for inactivation of various normal and tumour human cell lines. J Radiat Res 49:597–607.

Blakely EA, Kronenberg A (1998) Heavy-ion radiobiology: new approaches to delineate mechanisms underlying enhanced biological effectiveness. Radiat Res 150:126–145.

Brown JM, Wilson WR (2004) Exploiting tumour hypoxia in cancer treatment. Nat Rev Cancer 4:437–447.

Buxton GV, Greenstock CL, Helman WP, Ross AB (1988) Critical review of rate constants for reactions of hydrated electrons, hydrogen atoms and hydroxyl radicals in aqueous solution. J Phys Chem Ref Data 17:513–886.

Chadwick KH, Leenhouts HP (1973) A molecular theory of cell survival. Phys Med Biol 18:78–87.

Collins FC, Kimball GE (1949) Diffusion-controlled reaction rates. J Colloid Sci 4:425–437.

Curtis SB (1986) Lethal and potentially lethal lesions induced by radiation—a unified repair model. Radiat Res 106:252–270.

Durante M, Loeffler JS (2010) Charged particles in radiation oncology. Nat Rev Clin Oncol 7:37–43.

Friedland W, Schmitt E, Kundrát P, Dingfelder M, Baiocco G, Barbieri S, Ottolenghi A (2017) Comprehensive track-structure based evaluation of DNA damage by light ions from radiotherapy-relevant energies down to stopping. Sci Rep 7:45161.

Friedrich T, Scholz U, Elsässer T, Durante M, Scholz M (2013) Systematic analysis of RBE and related quantities using a database of cell survival experiments with ion beam irradiation. J Radiat Res 54:494–514.

Furusawa Y, Fukutsu K, Aoki M, Itsukaichi H, Eguchi-Kasai K, Ohara H, Yatagai F, Kanai T, Ando K (2000) Inactivation of aerobic and hypoxic cells from three different cell lines by accelerated 3He-, 12C- and 20Ne-ion beams. Radiat Res 154:485–496.

Goodhead DT (1994) Initial events in the cellular effects of ionizing radiations: clustered damage in DNA. Int J Radiat Biol 65:7–17.

Gray LH, Conger AD, Ebert M, Hornsey S, Scott OC (1953) The concentration of oxygen dissolved in tissues at the time of irradiation as a factor in radiotherapy. Br J Radiol 26:638–648.

Grimes DR, Kannan P, McIntyre A, Kavanagh A, Siddiky A, Wigfield S, Harris A, Partridge M (2016) The role of oxygen in avascular tumor growth. PLoS One 11:e0153692.

Grimes DR, Partridge M (2015) A mechanistic investigation of the oxygen fixation hypothesis and oxygen enhancement ratio. Biomed Phys Eng Express 1:045209.

Helton JC, Johnson JD, Sallaberry CJ, Storlie CB (2006) Survey of sampling-based methods for uncertainty and sensitivity analysis. Reliab Eng Syst Saf 91:1175–1209.

Horsman MR, Overgaard J (2016) The impact of hypoxia and its modification on the outcome of radiotherapy. J Radiat Res 57:i90–i98.

Inaniwa T, Kanematsu N, Matsufuji N, Kanai T, Shirai T, Noda K, Tsuji H, Kamada T, Tsujii H (2015) Reformulation of a clinical-dose system for carbon-ion radiotherapy treatment planning at the National Institute of Radiological Sciences, Japan. Phys Med Biol 60:3271–3286.

Jeggo PA, Löbrich M (2007) DNA double-strand breaks: their cellular and clinical impact? Oncogene 26:7717–7719.

Kellerer AM, Rossi HH (1972) Theory of dual radiation action. Curr Top Radiat Res Q 8:85–158.

Kinner A, Wu W, Staudt C, Iliakis G (2008) γ-H2AX in recognition and signaling of DNA double-strand breaks in the context of chromatin. Nucleic Acids Res 36:5678–5694.

Lomax ME, Folkes LK, O'Neill P (2013) Biological consequences of radiation-induced DNA damage: relevance to radiotherapy. Clin Oncol 25:578–585.

Mozumder A (1999) Fundamentals of radiation chemistry. Academic Press, San Diego.

Nikjoo H (2003) Radiation track and DNA damage. Iran J Radiat Res 1:3–16.

Nikjoo H, O'Neill P, Wilson WE, Goodhead DT (2001) Computational approach for determining the spectrum of DNA damage induced by ionizing radiation. Radiat Res 156:577–583.

Nikjoo H, Uehara S, Emfietzoglou D, Cucinotta FA (2006) Track-structure codes in radiation research. Radiat Meas 41:1052–1074.

Paganetti H (2014) Relative biological effectiveness (RBE) values for proton beam therapy: variations as a function of biological endpoint, dose, and linear energy transfer. Phys Med Biol 59:R419–R472.

Prise KM, Pinto M, Newman HC, Michael BD (2001) A review of studies of ionizing radiation-induced double-strand break clustering. Radiat Res 156:572–576.

Rezaee L (2026a) A mechanistic and time-resolved analytical model of oxygen-mediated DSB fixation: bridging LET physics and hypoxic biology for predictive heavy ion radiotherapy. Phys Med Biol 71:055002.

Rezaee L (2026b) Occupancy-driven attenuation in radiation-sensitive chromatin domains as a statistical-mechanical model of the overkill effect and RBE maximum. Sci Rep 16:36203.

Roots R, Okada S (1972) Protection of DNA molecules of cultured mammalian cells from radiation-induced single-strand scissions by various alcohols and SH compounds. Int J Radiat Biol Relat Stud Phys Chem Med 21:329–342.

Saltelli A, Ratto M, Andres T, Francesca C, Cariboni J, Gatelli D, Saisana M, Tarantola S (2008) Global sensitivity analysis: the primer. John Wiley & Sons, Chichester.

Schardt D, Elsässer T, Schulz-Ertner D (2010) Heavy-ion tumor therapy: physical and radiobiological benefits. Rev Mod Phys 82:383–425.

Scholz M, Friedrich T, Magrin G, Colautti P, Ristic-Fira A, Petrovic I (2020) Characterizing radiation effectiveness in ion beam therapy. Part I: Introduction and biophysical modeling of RBE using the LEM IV. Front Phys 8:272.

Scholz M, Kraft G (1996) Track structure and the calculation of biological effects of heavy charged particles. Adv Space Res 18:5–14.

Surdutovich E, Solov'yov AV (2019) Science vs. technology in radiation therapy from X-rays to ions. Cancer Nanotechnol 10:9.

Tinganelli W, Ma NY, Neubeck CV, Maier A, Schicker C, Kraft-Weyrather W, Durante M (2013) Influence of acute hypoxia and radiation quality on cell survival. J Radiat Res 54:23–30.

Vaupel P, Thews O, Hoeckel M (2001) Treatment resistance of solid tumors: role of hypoxia and anemia. Med Oncol 18:243–259.

von Sonntag C (2006) Free-radical-induced DNA damage and its repair. Springer, Berlin.

Wang W, Li C, Qiu R, Chen Y, Wu Z, Zhang H, Li J (2018) Modelling of cellular survival following radiation-induced DNA double-strand breaks. Sci Rep 8:16202.

Ward JF (1988) DNA damage produced by ionizing radiation in mammalian cells: identities, mechanisms of formation, and reparability. Prog Nucleic Acid Res Mol Biol 35:95–125.

Ward JF (1994) The complexity of DNA damage: relevance to biological consequences. Int J Radiat Biol 66:427–432.

Wardman P (2016) Time as a variable in radiation biology: the oxygen effect. Radiat Res 185:1–3.

Wenzl T, Wilkens JJ (2011) Modelling of the oxygen enhancement ratio for ion beam radiation therapy. Phys Med Biol 56:3251–3268.

Weyrather WK, Ritter S, Scholz M, Kraft G (1999) RBE for carbon track-segment irradiation in cell lines of differing repair capacity. Int J Radiat Biol 75:1357–1364.