Double strand breaks in DNA resulting from double-electron-emission events

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A mechanism of double strand breaking (DSB) in DNA due to the action of two electrons is considered. These are the electrons produced in the vicinity of DNA molecules due to ionization of water molecules with a consecutive emission of two electrons, making such a mechanism possible. This effect qualitatively solves a puzzle of large yields of DSBs following irradiation of DNA molecules. The transport of secondary electrons, including the additional electrons, is studied in relation to the assessment of radiation damage due to incident ions. This work is a stage in the inclusion of Auger mechanism and like effects into the multiscale approach to ion-beam cancer therapy.

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The analysis and assessment of radiation damage are important in relation to a wide range of applications from cancer therapy to radiation protection of humans and electronics. Studies of biodamage due to irradiation with ion beams, centered on the analysis of pathways of DNA damage, are discussed in a large number of papers observed in reviews \cite{1,2}; the multiscale approach to the physics of ion-beam cancer therapy \cite{2,3} is also among these studies. A double strand break (DSB) in DNA is the most pernicious kind of damage that happens as a result of radiation impact. It is defined as the simultaneous breaking of the two strands of a DNA molecule within the distance of 10 base pairs along the helix, which corresponds to a single convolution of a DNA molecule. This type of lesion is emphasized because of the difficulties of its repair and thus close connection to cell lethality. What processes lead to this lesion?

If the primary ionizing projectiles are ions, a substantial fraction of damage is done by secondary electrons, formed in the process of ionization of the medium. A number of different pathways of damage due to these electrons were considered in Refs. \cite{4,5}. The direct measurements of DNA damage due to incident electrons were presented in, e.g., Ref. \cite{6}, 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., Refs. \cite{7,8,9}, with emphasis on low (under ionization threshold) energy of the incident electrons.

Unexpectedly high yields of DSBs compared with SSBs in Ref. \cite{7} lead to a hypothesis that DSBs can be caused by a single electron. This logic has been widely accepted and used by the present authors to calculate the yields of DSBs due to ions \cite{3}. 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 \cite{7}. In Ref. \cite{3}, 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 primary ionization with an ion was not nearly enough for this effect to be considerable in comparison with DSBs due to single electron action.

In this work, we argue that additional electrons emitted in the vicinity of a DNA molecule as a result of the Auger-like mechanism augment the above effect and thus constitute a mechanism for a DSB. We explore the probability of two electrons, produced in the vicinity of a DNA molecule, be incident on a single convolution of this molecule. These additional electrons emerge as a result of double ionization events such as the Auger effect in single molecules, e.g., Refs. \cite{10,11} for water, or to the effect of intermolecular coulombic decay (ICD), studied in Refs. \cite{12,13} for water clusters. The actual mechanism of double ionization is not important for our analysis. We will use a generic term “double-ionization-events” to describe all relevant events leading to a production of additional electrons, and we will refer to the additional electron as an Auger electron, even if it originates from ICD.

1. 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 Fig. 1. 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 a corresponding dynamics of the DNA molecule and possible further interaction with these three electrons. If a water molecule (cluster) happen at the origin. We consider a three-electron cluster, are likely to be below 15 eV. An average ionizing electron is left with less than 15 eV while the other two will have even smaller energies. 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 an Auger electron 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 1σ1 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 the Auger mechanism, let us consider an event of ionization with Auger emission caused by a secondary electron, produced by an incident carbon ion. The goal of this example is to calculate the transport of three electrons emerging from the ionization locality, which we will treat as a point, to a nearby DNA convolution.

Let an event of double ionization of a water molecule (cluster) happen at the origin. We consider a three-dimensional random walk of electrons from this point. We represent a single DNA convolution with a cylinder of radius \( a = 1.15 \) nm and a length of 3.4 nm. For simplicity and definiteness, we situate this cylinder symmetrically with respect to the \( y \)-axis, with the cylinder’s axis parallel to the \( x \)-axis and lying in the \( xy \) plane, as shown in Fig. 1. The distance between the origin and the cylinder’s axis, \( \rho \), exceeds \( a \) so that the Auger electron is emitted outside the convolution.

If one electron is emitted from the origin at \( t = 0 \), according to Ref. [21], its rate, \( dp_1/dt \), of passing through the patch, \( d\vec{A} \), located at a distance \( r \) from the origin, is given by the expression

\[
\frac{dp_1(\vec{r}, t)}{dt} = d\vec{A} \cdot \vec{D}_\nu \frac{\partial P(t, r)}{\partial \rho},
\]

where \( \vec{D} = \vec{v}l/6 \) is the diffusion coefficient, \( \vec{v} \) is the speed of the electron, \( \vec{D}_\nu \) is a unit vector in the radial direction, and

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

is the probability density to observe a randomly walking electron at a time \( t \) and a distance \( r \) from the origin. Eq. (1) should be integrated over both the time and \( d\vec{A} \), in order to calculate the probability for the electron to encounter the cylinder.

The time dependence in Eqs. (1, 2) can be translated into the dependence on number of steps, \( k \), using \( \bar{v}t = kl \), where \( l \) is the elastic mean free path of electrons in the medium. Then, we rewrite Eq. (1), substituting (2), and

\footnote{In order to kick out an electron from 1σ1 MO of \( H_2O \) molecule, the secondary electron has to have the energy above 540 eV. Such electrons are very rare. Ionization of other state cannot produce Auger electron because of the lack of energy.}
The probability decreases with increasing $r$. This probability is proportional to that of producing a strand break or a different type of lesion on the length of a given DNA convolution. The corresponding coefficient is the probability of inducing an SSB in a single electron action, $\Gamma$, remains largely unknown and its calculations and measurements remain a task for atomic physicists and quantum chemists.

The second and third electrons from the three, produced in the double ionization event, are independent from the first one and, hence, the probability of two electrons to impact the cylinder, $p_2$, is given by

$$p_2 (r) = 3 \rho_1^2 (r) .$$

The dependence of this probability on the distance of the cylinder axis from the origin is shown in Fig. 2. It is remarkable, that for $r < 2 \text{nm}$ the probability of the impact of two electrons is comparable to that of one. Of course, Fig. 2 includes neither the value of $\Gamma$, nor the probability of an ionization event with the following

Auger emission, but still, a substantial quantity of this fluence makes the Auger-mechanism influence on DSB yield viable.

2. Auger electrons emitted from the ion’s path as a result of primary ionization propagate similarly to secondary electrons, so the correction to the number of agents interacting with a DNA molecule situated at a distance from the path can be made after the calculation of the probability of Auger electron emission during the primary ionization. Our goal in this section is to consider the Auger electrons emitted as a result of the ionization of water molecule clusters by secondary electrons.

The scenario is as follows: Secondary electrons originate on the ion’s path and diffuse (through a random walk) away from the path. Their interactions with water molecules are primarily elastic until they ionize a water molecule (cluster). This happens about once per every 30 elastic collisions at relevant energies of secondary electrons. A typical secondary electron ionizes one water molecule before it becomes thermalized and finally bound. More rare energetic $\delta$-electrons are not considered in this discussion. For simplicity, let us assume that ionization happens on a certain step in the random walk of a 45-eV electron. At that time, this electron is most likely situated at a distance from the path, given by the expression,

$$\bar{\rho} = \int \rho P(k, r) d^3 r ,$$

where $k = 30$ and $\rho$ is the radial distance from the path. The calculations, with the above parameters for secondary electron propagation in water, give $\bar{\rho}$ approximately equal to 1 nm. This means that the locus of first ionization events is a cylinder with a radius of 1 nm on the axis of the ion path. Then, we can calculate the fluence at a distance $\rho$ from the path due to Auger electrons emitted from the surface of this cylinder. It is given by the integration of Eq. (3) normalized by $dA$ over the surface of the cylinder:

$$p_A (\rho) = \int_S \frac{|\vec{r} \cdot \vec{n}_\rho|}{r} \frac{dp_1 (r, k)}{dA} \frac{d\sigma}{S}$$

where $r^2 = \rho^2 + \zeta^2 + \rho^2 - 2\rho \rho \cos \phi$, $\zeta$ is the coordinate along the path, $\phi$ is the azimuthal angle, and $\vec{n}_\rho$ is a unit vector in the radial direction. The rest of the geometry is shown in Fig. 4 along with the results for $p_A (\rho)$. The fluence per one electron from the cylinder is compared to that of electron coming from the path. Starting from a small distance from the cylinder, the fluences are equal, which means that outside some domain, the total fluence is equal to the fluence of secondary electrons emitted on the path multiplied by $(1 + 2 \psi)$, where $\psi$ is the probability of the double-ionization event on impact and the factor of two is due to an extra electron emitted in this process.

3. The quintessence of this paper is that due to the Auger mechanism, events in which two or more electrons interact with a single DNA convolution are not rare. Double
strand breaks or other types of complex damage may result from these interactions. Thus, this effect qualitatively provides a solution to the puzzle of high yields of DSBs by finding sources of high local electron density near sites of damage. 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 Auger electrons and made first steps to including the Auger electrons in the multiscale approach to the calculation of radiation damage by ions. Besides the consideration of a two-electron mechanism for DSBs, our findings also correct the fluence of secondary electrons through the DNA convolution due to the Auger mechanism. The inclusion of this effect into the multiscale approach is an important step, since, in general, the Auger mechanism plays a significant role in radiation damage \[22\].

Future research in this route will be based on the calculations and measurements of the cross sections of ionization of water molecules and clusters with a consequent emission of Auger electrons and the cross sections of DSBs due to two incident electrons.

The calculation of the fluence of Auger electrons presented in the previous section gives a framework for the calculation of the transport of free radicals formed due to an ion’s traverse through a medium. This calculation, without the use of Monte Carlo simulations has long been desired. Finally, the analysis presented in this paper can be extended to the calculation of complex damage as in Ref. \[4\] with the inclusion of the Auger mechanism.

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