Multiscale physics of ion-beam cancer therapy

E Surdutovich\textsuperscript{1, 2} and A V Solov’yov\textsuperscript{2, 3}

\textsuperscript{1} Department of Physics, Oakland University, Rochester, Michigan 48309, USA
\textsuperscript{2} Frankfurt Institute for Advanced Studies, Ruth-Moufang-Str. 1, 60438 Frankfurt am Main, Germany
\textsuperscript{3} On leave from A.F. Ioffe Physical Technical Institute, St. Petersburg, Russia

E-mail: solovyov@fias.uni-frankfurt.de

Abstract. We review a multiscale approach to the physics of ion-beam cancer therapy, an approach suggested in order to understand the interplay of a large number of phenomena involved in radiation damage scenario occurring on a range of temporal, spatial, and energy scales. We briefly overview its history and present the current stage of its development. The differences of the multiscale approach from other methods of understanding and assessment of radiation damage are discussed as well as its relationship to other branches of physics, chemistry and biology.

1. The roots of the multiscale approach
The scientific interest in obtaining a deeper understanding of radiation damage is motivated by the development of ion-beam cancer therapy and other applications of ions interacting with biological targets. A number of important scientific questions, especially related to DNA damage assessment on the molecular level, have not yet been resolved. Therefore, recently this field has attracted much attention from the scientific community [1–5]. There are a series of conferences devoted to these subjects, such as RADAM [1] and later Nano-IBCT [6]. The latter became possible due to the support of the European framework for Cooperation in Science and Technology (COST). The COST Action, “Nano-scale insights into ion beam cancer therapy (Nano-IBCT)” [7] was approved in 2010. Among these studies is the multiscale approach to the assessment of radiation damage induced by irradiation with ions. It is aimed at a phenomenon-based quantitative understanding of the scenario from the incidence of an energetic ion on tissue to the cell death. This method combines many spatial, temporal, and energy scales, and is therefore a truly multiscale approach.

1.1. Different approaches to radiation damage assessment
The understanding and assessment of radiation damage due to ionizing radiation are at the focus of radiation biophysics, which has a wide scope of important applications from radiation protection to radiation therapy. The standard scope of radiation biophysics spans from the interaction of ionizing projectiles with matter, radiation chemistry that includes interactions of radiation and secondary particles with water and biomolecules, to the analysis of models of cell survival [8–10]. The details of biodamage, such as different types of DNA lesions, single and double strand breaks (DSB) in DNA along with different pathways of their repair, are thoroughly
discussed. The rest is devoted to biological effects, such as the variety of responses to different quantities or qualities of radiation on different levels from the subcellular to the organismic.

The physical part of this analysis indeed starts with a projectile entering tissue. These projectiles – x-rays, electrons, protons or heavier ions, neutrons, or other more exotic particles – are quite energetic in the beginning and ionization of the medium is the main channel of their energy loss. Therefore, these types of radiation are referred to as ionizing; even though there are other important channels of energy loss, such as nuclear fragmentation. Then, of course, there is a physical question “how does the radiation damage happen?” X-rays or $\gamma$-particles lose energy exponentially with respect to the traveled distance and this results in certain spectra and loci of secondary particles such as electrons, free radicals, etc. Other (massive) projectiles lose their energy differently and their energy loss per increment of trajectory $|dE/dx|$, called the linear energy transfer (LET), features a Bragg peak near the end of their path. This peak is the main physical reason for using particles as projectiles for radiotherapy, because the energy deposition in many cases can be localized, thus focusing on a tumor and sparing healthy organs. The next question is inevitably about the relation between energy deposition and the biological damage. This is where physics, chemistry, and biology overlap and this issue is arguably one of the most important in radiobiology.

One way to address the problem of biological damage starts from the analysis of so-called survival curves. The survival curve is a relation between the logarithm of cell-survival fraction and the deposited dose. These curves can be obtained experimentally and they differ for different species, cells, radiation modality, etc. Nevertheless, the main feature of these curves is that they are approximately parabolic, i.e.,

$$\ln S/S_0 = \alpha D + \beta D^2,$$  \hspace{1cm} (1)

where $S/S_0$ is the normalized cell survival, $D$ is the dose, and $\alpha$ and $\beta$ are coefficients. Several features of these curves have been discussed, one of which is the ratio of $\alpha/\beta$. If this ratio is large, the survival curve is “steep” and more like a straight line; if it is small then it is a “shouldered” curve. Naturally, the next question is how to explain this, and there has been a series of models suggested since 1955 [8]. It is important to know that when a cell or a subcellular target like a cell nucleus, membrane, or mitochondrion is irradiated, there is an initial damage, e.g., a strand breaking in a DNA molecule, which can be described by atomic physics and chemistry. Then, there is a subsequent biological effort in order to repair the initial damage in which biological and biochemical mechanisms are invoked. The resultant damage revealed in survival curves is the result of these two phases. The models explaining survival curves relate the dose to the initial damage and its partial repair to obtain the parameters $\alpha$ and $\beta$ in equation (1).

Typical statements resulting from applications of different models may sound like this: If there is no repair mechanism and every (single) hit of the target results in cell inactivation with a given probability, the ratio of $\alpha/\beta$ is very large, the first term on the right hand side of equation (1) is dominant, the survival curve is a straight line, i.e., inactivation is exponential with respect to the dose. Or if there is no repair and several hits are necessary to inactivate a cell, the curve is shouldered with zero derivative at $D = 0$. Or if there is repair, then the curve is always shouldered. For many practical purposes, an experimentally obtained curve, given by equation (1) is sufficient information for the evaluation of radiation damage, and it has been used for many years for treatment planning and optimization.

Notice, that in the above examples we never mentioned any atomic or molecular interactions; these and more information are hidden in the purely empirical coefficients $\alpha$ and $\beta$. If the dose distribution is uniform, it is possible to not open the “Pandora’s box” of atomic/molecular physics, since it brings up too many difficult questions involving interactions with biomolecules that seem irrelevant as compared to the biological unknowns related to repair mechanisms. This was acceptable when only x-rays were used as projectiles. For x-rays, the dose distribution is
uniform and treatment plans had to deliver certain doses to certain locations in order to achieve desired results.\textsuperscript{1}

Particle projectiles change this picture. The dose distribution around each particle’s path is highly nonuniform because of the number of secondary electrons released by the ionized molecules of the medium on every nm of the path. These electrons as well as holes and radicals comprise a complicated track structure with a radial distribution of the dose, while the space between different tracks is largely undisturbed.

A solution to this problem was suggested by the Katz approach in which the radial dose distribution is calculated and related to the inactivation of sub-cell-nucleus targets \[11–14\]. The quality factor of radiation was introduced in order to relate the survival curve parameters to a given radiation, differentiating between track types, inactivation modes, the structural complexity of targets, etc. The eventual goal of the Katz model was to calculate the relative biological effectiveness (RBE) \[2,8,10\], one of the key integral characteristics of the effect of ions compared to that of photons. This ratio compares the doses of different projectiles leading to the same biological effect. Nevertheless, the biological relation of the radial dose distribution with the cell survival probability was done based on the survival curves for x-rays, without analyzing particular physical processes, i.e., the empiric coefficients $\alpha$ and $\beta$ remain central to this approach.

The Local Effect Model (LEM), developed at GSI\textsuperscript{2}, calculates the RBE assuming that the biological effect of radiation is entirely determined by the spatial distribution of the radial dose inside the cell nucleus. It relates the response of biological systems, following ion irradiation, to the corresponding response after x-ray irradiation \[2,15\]. Corrections for the quality of damage was included in a later version of the LEM \[2\]. This model operates on the schematic level using equation (1) with empirical coefficients $\alpha$ and $\beta$. The LEM solves technical problems related to the optimization of treatments, leaving no place for \textit{ab initio} approaches and physical, chemical, or biological effects in general; even a consideration of DNA lesions such as DSBs is beyond the scope of LEM \[1,2\].

A defining feature of high-LET irradiation is not only the high concentration of dose \textit{per se}, but the quality that this high concentration brings. In order to explain this, we have to explain some mechanisms of DNA damage. When tissue is irradiated with x-rays, they ionize and excite the medium and this results in a massive uniform production of hydroxyl radicals, which “attack” DNA molecules and induce damage in a series of chemical reactions. These processes were extensively studied in 1980s-1990s \[16–18\]. The concentration of events in such conditions is small and clustered damage is rare. The cell survival in this condition depends on the chemical environment (e.g., the presence of oxygen is deemed very important for radio resistivity), on how advanced the repair mechanisms in a given type of cells are, and on the stage in a cell cycle during which the primary damage occurs. A double strand breaking in DNA is the most severe lesion, but it can still be repaired \[19–21\]. The survival curves for many types of human cells are shouldered \[10\].

Particle projectiles, especially ions characterized with high LET, change this picture. A DNA segment sufficiently close to the ion’s path can be hit a number of times. This causes complex damage, which is more lethal than a simple DSB \[22\]. This results in an obvious increase of the $\alpha/\beta$ ratio.\textsuperscript{3} The LEM took this effect into account by introducing an extra empirical parameter \[2,23\], but this is just one example of the consequences of high-LET radiation! There are many other effects or possible environments, such as the application of sensitizers, which affect the number of secondary electrons, the application of an external magnetic field in the Bragg peak area, laser-driven beams, etc. It is hard to imagine how models, without theoretical

\textsuperscript{1} We leave aside optimizations related to reducing dose deposition in healthy regions and treatment partitioning.

\textsuperscript{2} Gesellschaft für Schwerionenforschung mbH, Darmstadt, Germany

\textsuperscript{3} The mechanism of cell death is attributed to apoptosis \[10\].
Table 1. Disciplines and scales of ion-beam cancer therapy

| Phenomenon                                              | Discipline            | Space scale | Time scale          |
|---------------------------------------------------------|-----------------------|-------------|---------------------|
| Beam generation                                         | High energy physics   | m–km        |                     |
| Beam transport                                          | Radiation physics     | 1–100 cm    | $10^{-7}$ s         |
| Nuclear collisions and fragmentation                    | Nuclear physics       | fm          | $10^{-22}$ s        |
| Primary ionization, transport of secondaries             | Atomic/molecular      | 0.1–10 nm   | $10^{-17} - 10^{-12}$ s |
| Branching of secondaries, radicals, excited species, chemical equilibrium | Chemistry         | 1–10 nm     | $10^{-12} - 10^{-5}$ s |
| Local heating, heat transfer, stress                    | Thermo/hydrodynamics | 1–10 nm     | $10^{-14} - 10^{-9}$ s |
| Dissociative electron attachment to molecules and other reactions | Quantum chemistry   | Å           | $10^{-15} - 10^{-12}$ s |
| Initial damage effects                                  | Biochemistry          | 0.1–10 nm   | $10^{-5}$ s         |
| Repairing mechanisms                                    | Molecular biology     | 1–100 nm    | s–min               |
| Cellular network and interaction (Tumor) Cell death      | Cell biology          | µm          | min                 |
|                                                         | Medicine              | mm          | min–years           |

base under the coefficients like $\alpha$ and $\beta$, can be sufficiently versatile to meet these challenges.

1.2. The alternative of the multiscale approach

The multiscale approach was formulated in references [4, 24], where a scenario leading to DNA damage was suggested. Then, it was elaborated upon as different aspects of the scenario were added in a series of work [5, 25–30]. Its name emphasizes the fact that important interactions involved in the scenario happen on a variety of temporal, spatial, and energy scales, as shown in table 1 [31].

Right from the beginning, the approach was formulated as phenomenon-based and was aimed at elucidating the physical, chemical, or biological effects that are important or dominating on each scale in time, space, and energy. The scheme of the multiscale approach is shown in figure 1 [4].

The formula, which defined the scenario, given in references [4, 24],

$$N_{DSB} = \Gamma_{DSB} \int dk \int d\mathbf{A} \cdot D \nabla P(k, r) \epsilon(k) \frac{dN}{d\zeta} d\zeta,$$

(2)

manifests the interplay of different scales. While the details of the derivation of this equation will be discussed below, notice that the equation predicts that the probability of a DSB ($N_{DSB}$) at a given segment of DNA is given by the probability of a DSB on impact by an electron, $\Gamma_{DSB}$, multiplied by the number of secondary electrons incident on this segment. That number is calculated as a result of secondary electron production ($\frac{dN}{d\zeta}$) and diffusion ($D \nabla P(k, r) \epsilon(k)$) of these electrons to reach the target. Thus, a number of scales is included in this expression. The first calculation done using equation (2) analyzed the effect of orientation of a DNA twist with respect to the ion’s path and it was concluded that the orientation might not be important for distances exceeding 2 nm, as shown in figure 2.

The multiscale approach raised questions about the nature of the effects that take place and lead to survival curves and the calculation of RBE and other macroscopic quantities,
e.g., by the end of the day it should answer the question of what is behind the coefficients in equation (1). The criticism that we often hear claims that our approach is not practical since the main questions have already been answered and the existing Monte Carlo (MC) simulations are capable of taking care of every single detail on every scale. Although we find simulations on different scales [32–38] to be very important in radiation damage assessment, we doubt both qualitative and quantitative comprehensiveness and exhaustiveness of the MC simulations. Two examples to this are the thermomechanical mechanisms discussed in references [28–30] and the double-electron-emission effects on DSBs discussed in reference [39]. Assurances about impracticality, infeasibility, and elusiveness have seldom stopped the scientific search for the truth.

2. A palette of physical effects on different scales

Here we review the achievements of the multiscale approach at different scales. The main issues addressed by the multiscale approach are ion stopping in the medium, the production and transport of secondary electrons produced as a result of ionization and excitation of the medium, the interaction of secondary particles with biological molecules, the most important being DNA, the analysis of induced damage, and the evaluation of the probabilities of subsequent cell survival or death. These effects are happening on time scales ranging from $10^{-21}$ to $10^{-5}$ s, i.e., from nuclear to biochemical times. The aim of the physical part of the analysis is the calculation of the spatial distribution of primary DNA damage, including the degree of complexity of this damage.

2.1. Ion stopping and the Bragg peak

The multiscale approach started with the analysis of ion propagation in a medium. Liquid water was used as the medium because human tissues on the average consist of 75% water. These work [25,27] resulted in the description of the Bragg peak and the energy spectrum of secondary electrons. The Bragg peak in the stopping power of massive charged particles is obtained using a version of the Bethe - Bloch formula [40–42]. This formula provides the dependence of the stopping power on the energy of the ion and practically depends on the mean excitation energy. This energy for liquid water is chosen somewhere between 70 and 80 eV [36,43].
approach to this problem was different. We chose to use the singly-differentiated (with respect to the secondary electron energy) ionization cross sections of water molecules in the medium as a physical input. These cross sections were taken from experiments [44] with parameters tuned for liquid water [27]. The parametrizations were also modified to take into account relativistic effects in the beginning of the ion’s path. Even a slight change in cross sections in the entrance channel (plateau region of LET curve) may significantly affect the position of the Bragg peak. Energy loss due to excitation of water molecules has also been included in the calculations [25]. The effect of charge transfer strongly affects the height of the Bragg peak, since it is proportional to the square of the effective charge of the projectile and the latter decreases as the projectile slows down because of the pick off electrons. Barkas’s parametrization [45] was used for the calculation of the effective charge. The next effect, included in reference [25], was the scattering of projectiles that naturally occurs as they propagate in the medium. This causes the spread in longitudinal velocities or the so-called energy straggling. This widens and substantially diminishes the Bragg peak for the beam of projectiles. Another effect on this scale, not yet included in the multiscale approach, is the nuclear fragmentation that happens quite often when projectiles collide with the nuclei of the medium. This effect is deemed to be significant, especially for the calculations of the tail in the stopping power curve beyond the Bragg peak [36]. As a consequence, we were able to describe the Bragg peak in good agreement with simulations and experiments [25–27] as shown in figure 3.

![Figure 3. Linear energy deposition for carbon ions for different initial energies $T_0$: our model (all lines) compared to experiments from GSI [46] (all dots). Different labels and colors indicate curves at different initial ion-energies $T_0$ [27].](image-url)

An important difference of our approach, relying on the singly-differentiated ionization cross section, allowed us to not only describe the Bragg peak, but also to use these cross sections to calculate the energy spectrum of secondary electrons, which turned out to be quite useful on the following scale of the electron transport and interactions of electrons with the medium.

2.2. Transport of secondary electrons and its relation to DNA damage
The next scale in energy and space is related to the transport of the secondary particles, which has been considered in references [4, 5, 39, 47]. These papers were built on the inference from the analysis of the energy distribution of secondary electrons that the average energy of these electrons is about 45-50 eV. At these and lower energies, the ionization cross sections are nearly isotropic, which allows one to employ a random walk approximation, i.e., assume that most of secondary electrons (excluding the more energetic $\delta$-electrons) diffuse out from the ion’s path. This diffusion was explored in a series of problems. First, we considered a random walk of...
electrons from the ion’s path to a twist of DNA located at some distance from the path [4]. A single twist of a DNA molecule was chosen because it is an important unit for DSB analysis. This study predicted that the damage probability on impact does not strongly depend on the orientation of the DNA segment with respect to the ion’s path. In that paper, we made an important and quite reasonable comparison of an estimate of the number of DSBs per µm of the ion’s path with biophysical experiments [48, 49].

A later development of that work in reference [5] explored a random walk approximation in order to assess the complex DNA damage. Complex DNA damage, investigated by biologists in references [22, 50–52], is defined as a multiple number of primary DNA lesions happening on a length of two DNA twists. Such a correlation of lesions is called a cluster with a size equal to the number of singly-damaged sites. Different types of lesions may be qualified as effective, e.g., single strand breaks (SSBs), DSBs, base-damages, abasic sites, etc. The size of a cluster is related to the probability of its enzymatic repair. It is deemed that clusters of a sufficiently large size (larger than three or four lesions) are lethal for the cell. Thus, the problem of assessment of complex damage can, on the one hand, be tackled in the same fashion as the problem of DSB, described above; on the other hand, its solution is directly related to the assessment of cell survival as a result of irradiation with ions. The target for a complex damage site is a two-twist segment of a DNA molecule. The original idea for the calculation of complex damage was formulated in reference [47]. There, it was suggested that each lesion that counts in a cluster is due to an action of a single agent such as a secondary electron, a radical, etc. Then, if the average number of lesions per target \( N_i \) is calculated, the probability of occurrences of clusters of different size, \( P\nu(N) \), can be calculated using a Poisson distribution,

\[
P\nu = \exp \left( -N_i \right) \frac{N_i^\nu}{\nu!},
\]

where \( \nu \) is the degree of complexity [5, 31]. Then, the problem of how to calculate \( N_i \) can be approached differently. The first method is to use the random walk approximation and calculate the number of particles (secondary electrons) incident on a given target as a consequence of irradiation or, much simpler, as a consequence of a single ion’s traverse, as described below.

### 2.3. A random walk approach

The most general problem can be set up in the following way. We consider a three-dimensional axially symmetric random walk of secondary electrons from the axis, determined by the ion’s path. The key quantity is the flux of secondary electrons through a patch \( dA \) located at a distance \( r \) from a segment \( d\zeta \) of the ion’s path from which the secondary electrons originate. It is given [5, 53, 54] by the following expression:

\[
\frac{dN_A(r, t)}{dt} = dA \cdot D \nabla P(t, r) \frac{dN}{d\zeta} d\zeta
\]

\[
= dA \cdot Dn_r \frac{\partial P(t, r)}{\partial r} \frac{dN}{d\zeta} d\zeta
\]

where, \( D = \bar{v}l/6 \) is the diffusion coefficient, \( \bar{v} \) is the average speed of the electron, \( l \) is the elastic mean free path of electrons in the medium, \( n_r \) is a unit vector in the radial direction (from the segment to the center of the patch \( dA \)),

\[
P(t, r) = \left( \frac{3}{2\pi \bar{v}tl} \right)^{3/2} \exp \left( -\frac{3r^2}{2\bar{v}tl} \right)
\]

is the probability density to observe a randomly walking electron at a time \( t \) and a distance \( r \) from the electron’s origin, and \( \frac{dN}{d\zeta} \) is the number of secondary electrons emitted from a \( d\zeta \)-segment of the path.
It is beneficial to integrate equation (4) over time and then obtain the fluence through \( dA \). In order to do this, we change variables from \( t \) to the number of steps done by secondary electrons \( k \) using \( \bar{vt} = kl \). We rewrite equation (4), substituting (5), and switching from variable \( t \) to \( k \) as

\[
dN_A(r) = \int \frac{dN_A(r,t)}{dt} dt = dA \cdot n_r \frac{dN}{d\zeta} \int_{r/l}^{\infty} dk \frac{r}{2k} \left( \frac{3}{2\pi kl^2} \right)^{3/2} \exp \left( - \frac{3r^2}{2kl^2} - \gamma k \right). \tag{6}
\]

An attenuation factor, \( e^{-\gamma k} \), is introduced to account for electrons falling out from the random walk. The constant \( \gamma \) is equal to the ratio of the cross section of electron-inactivating processes to the total cross section. The integration over \( k \) is carried out from the minimal number of steps, necessary to reach distance \( r \), to infinity.

The last integration is done over \( dA \) and it depends on the particular situation. As a result, the average number of incidences on the target \( N_A \) is calculated and this information may be quite useful [39]. \( N_i \) is calculated as a product of \( N_A \) and the probability of ionization or any other qualified damage on impact.

A number of problems can be solved using this approach. Two of them, the investigation of SSB and DSB yields and the assessment of complex damage, were considered in references [4,5]. An example of the dependence of cluster damage probabilities on the radial distance from the ion’s path, calculated using this method, is shown in figure 4 [5]. Another important investigation is presented in reference [54]. The purpose of this study was to compare the random walk approach with MC simulations for nano-dosimetric applications. In this study, the biomolecules are not involved and \( N_i \) is the number of ionizations in the target. This number can also be measured or related to measurements. Such a study provides a way of validating our random walk approach and makes this method useful to the nano-dosimetry community [37, 55].

Still another application of the random walk can be found in the analysis of the relation of double ionization events to DSBs.

**Figure 4.** An example of radial distribution of clusters of two (solid line) and clusters of three lesions (dashed line) [5].
2.4. Double electron emission and DSBs
If the primary ionizing projectiles are ions, a substantial fraction of damage is done by secondary electrons, formed in the process of the ionization of the medium. A number of different pathways of damage due to these electrons were considered in references [3,5,19]. The direct measurements of DNA damage due to incident electrons were presented in, e.g., reference [56], which brought to light the possibility that low energy electrons were important agents of DNA damage. Since then, the mechanism of a SSB due to the action of a single electron, related to the formation of a transient negative ion (TNI) as a part of the process of dissociative electron attachment (DEA), has been widely discussed in the literature, e.g., references [3,57,58] with emphasis on low energy (under ionization threshold) of the incident electrons.

Unexpectedly high yields of DSBs compared with SSBs, in reported reference [56], lead to an hypothesis that DSBs can be caused by a single electron. This logic has been widely accepted and used in reference [4]. However, the mechanism of DSBs due to low-energy electrons is still quantitatively unclear despite qualitative arguments, suggesting that the breaks in the second strand are due to the action of debris generated by the first SSB [56]. In reference [4], the production of DSBs by two separate electrons was also considered, but that analysis was then shelved, since the number density of secondary electrons due to the primary ionization with an ion was not nearly enough for this effect to be considerable in comparison with DSBs due to a single electron action.

In reference [39], we argued that additional electrons emitted in the vicinity of a DNA molecule as a result of double-electron-emission events increase the above effect and thus constitute a mechanism for a DSB. We explored the probability of two electrons, produced in the vicinity of a DNA molecule, be incident on a single twist of this molecule. These additional electrons emerge as a result of double ionization events such as the Auger effect in single molecules, e.g., references [59–62] for water, or due to the effect of intermolecular coulombic decay (ICD), studied in references [63–67] for water clusters. The actual mechanism of double ionization is not important for this analysis. We used a generic term “double ionization events” to describe all relevant events leading to a production of additional electrons.

Auger electrons are produced as a result of non-radiative relaxation of holes produced by primary and secondary ionization. They may emerge consequent to the ionization of water or other molecules or clusters of the medium. If a secondary electron ionizes a molecule by kicking out one of its inner-shell electrons, a hole is formed on this molecule. If this hole then relaxes via a non-radiative channel (an Auger electron is emitted from the same molecule or an adjacent molecule in a cluster) the total number of electrons, emerging from a sub-nm locality, is equal to three, the ionizing electron, the released electron, and the Auger electron, as shown in reference 5. If a double-ionization event occurs on a DNA molecule, the probability of damage, such as a DSB, comprises the sequence of these processes with the corresponding dynamics of the DNA molecule and possible further interaction with these three electrons. If a water molecule (cluster) of the medium located in the vicinity of a DNA molecule is a host of a double-ionization event,
then these three electrons can independently diffuse and stumble onto a DNA convolution and produce two SSBs, possibly yielding a DSB. We considered the latter scenario in more detail.

It is interesting to notice that the energies of each of the three electrons, emerging from a water molecule or cluster, are likely to be below 15 eV. An average ionizing electron has an energy around 45-50 eV, corresponding to the average energy of electrons produced by an ion [25]. After this ionization event, it loses about 30 eV [64]. Thus, the ionizing electron is left with less than 15 eV while the other two will have even smaller energies [65]. These low-energy electrons are likely to be engaged into the DEA channel leading to SSBs. How does this scenario make a difference in the DSBs production?

The number density of secondary electrons, produced on the ion’s path, reduces rather steeply with the increasing distance from the path, so that the probability of two electrons incident on a single convolution of a DNA molecule, located a few nm from the path is very small. However, when ionization of a water molecule (cluster) producing extra electrons occurs at a distance from the path, three electrons emerging from the same spot substantially boost the local number density of electrons and, hence, the probability of a nearby DNA convolution to be hit with two electrons. A similar process may take place if the primary projectile is a photon. In that case, two (instead of three) electrons are produced in a locality and are capable of producing a DSB in a DNA molecule. If incident photons ionize the $1a_1$ state, then a cascade of Auger electrons may follow, rapidly increasing the number density of electrons.

In order to give a quantitative example of the effect caused by double-ionization events, we considered a double ionization event caused by a secondary electron, produced by an incident carbon ion. We considered a random walk of secondary electrons from the point of the event and calculated the probability that two of these electrons hit a given DNA convolution. The results of these calculations are presented in figure 6.

![Figure 6](image-url)

**Figure 6.** The probability for two electrons to pass through a single convolution of DNA (solid line) compared to that of one electron (dashed line) [39].

It is remarkable, that for $r < 2$nm the probability of the impact of two electrons is comparable to that of one. Of course, figure 6 includes neither the value of the probability of DEA on impact, nor the probability of a double electron emission event, but still, the substantial quantity of this fluence elevates the interest to study such events and their influence on DNA damage.

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4 The discussed double-ionization events do not concern electrons from the $1a_1$ MO of an H$_2$O molecule, because in order to kick these electrons out, the secondary electron has to have an energy above 540 eV. Such electrons are very rare.
The conclusion of that paper is that due to double-electron emission events, two or more electrons interact with a single DNA convolution with a sizable probability. Double strand breaks or other types of complex damage may result from these interactions. Since the Auger emission may result from the ionization of a water molecule by an incident photon, the above two-electron mechanism can also contribute to the DSB yield consequent to an irradiation of tissue with photons.

We considered the major concepts related to the transport of extra electrons and made first steps to including these electrons in the multiscale approach for the calculation of radiation damage by ions. The inclusion of Auger-like effects into the multiscale approach is an important step, since they play a significant role in radiation damage [68].

Future research in this route will be based on the calculations and measurements of the cross sections of double ionization of water molecules and clusters and the cross sections of DSBs due to two incident electrons. The calculation of the fluence of extra electrons, also presented in the paper, gives a framework for the calculation of the transport of free radicals formed due to an ion’s traverse through a medium.

2.5. Radial dose based approach

There is an alternative to the calculation described above for the fluence using the random walk approach in determining the average number of lesions or ionizations per target. This approach is based on the calculation of the radial dose and integrating it over the target volume. This approach is somewhat reminiscent of the Katz approach, except the radial dose is calculated using the random walk approximation. The radial dose was first calculated using this method in reference [47] and then improved in reference [5]. The state of the art is presented in reference [69].

The calculations performed using the random walk approach are based on the integration of equation (6) over the area of a cylinder coaxial with the ion’s path. The number of ionization events in a cylindrical slice between \( \rho \) and \( \rho + d\rho \) is proportional to the number of secondary particles (of a given energy) incident on the inner cylindrical surface multiplied by the probability of ionization per electron (effective area over total area), which is equal to the number of water molecules inside the volume (number density times volume \( n2\pi\rho L d\rho \)) multiplied by the ionization cross section \( \sigma \) and divided by the total area of the cylinder \( 2\pi\rho L \),

\[
dN = N_A(\rho) \frac{n\sigma 2\pi\rho L d\rho}{2\pi\rho L} = N_A(\rho)n\sigma d\rho .
\]

The energy, \( d\mathcal{E} \), deposited in this slice is equal to the product of this number of events by the average energy per event \( \bar{W} \):

\[
d\mathcal{E} = \bar{W} N_A(\rho)n\sigma d\rho .
\]

Finally, the radial dose, \( d\mathcal{D} \), is the volume density of the deposited energy, i.e., equation (8) divided by the volume of the slice \( 2\pi\rho L d\rho \):

\[
d\mathcal{D} = \bar{W} \frac{N_A(\rho)n\sigma d\rho}{2\pi\rho L} = \bar{W} \frac{N_A(\rho)n\sigma}{2\pi\rho L} .
\]

The radial dose, given by equation (9) can be compared to the experimental measurements and simulations. Then, the number \( N_i \) can be obtained by dividing equation (9) by \( \bar{W} \).

3. Thermomechanical damage

In this section, we describe a study of the possibility of producing DNA damage as a result of a thermomechanical effect caused by ions stopping in a tissue. Thermomechanical effects in
this case can be described as a dynamical change in temperature and pressure in the medium causing forces that may rupture bonds in DNA molecules [70]. The understanding of such a possibility evolved from the estimates of the temperature increase in the medium as a result of ion propagation [25], then from the analysis of thermal and pressure spikes in liquid water [28].

As we discussed above, an ion passing through the medium loses its energy. The energy loss is quantified by the LET and occurs mainly through ionization of the medium, and the energy is carried away by the secondary electrons produced in this process. Secondary electrons lose their acquired energy in a series of consecutive collisions with the molecules of the medium (predominantly water), which are likely to get excited in this process. Finally, these molecules relax and most of their energy is distributed between their translational degrees of freedom; the temperature inside a sub-nm cylinder surrounding the ion’s path becomes very high. These predictions were made as a result of the calculations of heat transfer in the vicinity of ion paths in water using the inelastic thermal spike model [28].

A preliminary study of a biomolecule, a small protein ubiquitin, exposed to transient heating was carried out in reference [31]. That study showed that the temperature spike caused by a carbon ion “unglues” a protein molecule. A further dynamics study was not feasible until the pressure development scenario was understood in reference [29]. That work predicted that a sharp increase of temperature and pressure in the vicinity of the ion’s path causes a shockwave, characterized by the rapid cylindrical expansion with a steep rise of pressure on the wavefront and its drop in the wake. The dependence of the pressure at the wavefront on its distance from the ion’s path for a carbon ion is shown in figure 7 [29]. It was shown that forces, caused by high-pressure gradients emerging as a result of local heating of the medium by passing ions, can be strong enough to break covalent bonds (more than 10 nN), but act only for a very short time and it remained unclear whether this was sufficient to break covalent bonds and cause severe damage to DNA molecules. This question was analyzed in references [30, 71] using a Molecular Dynamics (MD) simulation of a shockwave propagating through a nucleosome.

The results of the MD simulations demonstrate that the three dimensional structure of a nucleosome experiences noticeable obliteration as shown in figure 8 [30]. The propagating shockwave distorts the stacking interactions and the hydrogen bonds stabilizing the nucleotides of the DNA and leads to the partial destruction of the DNA secondary structure.

The analysis of stresses on the covalent bonds of the DNA backbone chain during the shock
wave propagation shows that the probability to induce a thermomechanical breakage of the DNA backbone chain in a single event of a carbon ion’s close passage (1 nm from the surface of nucleosome) is equal to 0.5% [30]. This number significantly increases as the distance between the trajectory and the nucleosome decreases and/or with the increase of the effective charge of the ion [71, 72]. Thus, for ions such as iron, the thermomechanical mechanism of DNA damage may become dominant.

4. Conclusion
We have reviewed the multiscale approach to radiation damage by ions. We showed that the main difference from other approaches is the in-depth focusing on physical effects that we call a phenomenon-based approach. The state of the art of this approach is discussed with demonstration of some techniques of calculations. This is the first comprehensive review of our approach and we hope that its development will continue along the lines indicated in this review.

The main advantages of the multiscale approach follow from its architecture and are its fundamentality and versatility. The approach evaluates the relative contributions and significance of a variety of phenomena; it elucidates a complex multiscale scenario in sufficient detail and has a solid predictive power. It is structurally simple and inclusive, and allows for modifications and extensions by including new effects on different scales and improvements on the way.

Examples of innovative developments that we have discussed are the relation of double-ionization events with the nature of DSBs and thermomechanical mechanisms of biodamage. However, there are more to come. There are effects related to the action of sensitizers, to hypoxic/aerobic environments, and other conditions which can be treated as different phenomena and we believe that such treatments can be beneficial. A series of new opportunities will be related to the imminent proton beams produced by high-power lasers [73]. The calculation of RBE in such environments will require a more physical input.

Certainly, our goal and hope in developing the multiscale approach is to make a worthwhile tool for the assessment of radiation damage on the molecular level. While its practicality is still in question, its fundamental basis and depth related to atomic/molecular physics is becoming more and more evident.
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