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Occupancy-Driven Attenuation in Radiation-Sensitive Chromatin Domains: A Statistical-Mechanical Model of the Overkill Effect and RBE Maximum

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Abstract

The reduction in biological effectiveness at high linear energy transfer (LET), commonly referred to as the overkill effect, remains an active area of investigation in high-LET radiobiology. Here, we present a statistical-mechanical framework in which attenuation emerges from the progressive occupancy of a finite population of radiation-sensitive chromatin domains. An effective free-energy formalism is used to describe the equilibrium occupancy state, yielding an LET-dependent occupancy fraction and an attenuation function representing the fraction of chromatin domains remaining available for the formation of additional biologically independent lethal events. The model predicts a continuous occupancy transition accompanied by a fluctuation maximum, identifying a characteristic LET range in which occupancy effects become most pronounced. When combined with a previously published LET-dependent damage-production model for carbon-ion irradiation of V79 cells, the framework predicts a maximum in lethal-lesion yield followed by a decline despite continued increases in damage production. A qualitative comparison with published relative biological effectiveness (RBE) data reproduces the characteristic rise, maximum, and subsequent decrease in biological effectiveness. These results suggest that finite chromatin-domain occupancy may provide a possible physical interpretation of attenuation, the overkill effect, and the emergence of an RBE maximum.

Keywords: Statistical mechanics; High-LET radiation; Chromatin-domain occupancy; Overkill effect; Relative biological effectiveness (RBE); DNA damage.

1. Introduction

High linear energy transfer (LET) radiation plays an important role in particle therapy because of its greater biological effectiveness than conventional photon irradiation [1,2]. As LET increases, energy deposition becomes more localized along particle tracks, leading to dense ionization clusters and complex DNA damage that may be more difficult for cells to repair [3-5]. These characteristics contribute to the therapeutic advantages of carbon-ion and other heavy charged-particle therapies [2,6].

A well-established observation in heavy-ion radiobiology is that biological effectiveness does not increase indefinitely with increasing LET. Experimental studies of relative biological effectiveness (RBE) show that it generally increases with LET up to a maximum and subsequently decreases at higher LET values, a behavior commonly referred to as the overkill effect [7-11]. Understanding the mechanisms underlying this behavior remains an important topic of investigation in radiobiology.

Although the overkill effect has been recognized for several decades, its physical interpretation remains incompletely understood. A commonly invoked explanation is that, at very high LET, additional energy deposition produces relatively little additional biological effect because substantial radiation-induced damage has already accumulated within sensitive cellular targets [12,13]. However, the microscopic processes that contribute to attenuation at very high LET remain an active area of investigation.

A number of radiobiological models have been developed to characterize LET-dependent biological effectiveness: dual radiation action theory [12], repair-misrepair models [14,15], local effect model [16,17], microdosimetric models, and track structure-based DNA damage induction [18-20]. While these models successfully reproduce many experimental observations of cell survival and RBE, attenuation at very high LET is often represented through empirical parameterizations whose physical interpretation is not always explicit.

Recent studies have highlighted the important role of DNA repair mechanisms in linking radiation track structure to biological response [21,22]. In particular, a fixation-based framework was recently used to predict the LET dependence of RBE and the onset of attenuation for carbon-ion irradiation of V79 cells [23]. These findings motivate the question of which physical mechanisms may contribute to the emergence of attenuation as LET increases.

From a structural standpoint, radiation-induced lesions are distributed among a finite population of chromatin regions that contribute to biologically relevant damage. As damage accumulates, an increasing fraction of these regions may already contain substantial lesions. This observation suggests that attenuation may be associated with the progressive occupancy of a finite population of radiation-sensitive chromatin regions.

This perspective motivates the use of a statistical-mechanical framework. Many systems containing a finite number of occupiable sites exhibit collective behavior associated with the progressive filling of available states [24-26]. Although radiation response should not be regarded as a true thermodynamic phase transition, analogous statistical-mechanical concepts may offer a useful conceptual framework for describing the progressive utilization of a finite target population.

In this study, a statistical mechanical framework is formulated based on the gradual occupancy of chromatin regions that are sensitive to radiation. We formulate an effective free-energy framework in which the occupancy state depends on LET. The resulting occupancy fraction is then used to describe the availability of chromatin regions for the generation of additional lethal lesions and thereby defines an attenuation factor. By

combining this framework with a previously developed LET-dependent damage-production model [23], we explore how increasing damage production and occupancy-driven saturation jointly influence lethal-lesion formation and cell survival.

2. Material and Methods

2.1. Microscopic Damage Generation and Fixation

The biological effectiveness of ionizing radiation is influenced by the induction and subsequent stabilization of DNA double-strand breaks (DSBs), which are widely regarded as critical lesions associated with radiation-induced cell death [3,27,28]. For heavy charged particles, the pattern of energy deposition is highly heterogeneous and strongly dependent on LET. As LET increases, ionization events become more spatially clustered along the particle track, leading to more complex DNA damage structures [3,5,18].

Here, N_{DSB} denotes the total number of DSBs induced in the cell nucleus. In the present model, both the yield and spatial organization of DNA damage depend on LET. However, biological outcome is not determined solely by the initial number of DSBs; lesion fixation is also required for biological persistence.

Based on our previous formulation of DSB fixation [23], each DSB is assumed to follow one of two parallel fixation pathways: oxygen-dependent and oxygen-independent fixation. The overall fixation probability is denoted by $P_{\text{fix}}^{\text{tot}}$, representing the probability that an initially repairable lesion is converted into a persistent form.

The number of fixed DSBs is then given by

$$N_{\text{fix}} = P_{\text{fix}}^{\text{tot}} \cdot N_{\text{DSB}} \quad (1)$$

Here, $P_{\text{fix}}^{\text{tot}}$ represents the total fixation probability, and N_{DSB} is the number of DSBs induced in the nucleus. The DSB yield is expressed as [29]:

$$N_{\text{DSB}} = D \cdot \phi(\text{LET}) \quad (2)$$

where D is the absorbed dose (Gy) and $\phi(\text{LET})$ is the LET-dependent DSB yield per unit dose (damage generation function).

The fixation probability represents the combined effects of oxygen-dependent chemistry, oxygen-independent radical processes, clustered damage effects, and chromatin-level constraints [21,23,27,30]. Explicit modeling of oxygen transport and reaction-diffusion kinetics is not included here, as these effects are incorporated into the effective parameter $P_{\text{fix}}^{\text{tot}}$.

In this framework, LET determines the spatial organization of energy deposition and hence the initial damage structure, whereas $P_{\text{fix}}^{\text{tot}}$ determines the fraction of lesions entering subsequent stages of the model.

2.2. Effective Lethality Conversion

The presence of a DSB does not necessarily imply cell death. Experimental and theoretical studies indicate that the relationship between DNA damage and clonogenic survival is nonlinear and depends on lesion complexity and spatial organization [14,15,18,29].

To distinguish biologically lethal lesions from fixed DNA damage, we introduce an effective conversion step. If N_{L} denotes the number of lethal lesions responsible for loss of reproductive integrity, then

$$N_{\text{L}} = \psi \cdot P_{\text{fix}}^{\text{tot}} \cdot N_{\text{DSB}} \quad (3)$$

where ψ is an LET-dependent attenuation factor describing the efficiency with which fixed lesions contribute to biologically independent lethal events.

The factor ψ reflects the experimentally observed non-monotonic dependence of RBE on LET, which typically increases, reaches a maximum, and decreases at very high LET values (overkill effect) [7–11]. Any mechanistic interpretation of high-LET effects should therefore be consistent with this saturation behavior.

Within the present framework, overkill is interpreted as a reduction in the efficiency of converting fixed damage into independent lethal events. At low and intermediate LET, additional energy deposition increases the yield of effective lesions. At very high LET, however, a larger fraction of energy deposition occurs in already damaged chromatin regions, reducing the incremental contribution to lethality.

Thus, ψ characterizes the efficiency of this conversion process and effectively represents the effects of partial saturation of radiation-sensitive chromatin regions.

This interpretation provides the basis for the statistical-mechanical framework developed in the following sections, in which overkill is considered as a possible consequence of the progressive occupancy of a finite population of radiation-sensitive chromatin domains. Such systems may be described using occupancy-based statistical mechanics, where macroscopic behavior emerges from the distribution of microscopic states [24,25].

The next section introduces the corresponding occupancy variable.

2.3. Chromatin Domain Occupancy Model

Experimental and theoretical studies have indicated that the biological response to densely ionizing radiation depends not only on the number of induced DNA lesions but also on their spatial distribution within chromatin [3,18,28]. Chromatin is organized into structural domains that participate in DNA damage recognition, signaling, and repair processes [31,32].

Within the present framework, a chromatin domain is treated as an effective coarse-grained target region in which radiation-induced damage can accumulate and interact. The term does not refer to a specific anatomical chromatin structure, such as a chromatin loop or topologically associating domain, but rather to an effective region relevant for damage clustering and repair processes. Consistent with current understanding of chromatin organization, such effective regions may correspond to structures spanning length scales from tens to hundreds of kilobases [28,32]. At low and intermediate LET values, newly induced DSBs are expected to be distributed across a relatively large number of chromatin domains, allowing additional energy deposition to generate new biologically relevant lesions. At very high LET, however, the increasing density of ionization events along particle tracks raises the probability that newly induced lesions occur within chromatin domains that already contain substantial damage [3,4,18]. As a result, the efficiency with which additional energy deposition generates new biologically independent lethal events may gradually decrease.

To describe this behavior quantitatively, we introduce the following chromatin-domain occupancy parameter,

$$\Theta = \frac{n_{\text{occ}}}{n_{\text{tot}}} \quad (4)$$

Here, n_{occ} denotes the number of chromatin domains containing at least one fixed DSB, n_{tot} is the total number of radiation-sensitive chromatin domains available within the nucleus, and Θ represents the fraction of vulnerable domains occupied by fixed DNA damage. By definition,

$$0 \leq \Theta \leq 1 \quad (5)$$

The dimensionless fraction Θ therefore characterizes the degree to which the available population of radiation-sensitive chromatin domains has been occupied by radiation-induced damage.

For low-LET irradiation, Θ remains small, indicating that most chromatin domains remain available for the formation of additional biologically independent lethal events. In this regime, biological effectiveness is expected to increase approximately with the accumulation of fixed lesions. As LET increases, ionization events become increasingly clustered, raising the probability that multiple lesions occur within the same vulnerable chromatin domains and causing Θ to increase progressively.

When a substantial fraction of domains becomes occupied, newly induced lesions are increasingly likely to occur within previously damaged regions. Under such conditions, additional energy deposition no longer leads to a proportional increase in biologically independent lethal events, since an increasing fraction of damage accumulates within domains that already contain substantial lesions.

The occupation parameter Θ can therefore be regarded as an emergent variable that reflects the use of chromatin regions sensitive to radiation. Within the present framework, the overkill effect is interpreted here as a possible consequence of the progressive saturation of the occupancy variable rather than a reduction in deposited energy or in the total number of induced DNA lesions.

To establish a quantitative connection between chromatin-domain occupancy and the efficiency of lethal-lesion formation, we consider the simplest assumption that the probability of converting fixed lesions into biologically independent lethal events decreases as the occupancy fraction increases. As a first-order approximation in the present model, the biologically effective fraction of chromatin domains is assumed to decrease linearly with occupancy. Thus, the attenuation factor considered in Sec. 2.2 shall be assumed to be dependent on Θ as

$$\psi = 1 - \Theta \quad (6)$$

This linear relation represents the simplest occupancy-dependent attenuation law that satisfies the limiting cases of a completely unoccupied and a fully occupied chromatin-domain population.

The above relationship fulfills the following limit conditions

$$\psi \rightarrow 1 \text{ for } \Theta \rightarrow 0 \quad (7a)$$

$$\psi \rightarrow 0 \text{ for } \Theta \rightarrow 1 \quad (7b)$$

These limiting conditions reflect the physical expectation that newly formed lesions remain fully effective when most radiation-sensitive chromatin domains are unoccupied, whereas the formation of additional biologically independent lethal events becomes progressively less efficient as chromatin-domain occupancy approaches saturation.

The occupancy variable Θ therefore serves as an effective microscopic state descriptor from which the attenuation function ψ is derived. Within the present framework, the emergence of the overkill effect is interpreted as a possible consequence of the progressive saturation of this occupancy variable. The next section develops a continuum statistical-mechanical description of occupancy and introduces the corresponding free-energy formalism.

2.4. Saturation Transition and Effective Free Energy

Within the present framework, the attenuation of biological effectiveness at high LET is interpreted as a consequence of a progressive saturation process occurring within a finite population of radiation-sensitive chromatin domains. As LET increases, the concentration of DNA damage rises and an increasing fraction of vulnerable domains becomes occupied. Because the number of such domains is finite, the system approaches a saturation regime in which the probability of generating additional biologically independent lethal events is progressively reduced.

To characterize this process, the occupancy fraction Θ is treated as a continuous state variable representing the fraction (or probability) of radiation-sensitive chromatin domains occupied by at least one fixed lesion. The behavior of this variable is described using an effective free-energy formalism analogous to mean-field approaches commonly employed in statistical physics [24–26,33].

To represent the occupancy state of radiation-sensitive chromatin domains, a mean-field statistical-mechanical description is adopted in which each domain may exist in one of two states: occupied by at least one fixed lesion or unoccupied. Under this binary-state approximation, the configurational entropy of the domain population is formally equivalent to that of a lattice-gas or Langmuir-type occupancy system [34,35]. The resulting effective free-energy expression contains an entropic contribution associated with the distribution of occupied and unoccupied domains and an energetic contribution describing the tendency of LET-dependent damage accumulation to promote occupancy.

The effective free-energy expression is written as

$$F(\Theta) = k_B T [\Theta \ln(\Theta) + (1 - \Theta) \ln(1 - \Theta)] - U(\text{LET}) \Theta \quad (8)$$

where k_B is Boltzmann's constant, T is an effective statistical temperature, and $U(\text{LET})$ is an LET-dependent occupancy potential that favors lesion accumulation within vulnerable chromatin domains.

The logarithmic terms arise from the configurational entropy associated with the distribution of occupied and unoccupied domains, whereas $U(\text{LET})$ acts as an effective driving field favoring domain occupancy.

The parameter T is not to be understood as the actual thermodynamic temperature of the biological system. Rather, T denotes the effective temperature, which can be used to scale the entropic part of the occupancy free energy. Effective-temperature concepts have been widely used in coarse-grained statistical descriptions of complex systems to quantify the balance between configurational disorder and an external driving field without requiring strict thermodynamic equilibrium [25,26]. In the current approach, the parameter $k_B T$ defines the typical energy scale that characterizes the competition between the occupancy entropy and the LET-dependent occupancy potential. The parameter T is not associated with any biological temperature, and serves solely as a scaling factor in the coarse-grained statistical description.

The first term in Eq. (8) stands for the configurational entropy related to the arrangement of occupied and unoccupied chromatin domains. The second term represents an effective driving tendency favoring occupancy as radiation-induced damage accumulates. It should be emphasized

that F is not interpreted as a thermodynamic free energy in the strict sense. Rather, it serves as an effective statistical potential governing the most probable occupancy state of the system.

The occupancy potential is assumed to contain two contributions: an intrinsic occupancy bias and an LET-dependent contribution associated with increasing damage accumulation,

$$U(\text{LET}) = U_0 + \lambda (\text{LET} - \text{LET}_0) \quad (9)$$

where U_0 represents a baseline occupancy bias representing an intrinsic tendency of radiation-sensitive chromatin domains to accumulate fixed lesions, λ determines the sensitivity of occupancy to changes in LET, and LET_0 denotes a characteristic LET scale associated with the onset of occupancy-driven attenuation.

A linear dependence on LET is adopted as the simplest phenomenological representation of the increasing probability of domain occupancy with increasing track density. Over the LET range considered here, this form provides a convenient first approximation for describing the progressive accumulation of fixed lesions within vulnerable chromatin domains. More complex nonlinear relations may be considered in future extensions of the model.

The equilibrium occupancy ratio is determined from the minimization of the effective free energy with respect to Θ ,

$$\frac{\partial F}{\partial \Theta} = 0 \quad (10)$$

Substituting Eq. (9) into Eq. (8) and applying the equilibrium condition yields

$$\ln\left(\frac{\Theta}{1-\Theta}\right) = \frac{U_0 + \lambda(\text{LET} - \text{LET}_0)}{k_B T} \quad (11)$$

Solving for Θ gives

$$\Theta(\text{LET}) = \frac{1}{1 + \exp\left[-\frac{U_0 + \lambda(\text{LET} - \text{LET}_0)}{k_B T}\right]} \quad (12)$$

Equation (12) describes a continuous increase in chromatin-domain occupancy with increasing LET. The parameter U_0 introduces an intrinsic occupancy bias that shifts the center of the transition. As a result, the occupancy fraction need not vanish at low LET, reflecting the possibility that a small fraction of vulnerable domains may already contain fixed lesions.

Within this formulation, LET_0 determines the approximate location of the occupancy transition, whereas the ratio $k_B T / \lambda$ controls its width. Larger values of λ correspond to sharper transitions, while smaller values produce a more gradual occupancy increase.

Within the present framework, attenuation is not introduced as an independent phenomenological assumption. Instead, it emerges directly from the equilibrium occupancy state of the finite-domain model. The attenuation function presented in Section 2.3 is derived immediately from the occupancy fraction. Using Eqs. (6) and (12), the attenuation function is expressed as

$$\psi(\text{LET}) = \frac{1}{1 + \exp\left[\frac{U_0 + \lambda(\text{LET} - \text{LET}_0)}{k_B T}\right]} \quad (13)$$

The above equation describes a continuous reduction in the efficiency with which fixed damage is converted into biologically independent lethal events as chromatin-domain occupancy approaches saturation.

The attenuation function derived from the occupancy model has the same logistic structure as the phenomenological attenuation function previously introduced for carbon-ion irradiation of V79 cells [23],

$$\psi(\text{LET}) = \frac{1}{1 + z_1 \exp[z_2(\text{LET} - \text{LET}_0)]} \quad (14)$$

In the previous study, this formula appeared as a phenomenological model for the attenuation law derived empirically from experimental observations. In the current context, the same mathematical form emerges naturally in the context of equilibrium occupancy theory for radiation sensitive chromatin regions. The comparison of the two formulas reveals that the phenomenological parameters correspond to

$$z_1 = \exp\left(\frac{U_0}{k_B T}\right) \quad (15a)$$

$$z_2 = \frac{\lambda}{k_B T} \quad (15b)$$

The statistical-mechanical formulation therefore offers a possible physical interpretation of the previously phenomenological attenuation function in terms of progressive chromatin-domain occupancy and saturation.

The resulting occupancy and attenuation functions constitute the principal theoretical results of the present framework and provide the basis for the quantitative analyses presented in the Results section.

2.5. Physical Interpretation and Parameterization of the Attenuation Function

The attenuation function defined in Eq. (13) provides a link between microscopic damage fixation and macroscopic biological effectiveness. In this context, attenuation is not presented in terms of an empirical correction coefficient. Instead, it emerges from the occupancy state of radiation-sensitive chromatin domains described in Sections 2.3 and 2.4 within the proposed statistical-mechanical framework.

From Eq. (6), it follows that the attenuation function is equal to the fraction of chromatin domains that remain available for the generation of new biologically independent lethal events. At lower values of LET, the fractional occupancy value is low, and most of the vulnerable sites are not occupied. Consequently, the attenuation function remains close to unity, and newly created lesions are effective in killing cells. As the LET increases, however, the occupancy fraction also increases, leaving fewer chromatin domains available for the formation of additional biologically independent lethal events.

The proposed framework offers a possible mechanistic interpretation of the overkill phenomenon observed experimentally. Unlike interpretations that attribute attenuation directly to damage production itself, in the current scenario, the reduced efficacy is attributed to the progressive saturation of a finite number of radiation-susceptible chromatin domains. With continued energy deposition, damage production still occurs, but more of the damage occurs in regions which have been heavily irradiated, thereby contributing less effectively to the formation of additional biologically independent lethal events.

The parameterization adopted in the present study was guided by experimental observations from carbon-ion irradiation of V79 cells and the attenuation model created earlier [23]. Analysis of published survival and RBE data for carbon-ion irradiation suggests that the decrease in biological efficiency started at

$$\text{LET}_0 \approx 150 \text{ keV}/\mu\text{m} \quad (16)$$

which corresponds to the beginning of the overkill region as observed experimentally [7-10]. In the present framework, LET_0 serves as an experimentally motivated reference scale marking the onset of attenuation.

According to the equilibrium occupancy theory of Section 2.4, the transition process proceeds gradually after the onset of the attenuation regime. In line with the attenuation pattern established in [23], the center of the occupancy transition was chosen as

$$\text{LET}_c = 380 \text{ keV}/\mu\text{m} \quad (17)$$

where LET_c represents the characteristic LET corresponding to the center of the occupancy transition. In the present framework, LET_c corresponds to the LET value at which the occupancy fluctuation function, $\psi \cdot \Theta$, reaches its maximum. This prediction is examined in Section 3.2.

In the absence of direct experimental measurements of chromatin-domain occupancy, a representative low-LET occupancy fraction of $\Theta_0 = 0.1$ was adopted for illustrative purposes. Substituting this value into Eq. (12) gives

$$U_0 = \ln\left(\frac{\Theta_0}{1-\Theta_0}\right) = -2.197 k_B T \quad (18)$$

The transition-width parameter was selected to reproduced approximately the attenuation range, which was experimentally observed starting from the point of overkill up to the saturation of high-LET radiation. Substituting the selected values of LET_0 , LET_c , and Θ_0 into Eq. (12) yields

$$\frac{\lambda}{k_B T} = 0.0105 \mu\text{m}/\text{keV} \quad (19)$$

This result is consistent with the attenuation slope parameter $z_2 = 0.01 \mu\text{m}/\text{keV}$ reported previously for carbon-ion irradiation of V79 cells [23], suggesting consistency between the occupancy-based interpretation and the earlier phenomenological attenuation model.

An important feature of the present framework is the difference between the two distinct characteristic LET scales, namely, LET_0 and LET_c . In this regard, LET_0 indicates the point of experimental onset of biological attenuation, while LET_c is the point of the center of the occupancy transition predicted within the context of statistical mechanics. Biological attenuation begins near LET_0 ; however, the occupancy fraction keeps evolving throughout the wide LET interval and only reaches the point of maximum rate of change near LET_c . The scale difference reflects the gradual nature of the saturation process and provides a possible explanation for the extended LET range within which overkill phenomena can be observed experimentally.

The parameter set specified by Eqs. (17)-(19) was adopted for the illustrative calculations presented in the Results section. This choice is broadly consistent with the attenuation characteristics reported for carbon-ion irradiation of V79 cells and serves as a convenient tool for the formulation of the model under study. Within the present framework, attenuation is interpreted as arising from the gradual saturation of radiation-sensitive chromatin domains.

The present work focuses on the equilibrium occupancy state derived from the free-energy framework described above. Extensions incorporating stochastic fluctuations and nonequilibrium effects may be explored in future studies.

2.6. Connection to Cell Survival and Relative Biological Effectiveness

The statistical-mechanical model developed in the previous sections provides a framework for exploring how chromatin-domain occupancy may influence the conversion of fixed DNA damage into lethal lesions. To relate this framework to radiobiologically measurable endpoints, the occupancy-dependent attenuation mechanism is considered in the context of cell survival and relative biological effectiveness (RBE).

As discussed in Section 2.2, the expected number of lethal lesions depends on the combined effects of DNA damage induction, lesion fixation, lethal conversion, and occupancy-induced attenuation. The attenuation function derived in Section 2.4 may therefore provide a link between microscopic chromatin-domain occupancy and macroscopic biological response.

Following the classical target-theory description of radiation-induced cell killing [14,15], lethal lesions are assumed to be randomly distributed among irradiated cells. Under this assumption, cell survival follows Poisson statistics:

$$S = \exp(-N_L) \quad (20)$$

where S denotes the surviving fraction and N_L is the expected number of lethal lesions per cell (see Eq. (3)). Substituting Eqs. (2) and (3) into Eq. (20) yields

$$S(D, \text{LET}) = \exp[-P_{\text{fix}}^{\text{tot}} \cdot D \cdot \phi(\text{LET}) \cdot \psi(\text{LET})] \quad (21)$$

The same framework may also be related to RBE. In radiobiology, RBE is defined as the ratio of the doses of reference and test irradiation necessary to achieve the same biological endpoint [11,16,17]:

$$\text{RBE} = \frac{D_{\text{ref}}}{D_{\text{test}}} \quad (22)$$

Within the proposed framework, the LET dependence of RBE may reflect the interplay between damage generation and the occupancy-dependent attenuation mechanism described in Sections 2.2–2.5.

The framework outlined above provides a potential link between microscopic processes of DNA damage fixation, chromatin-domain occupancy, occupancy-dependent attenuation, and macroscopic radiobiological response. The resulting predictions for occupancy transitions, attenuation behavior, lethal-lesion formation, survival response, and their qualitative relationship to experimentally observed RBE patterns are examined in the following Results section. All the data sets that were used to produce theoretical plots presented here are included in the Supplementary Information and the Excel file.

3. Results

3.1. Emergence of the Occupancy Transition and Attenuation Function

The equilibrium chromatin-domain occupancy and the corresponding attenuation function predicted by the model are shown in Figure 1 as functions of LET. The calculations were performed using the parameter set presented in Section 2.5, which was selected to be broadly consistent

with published carbon-ion irradiation data for V79 cells and with the attenuation behavior reported in [23]. Numerical data used to plot this figure can be found in the Supplementary Information (Table S1.2) and Excel file.

The occupancy fraction is calculated from Eq. (12), whereas the attenuation function is obtained from Eq. (13). These two quantities are directly related since the attenuation function represents the fraction of radiation-sensitive chromatin domains that can be used to form new biologically independent lethal events.

At low LET, the occupancy fraction stays quite low, while the attenuation function remains close to its maximum value. Most radiation-susceptible chromatin domains stay available for further damage, and new lesions formed in the process can contribute effectively to creating more lethal lesions. The occupancy fraction remains finite even at low LET owing to the intrinsic occupancy bias, which is characterized by the parameter U_0 . This reflects the assumption that a fraction of chromatin domains remains available for lesion formation even under low-LET irradiation.

As LET increases, the occupancy fraction increases gradually, and the attenuation function decreases. The transition occurs gradually, and it spans a wide LET range. The dashed vertical line on Figure 1 marks $LET_0 = 150 \text{ keV}/\mu\text{m}$, the LET value corresponding to the onset of attenuation in carbon-ion irradiation experiments [7-10]. At higher LET values, occupancy effects become increasingly important for the efficiency of forming new biologically independent lethal lesions.

As LET increases further, the occupancy fraction approaches unity and the attenuation factor decreases progressively. Under these conditions, many vulnerable chromatin domains have already accumulated substantial damage. Consequently, additional energy deposition is increasingly likely to occur within domains that are already occupied, reducing the probability that newly induced lesions will generate additional biologically independent lethal events. The model does not assume a reduction in the total amount of DNA damage produced. Instead, the decrease in biological effectiveness at high LET is interpreted as a consequence of the reduced availability of previously unoccupied chromatin domains for generating additional biologically independent lethal events.

The coupled behavior of the occupancy and attenuation curves is consistent with an interpretation of the overkill effect in terms of chromatin-domain saturation. Attenuation is derived from the equilibrium occupancy state within the present framework, while not being imposed as an independent experimental adjustment. The results shown in Figure 1 suggest that progressive occupancy saturation may contribute to the attenuation of biological effectiveness at high LET.

3.2. Occupancy Fluctuations and the Transition Region

To characterize the transition between the unsaturated and saturated occupancy regimes, we introduce a dimensionless occupancy fluctuation function defined as:

$$\Lambda(\text{LET}) = \Theta(\text{LET})\psi(\text{LET}) = \Theta(\text{LET})[1 - \Theta(\text{LET})] \quad (23)$$

This quantity provides a statistical measure of the balance between occupied and unoccupied chromatin domains. Within the statistical-mechanical framework developed in Section 2.4, the parameter $\Lambda(\text{LET})$ is a measure of occupancy fluctuations.

The fluctuation function is shown in Figure 2. Numerical values are provided in Supplementary Information (Table S2.1) and Excel file. In contrast to the monotonic behavior of the occupancy fraction and attenuation functions that are plotted in Figure 1, the fluctuation function exhibits a well-defined maximum. This behavior arises because occupancy fluctuations are smallest when either of two types of chromatin states dominate and reach their maximum when both states are equally represented.

With low values of LET, the occupancy ratio will remain relatively small, with many of the radiation-sensitive chromatin domains being available for lesion formation. In such a situation, the occupancy fluctuations remain relatively small because the population is dominated by unoccupied domains.

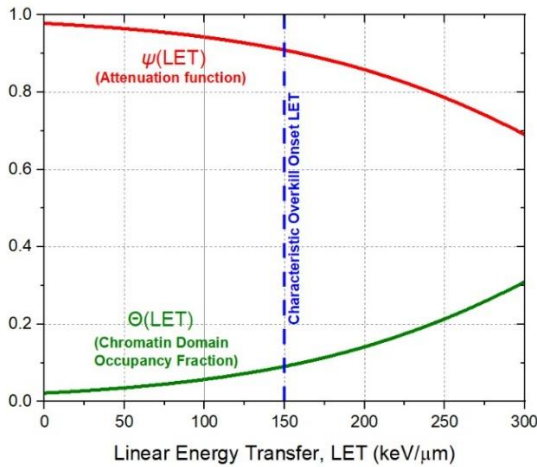


Figure 1. Chromatin-domain occupancy fraction, Θ , and attenuation function, ψ , as a function of linear energy transfer (LET). The dashed vertical line corresponds to the experimental cut-off of the attenuation onset scale ($LET_0 = 150 \text{ keV}/\mu\text{m}$). Calculations were performed using the parameter values specified in Section 2.5.

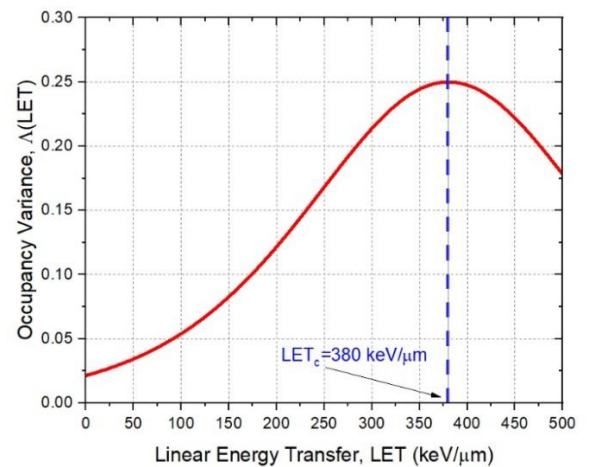


Figure 2. Occupancy transition function, $\Lambda(\text{LET})$, versus linear energy transfer (LET) for carbon ion irradiation of V79 cells. The maximum near LET_c marks the occupancy transition region, where occupied and unoccupied chromatin domains are present in comparable proportions.

The occupancy fraction increases as the LET value goes up. The fluctuation function therefore increases as the populations of occupied and unoccupied domains become more balanced, that is, reaching its maximum when both states are equally represented. In the present model, this occurs at $\theta = 1/2$.

For the parameter values adopted in this study, the fluctuation maximum occurs near $LET_c \approx 380 \text{ keV}/\mu\text{m}$, corresponding to the occupancy transition point discussed in Section 2.5. In this case, the LET value is in the high-LET regime where attenuation effects become increasingly important and lies within the LET range where overkill behavior has been reported experimentally for carbon ions [7-10].

Beyond the transition region, the occupancy fraction saturates and the number of available chromatin domains decreases progressively. Consequently, occupancy variation diminishes since most of the domains are in the occupied phase. Additional energy deposition increasingly occurs within chromatin regions that already contain substantial damage. As a result, the probability that newly formed lesions generate biologically independent lethal events decreases.

The fluctuation maximum may be interpreted as indicating a transition zone with specific properties between two regimes of damage accumulation. Below the transition region, the response is dominated primarily by the availability of vacant chromatin regions. Above the transition region, the occupancy effects become increasingly important.

From a statistical-mechanical perspective, the presence of a fluctuation maximum is analogous to fluctuation peaks observed near continuous phase transitions in finite-size systems [25,26,33]. Although the present model does not describe a true thermodynamic phase transition, it predicts a characteristic transition region separating unsaturated and saturated occupancy regimes.

3.3. Consequences for Lethal Lesion Production

The attenuation factor introduced in the previous sections may influence biological effectiveness through its effect on the formation of lethal lesions. While an increase in LET results in the increased generation of DNA damage, the probability that newly generated damage will produce additional biologically independent lethal events decreases as the occupancy of the chromatin domains reaches saturation.

To describe this relationship, we define an effective lethal-lesion production function:

$$L_{\text{eff}}(\text{LET}) = \phi(\text{LET})\psi(\text{LET}) \quad (24)$$

Within the present framework, $L_{\text{eff}}(\text{LET})$ represents the effective contribution of radiation-induced damage to the formation of biologically independent lethal lesions.

For $\phi(\text{LET})$ of damage-production component, we use the same LET-dependent function that has been used earlier for carbon-ion irradiation of V79 cells [23]. This function describes the increase in damage production with increasing LET values, whereas ψ describes the gradual reduction in lesion effectiveness associated with increasing chromatin-domain occupancy.

For visualization purposes, $L_{\text{eff}}(\text{LET})$ is normalized to its maximum value of LET. The resulting normalized response is shown in Figure 3. Numerical values are provided in Supplementary Information (Table S3.2) and Excel file. In contrast to the monotonically increasing trend expected for physical damage production alone, the dependence of the effective lethal lesion production function exhibits a maximum near

$$LET_{\text{peak}} \approx 192 \text{ keV}/\mu\text{m} \quad (25)$$

and followed by a gradual decrease at higher LET. This behavior can be understood as arising from the competition between the growth of damage production and the attenuation due to occupancy. Damage production dominates at low and intermediate LET, whereas attenuation becomes increasingly important at high LET.

At low LET, attenuation remains weak, whereas the effect of increase in damage production prevails. Therefore, the lethal-lesion yield increases rapidly with LET. In such conditions, a majority of the radiation sensitive chromatin domains remain available for the formation of additional biologically independent lesions, which will add to biological inactivation. This behavior is consistent with the proposed occupancy-based interpretation, in which the probability that newly induced damage occurs within previously occupied chromatin domains increases as occupancy rises [3,4,18].

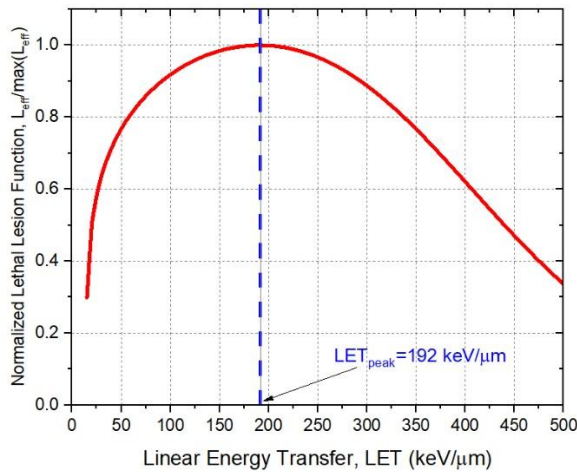


Figure 3. Normalized effective lethal-lesion production function for carbon ion irradiation of V79 cells. The maximum arises from the interplay between increasing damage production and attenuation associated with chromatin-domain occupancy.

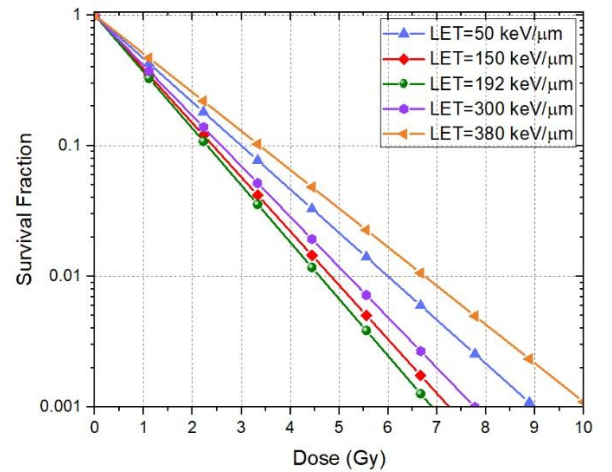


Figure 4. Calculated survival curves as a function of absorbed dose for representative LET values according to the occupancy-based attenuation model. The steepest predicted decline in survival occurs near $LET_{\text{peak}} \approx 192 \text{ keV}/\mu\text{m}$, where the normalized lethal-lesion yield reaches its maximum.

As LET increases, chromatin-domain occupancy also increases (see Figure 1), and the attenuation effect becomes more pronounced. However, even after occupancy saturation begins, the damage-production function continues to increase, and the lethal-lesion yield also continues to increase.

The maximum in Figure 3 may be interpreted as the area at which the increased production of lesions is balanced by the reduced effectiveness associated with occupancy saturation. Outside of this area, the phenomenon of occupancy-induced attenuation plays an increasingly important role in the behavior of the response. Although the production of fixed DNA lesions continues to increase, the proportion of lesions that occur in domains of chromatin that have already suffered damage grows. As a result, the probability of generating new lethal events decreases.

The decline observed at high LET is consistent with an occupancy-based interpretation of the overkill effect. Within the present framework, the overkill effect is not attributed to a reduction in physical damage yield. Instead, within this approach, the biological effectiveness of newly generated damage may be reduced due to the fact that the population of sensitive chromatin domains becomes saturated. Thus, extra energy leads to repeated damage in previously damaged chromatin regions and, hence, contributes less effectively to the formation of additional lethal events. As illustrated in Figure 3, the production of physical damage and biological effectiveness need not exhibit the same LET dependence. Although the induction of DNA damage can keep increasing monotonically with LET, the production of biologically effective lethal damage exhibits a maximum because of occupancy-induced attenuation. Within the present framework, the non-monotonic behavior shown in Figure 3 may be interpreted in terms of finite chromatin-domain occupancy and the associated attenuation mechanism.

3.4. Survival Curves Across the Occupancy Transition

The occupancy-based attenuation mechanism described above can also be examined in terms of its implications for cell survival. Although Figures 1–3 illustrate how chromatin-domain saturation influences the efficiency of lethal-lesion formation, its biological consequences can be examined more directly by incorporating this mechanism into the survival model introduced in Section 2.6.

The resulting survival curves are shown in Figure 4 for representative LET values spanning the low-, intermediate-, and high-LET regions. Numerical values are provided in Supplementary Information (Table S4.1) and Excel file. The survival curves exhibit a systematic dependence on LET. The steepest decline in survival is observed near $LET_{peak} = 192 \text{ keV}/\mu\text{m}$, corresponding to the maximum of the normalized lethal-lesion yield shown in Figure 3, where the model predicts the highest yield of biologically effective lesions.

For LET values of 50 and 100 $\text{keV}/\mu\text{m}$, the yield of radiation-induced damage remains relatively low, and thus the survival curves become shallower. While attenuation is minimal in this regime, the lethal-lesion yield remains below its maximum level due to the fact that fixed damage formation is not yet maximized.

For relatively high LET values, such as 300 and 380 $\text{keV}/\mu\text{m}$, the slopes of the survival curves flatten out despite the relatively higher value of LET. This behavior reflects the increasing influence of occupancy saturation on the effectiveness of newly generated lesions. Even as the production of physical damage increases with an increase in LET, the attenuation factor falls significantly owing to the increased occupancy of radiation-sensitive chromatin domains.

The ordering of the survival curves is consistent with the characteristic non-monotonic behavior associated with the overkill phenomenon. Within the present framework, biological effectiveness reaches a maximum at intermediate LET values rather than at the highest LET values because of the competition between damage production and occupancy-dependent attenuation. Similar non-monotonic dependence of biological effectiveness on LET has been observed experimentally in carbon ion radiobiology [7,8,11].

An important feature of Figure 4 is that the non-monotonic survival response emerges naturally from the occupancy-dependent attenuation mechanism without introducing any additional empirical correction into the survival model. Within the present framework, the LET dependence of survival can be interpreted as the combined consequence of the occupancy transition described in Figures 1 and 2 and the corresponding behavior of lethal-lesion production shown in Figure 3. The calculated survival curves may therefore be viewed as a macroscopic manifestation of finite chromatin-domain occupancy and its influence on the formation of biologically effective lethal lesions at high LET.

3.5. Implications for the Origin of the RBE Maximum

The results presented above provide a possible explanation for the occurrence of the well-known maximum in RBE observed for high-LET radiation. Although RBE was not used directly in the model formulation, the model captures a sequence of physical processes that may contribute to the rise and subsequent decline of biological effectiveness as a function of LET [8,11,17].

Within the proposed framework, the biological response is influenced by two competing processes. The first is the increase in fixed DNA damage production with increasing LET (represented by the function $\phi(LET)$). As ionization density increases, energy deposition becomes more concentrated along the particle track, leading to enhanced production of complex and clustered DNA damage [3,4,18]. In the absence of competing mechanisms, this process would be expected to produce a monotonic increase in biological effectiveness.

The second process arises from the finite occupancy of radiation-sensitive chromatin domains. As shown in Figure 1, the equilibrium occupancy fraction increases with LET, while the attenuation factor decreases. Within the present framework, attenuation is associated with a reduced probability that newly induced lesions occur in previously unoccupied chromatin domains. Consequently, an increasing fraction of newly induced damage accumulates in chromatin regions that already contain radiation-induced lesions.

Figure 2 highlights the LET range over which the occupancy state changes most rapidly. The fluctuation maximum marks the transition region between a regime dominated by largely unoccupied chromatin domains and a regime in which occupancy saturation becomes increasingly important.

The consequences of this competition are illustrated in Figure 3. At low and intermediate LET values, increasing damage production dominates, resulting in an increase in lethal-lesion yield. Beyond the transition region, however, occupancy saturation becomes progressively more important, reducing the efficiency with which newly induced damage contributes to biologically independent lethal events. The interplay between these competing tendencies produces a maximum in the predicted lethal-lesion yield, followed by a gradual decline at higher LET.

Figure 4 further illustrates the influence of the same mechanism on cellular survival. The steepest decline in survival occurs near the LET value at which the lethal-lesion yield reaches its maximum. At higher LET values, occupancy saturation progressively limits the formation of additional

biologically independent lethal events. This non-monotonic behavior is qualitatively consistent with experimental observations of the overkill effect in heavy-ion radiobiology [7,8,10].

In summary, the present results suggest that finite chromatin-domain occupancy may contribute to the emergence of an RBE maximum. Within the proposed framework, the overkill effect is interpreted as arising primarily from occupancy-dependent saturation rather than from a reduction in physical damage production at high LET. Instead, damage production continues to increase with LET, while the ability of radiation-sensitive chromatin domains to support additional biologically independent lethal events becomes progressively constrained.

The proposed statistical-mechanical framework offers a possible conceptual connection among occupancy saturation, attenuation, overkill, lethal-lesion production, and survival response. Within this interpretation, these phenomena may be viewed as related consequences of occupancy-driven saturation in a finite population of radiation-sensitive chromatin domains. Although additional experimental and theoretical studies are required to assess the quantitative applicability of the model, the present results suggest that chromatin-domain occupancy may offer a useful perspective for interpreting saturation effects observed in high-LET radiobiology.

3.6. Comparison with Experimental RBE Data

To assess whether the occupancy-based attenuation framework is consistent with high-LET observations, model predictions were compared with published RBE data for carbon-ion irradiation of V79 cells. The experimental data sets were compiled from studies reported in [7–10], covering a broad LET range from approximately 30 to 500 keV/μm.

The reference prediction was obtained using the parameter set presented in Section 2.5. In addition, two supplementary curves were calculated by introducing small variations in the overall attenuation strength. These curves define lower and upper bounds on the biological effectiveness predicted by the model and provide an indication of the sensitivity of the predicted response to variations in the occupancy-based attenuation mechanism. The shaded region therefore represents a predicted range of biological effectiveness rather than a statistical confidence interval.

Figure 5 presents the comparison results. Numerical values are provided in Supplementary Information (Table S5.1 and S5.2) and Excel file. The solid curve corresponds to the reference model prediction, whereas the shaded band indicates the range obtained using the procedure described above. Published experimental RBE values are also shown.

The experimental data exhibit the characteristic increase in biological effectiveness with increasing LET, followed by the appearance of a broad maximum and a subsequent decline at very high LET values. The occupancy-based model reproduces a broadly similar qualitative trend. Within the proposed framework, this behavior arises from the competition between increasing damage production and occupancy-induced attenuation. Notably, all experimental data sets considered here fall within the predicted response range shown in Figure 5. Because the model was not specifically fitted to these data, this level of agreement suggests that the occupancy-based attenuation framework is capable of reproducing several key qualitative features of the LET dependence of biological effectiveness for carbon-ion irradiation of V79 cells.

This comparison should nevertheless be interpreted with caution. The shaded region does not represent experimental uncertainties, and the present study is not intended as a quantitative fitting exercise. Rather, it serves as an initial evaluation of the proposed physical framework. Additional validation using independent data sets, different cell types, and other ion species would be important for assessing the broader applicability of the model.

Overall, the present results suggest that finite chromatin-domain occupancy may provide a plausible physical interpretation of attenuation, the overkill effect, and the emergence of an RBE maximum. Within the proposed framework, the decrease in biological effectiveness at very high LET is interpreted as arising from the progressively reduced availability of radiation-sensitive chromatin domains.

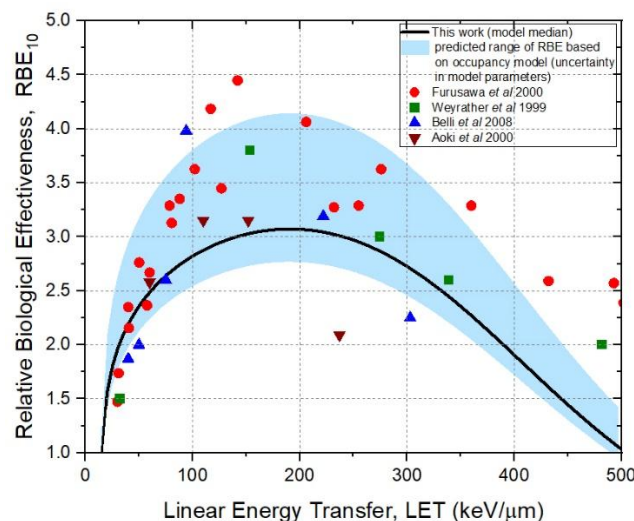


Figure 5. Comparison of the occupancy-based model prediction with experimental RBE data on carbon ion radiation of V79 cells from [7-10]. The solid line shows the reference model prediction, while the shaded area is the predicted response range based on small variations in the attenuation-model parameters.

4. Discussion

Within the present statistical-mechanical framework, the attenuation of biological effectiveness at high LET is interpreted in terms of the progressive occupancy of a finite population of radiation-sensitive chromatin domains. In this framework, attenuation is not introduced as a separate empirical parameter, but emerges from the decrease in the proportion of chromatin domains still available for creating biologically independent lethal events. The model is formulated in terms of an effective occupancy variable that describes the collective state of the chromatin-domain population and does not depend explicitly on the size of individual domains.

The occupancy-based mechanism provides one possible physical interpretation for the attenuation process in existing radiobiological models. Such models, which include the theory of dual action, repair-misrepair models, the local effect model, the microdosimetric kinetic model, and others, have successfully reproduced the dependency of the biological effectiveness upon LET under various physical and biological assumptions. In many existing radiobiological models, attenuation is associated with mechanisms such as lesion interaction, repair limitations, target overlap, or empirical LET-dependent relationships between radiation quality and biological effectiveness. In the present framework, attenuation is instead interpreted in terms of the progressive occupancy of radiation-sensitive chromatin domains. However, as occupancy increases, the proportion of domains still remaining available for the independent lethality events continues to diminish, thus providing a possible statistical-mechanical interpretation of the decrease in biological effectiveness at very high LET. Such an approach does not contradict the accepted notion that the complexity and clustering of DNA damages continue to rise along with increasing LET. Within the present framework, thus, the decrease in biological effectiveness is interpreted as resulting from a reduced efficiency with which newly induced damage contributes to additional biologically independent lethal events, rather than from a reduction in physical damage induction. The present framework is intended to complement existing models rather than replace them.

The occupancy-based approach offers an alternative interpretation of the maximum in relative biological effectiveness (RBE) seen in experimental observations. In this case, the emergence of the maximum can be understood as arising from a combination of two opposite tendencies. With the increase in LET, the complexity of DNA damage rises, while the occupancy of radio-sensitive chromatin domain results in fewer free domains available for causing new lethal independent events. Biological effectiveness therefore increases with the rise in LET up to some point and then decreases despite the fact that physical damage production continues to increase. A qualitative comparison indicates broadly similar trends with published experimental RBE values for carbon-ion irradiation of V79 cells. Even without direct calibration, the consistency of the general behavior suggests that chromatin-domain occupancy could represent one contributing factor of attenuation in the high LET regime. However, it should be noted that the proposed approach does not aim to substitute the already existing models of radiobiology, which provide comprehensive consideration of track structure, energy deposition, DNA damage induction, and the processes of repair. Instead, the focus here is on the impact of the limited number of radiation sensitive chromatin domains on the process of converting physical damage into biological effect.

The qualitative comparison of the proposed model with experimental RBE data on carbon ion irradiation of V79 cells (Fig. 5) provides an initial qualitative assessment of the proposed framework. An important feature of the model is that it reproduces the overall non-monotonic LET dependence without direct calibration to the experimental data. It has to be noted that such a comparison is qualitative in nature. However, the similarity in trends observed from both theoretical calculations and experimental data suggests that the occupancy-based framework captures several qualitative features of high-LET biological response and warrants further experimental evaluation.

It is important to emphasize that the present model is intentionally simplified and should therefore be regarded as a conceptual framework rather than a comprehensive description of the radiobiological response to high-LET radiation. Radiation-sensitive chromatin is represented by a single effective occupancy variable, which provides an effective average description of a finite population of chromatin domains but does not explicitly account for their structural and functional heterogeneity or differences in susceptibility to DNA damage, repair, and fixation. In addition, the model is formulated within an equilibrium statistical-mechanical framework and therefore does not explicitly describe the kinetics of damage induction, fixation, or repair. Other factors known to influence high-LET radiation response, including track structure, oxygenation, repair-pathway activity, and chromatin remodeling, are represented only indirectly through the effective model parameters. Consequently, the proposed occupancy framework should be regarded as one possible contribution to understanding attenuation at high LET rather than as a complete description of the underlying biological mechanisms. Future extensions of the model could incorporate heterogeneous chromatin populations, time-dependent occupancy dynamics, and stochastic fluctuations, together with quantitative validation across different cell types and ion species. Despite these limitations, the present results suggest that finite chromatin-domain occupancy may provide a physically motivated perspective on how increasing physical damage may be translated into biological response.

5. Conclusion

The present study develops a statistical-mechanical framework to investigate the potential role of finite chromatin-domain occupancy in the attenuation of biological effectiveness at high LET. Within this framework, radiation-induced irreversible DNA lesions progressively occupy a finite population of radiation-sensitive chromatin domains, reducing the fraction of domains available for the formation of additional biologically independent lethal events. The proposed framework predicts an occupancy transition accompanied by a fluctuation maximum, and a non-monotonic dependence of lethal-lesion yield and survival on LET that is qualitatively consistent with the overkill phenomenon. When combined with a previously established LET-dependent damage-production function, the model also yields the characteristic increase, maximum, and subsequent decline in biological effectiveness observed qualitatively in published RBE data for carbon-ion irradiation of V79 cells. Although this comparison is qualitative, it suggests that chromatin-domain occupancy may represent one possible contributing physical mechanism contributing to attenuation and the emergence of an RBE maximum. The present framework intentionally adopts a simplified representation of chromatin organization and does not explicitly incorporate repair kinetics, biological heterogeneity, or nonequilibrium damage evolution. It should therefore be regarded as a conceptual mechanistic framework rather than a predictive model. Future studies incorporating heterogeneous chromatin populations, time-dependent occupancy dynamics, and quantitative validation across different cell lines and ion species would be valuable for assessing the broader applicability of the proposed framework. Overall, the present results suggest that finite chromatin-domain

occupancy may provide a physically motivated statistical-mechanical perspective for interpreting attenuation, the overkill effect, and LET-dependent variations in biological effectiveness.

Data availability

All numerical data obtained from this study for all theoretical curves are included in the Supplementary Information and accompanying Excel file. All the RBE data used qualitatively in Fig. 5 for comparison were taken from the published literature as indicated in References. No additional experimental data sets have been produced in this study.

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In the present study no human (or animal) tissue was involved.

Additional information

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