Damage of DNA backbone by nanoscale shock waves

Alexander V. Yakubovich1,2, Eugene Surdutovich3 and Andrey V. Solov’yov1,2

1Frankfurt Institute for Advanced Studies, Ruth-Moufang Str. 1, Frankfurt am Main D-60438, Germany
2On leave from A.F. Ioffe Physical Technical Institute, Polytechnicheskaya 26, Saint-Petersburg, 194021, Russia
3Oakland University, Department of Physics, Rochester, MI 48309 USA
E-mail: yakubovich@fias.uni-frankfurt.de

Abstract. By means of full-atom molecular dynamics simulations we investigate the process of DNA backbone damage by nanoscale shock waves in a water environment. These shock waves are created by ions penetrating the medium with high linear energy transfer. The high rate of the ions’ energy transfer to the surrounding molecules leads to the rapid increase of the temperature in the vicinity of the ion trajectory, which causes the formation of shock waves propagating through the medium. We have investigated the ions’ linear energy transfer of 900, 2000 and 5000 eV/nm. In the case of a linear energy transfer of 5000 eV/nm the deposition exerts unsustainable stress on the DNA molecule, which leads to the breakage of DNA backbone covalent bonds by thermomechanical effects.

1. Introduction
The damaging effects of energetic radiation have been known for many years. It has been commonly accepted that high-energy tracks formed by photons, electrons and atomic ions ionise cell components along the track, thereby leading to various dissociation channels and to the formation of damaging radicals. This knowledge has triggered intensive research on radiation protection and the development of biomedical applications for different types of ionising radiation, generally referred to as radiotherapy, especially used for treatment of the tumorous diseases [1].

An event of DNA damage due to an incident ion is rather complicated. For example, secondary electrons produced by the projectile may directly interact with a DNA molecule and yield a lesion. Alternatively, such a lesion can be produced by the vacancy hole left by the ejected electron [2–5].

On the theoretical side, much work has investigated different mechanisms of DNA damage. From these studies, the direct effects are the most important pathways in connection to damage induced by ions [2, 3, 6, 7]. All these mechanisms are related to the interactions of low-energy electrons or holes with DNA molecules. Alternatively a purely physical mechanism of damage has been discussed in reference [8]. That work has been devoted to the heat transfer in the vicinity of ion tracks. The solutions to the coupled thermal conductivity equations for electronic and atomic components predicted short-time temperature spikes. It was argued that these spikes may contribute to other mechanisms of damage and affect the chemical environment of the DNA. Following that paper, the molecular dynamics simulations of a biomolecule in the
predicted temperature regimes were carried out [9]. The thermal spikes form on a time scale of $10^{-15} - 10^{-13}$ s after the ion’s traverse [8]. They result from the energy transfer from the secondary electrons to the vibrational degrees of freedom of molecules of the medium, which dominates the other channels of energy transfer [8,10]. Therefore, the energy per unit length of ion’s trajectory of the order of LET is deemed to be converted to the kinetic energy of the expanding medium. This expansion was considered in reference [11] and described as a cylindrical shock wave following a strong explosion at $10^{-13}$ s after the ion’s traverse. The first results of simulations of the effects of a heat spike in the vicinity of a nucleosome were reported in reference [12]. Those simulations were carried out taking into account all atoms in the system. It was shown that a high rate of energy transfer from an ion to the molecules of surrounding water environment leads to the formation of the nanoscale shock wave propagating through the medium, the same as predicted in reference [11]. The formed shock waves hitting the DNA can substantially deform its secondary structure. In reference [12], the linear energy transfer (LET) of the ion was taken to be 900 eV/nm, which corresponds to the carbon ion in the vicinity of its Bragg peak. Using the simple Boltzmann formalism, the probability of DNA backbone breakage was calculated, and the number of such strand breaks per one cell nucleus was estimated.

This work continues the study of the possibility of producing DNA lesions as a result of a thermomechanical effect caused by ions stopping in the tissue. By means of molecular dynamics simulations we investigate the effects of higher LET. The LET is higher due to a higher charge of the projectiles. In general, LET is proportional to the square of this charge. Initially fully charged ions tend to pick up electrons from the medium, and therefore, the initial charge becomes smaller as the speed of the projectiles decreases. The effective charge defining LET may be larger for heavier ions. Alternatively, the charge might be higher than the effective charge stemming from fluctuations due to collisions with molecules of the medium. Indeed, when ions are propagated through the medium they experience multiple collisions with molecules of the environment. These collisions lead to the continuous process of ions’ ionization and recharging by capture of the electrons from the surrounding molecules. We discuss this process in more detail in the following section.

In section 2, we give a description of the simulations and the theoretical formalism for calculating the effective charge of the ion. In section 3, we discuss the results before concluding in section 4.

2. Theoretical methods
The effective charge of an ion moving through a water medium can be evaluated by using the formalism developed by Barkas [13] as follows:

$$z_{eff} = z \left[1 - \exp\left(-125\beta z^{-2/3}\right)\right],$$  \hspace{1cm} (1)

where $z_{eff}$ is the effective charge of an ion, $z$ is the charge of the nucleus, $\beta = V/c$, where $V$ and $c$ are the velocity of an ion and speed of light, respectively.

The Bragg peak region of the ion’s trajectory corresponds to a kinetic energy of approximately 0.3 MeV per nucleon [14]. The velocity of the ion with this kinetic energy is $\sim 2.52 \cdot 10^{-2}c$. Substituting the ion’s charge and velocity to equation (1) one obtains for the case of carbon ions $z_{eff} \approx 3.70$.

The LET of the ion is proportional to its squared effective charge [14]. In this work we have investigated the ions’ LETs of 900 eV/nm, 2000 eV/nm and 5000 eV/nm, which correspond to carbon, magnesium and arsenic. The properties of the ions are summarized in table (1).

Note that equation (1) gives the mean effective charge of the propagating ion. However, the ion experiences multiple collisions with molecules of water. These collisions lead to continuous processes of ion recharging by capture of electrons from the surrounding molecules.
Table 1. Values of investigated LET and corresponding elements. $z_{\text{eff}}$ is the effective charge of an ion in its Bragg peak as follows from equation (1), $z$ is the total charge of the ion nucleus.

| LET (eV/nm) | $z_{\text{eff}}$ | $z$ | Element |
|-------------|-----------------|-----|---------|
| 900         | 3.70            | 6   | C       |
| 1080        | 4.04            | 7   | N       |
| 1257        | 4.36            | 8   | O       |
| 2000        | 5.50            | 12  | Mg      |
| 4072        | 7.86            | 26  | Fe      |
| 5000        | 8.72            | 33  | As      |
| 10527       | 12.64           | 82  | Pb      |
| 11503       | 13.21           | 92  | U       |

and ionizations. Therefore, the effective charge of ions fluctuates, and on some parts of the trajectory ions move with higher charge and, consequently, LET. For instance, if the charge of a carbon ion in the vicinity of its Bragg peak is +6 for certain parts of its trajectory, the LET there increases up to 2400 eV/nm. A more accurate analysis of these charge fluctuations is postponed for a future work.

Below we present the results of molecular dynamics (MD) simulations of the temperature spike in the vicinity of a nucleosome, i.e., a DNA fragment wrapped around a histone-protein complex. This unit is of particular interest in connection with a so-called complex DNA damage, which is deemed to be lethal to the cell [15]. The heat spike in the liquid water medium is caused by the propagation of a heavy ion [8]. We consider this effect at that part of the ion trajectory where the LET is the highest, i.e. at the so-called Bragg peak. In the vicinity of the Bragg peak the LET for carbon ions can be up to 900 eV/nm [8].

Figure 1. The structure of nucleosome solvated in a water cylinder 100 fs after heavy ion propagation. Water molecules located within 1 nm from ions track are shown by red spheres. All other water molecules in the system are shown by transparent blue surface.

The crystallographic structure of a nucleosome was taken from the Protein Data Bank (PDB) using the PDB ID 3LEL [16]. The structure of the nucleosome is defined by approximately one-
half of the sequence of human α-satellite constructs NCP147 or NCP146b. These constructs yield the best diffracting crystals to date [17]. Obviously, different nucleosomes have a different sequence of constituting DNA fragments. In the present work we investigate the thermomechanical damage for one particular nucleosome structure assuming that the effects of thermomechanical damage are essentially very similar for other DNA fragments. The original structure in the PDB consists of two nucleosome fragments. Only the fragment with smaller values of the coordinates the along $z$-axis was chosen for MD simulations. The nucleosome was solvated in the water cylinder with the radius of 175 Å and 70 Å in length. Sodium chloride ions with the concentration of 0.15 mol/L were added to the solution and the total charge of the system was equal to zero. A nucleosome has a roughly disk-like shape. The axis of this “disk” was chosen to be parallel to that of the cylinder. The distance from the cylinder axis to the closest atom of the nucleosome was equal to 15 Å. Periodic boundary conditions were applied along the $z$-axis of the water cylinder and repulsive boundary condition were applied on the cylinders $xy$ plane. After the optimization of the system using a conjugate gradient algorithm the system was equilibrated for 33 ps at 310 K using a Langevin thermostat with a damping constant equal to 5 ps$^{-1}$. All the MD simulations presented in this work were conducted using the NAMD software package [18] and the CHARMM22 [19] forcefield. Water molecules were simulated using the TIP3 model [19]. The cut-offs for Van-der-Waals and Coulomb interactions were chosen to be equal to 6 and 11.5 Å, respectively. The switching and pairlist distance for Coulomb interactions were chosen to be 10 and 12.5 Å, respectively. The long-range Coulomb interactions were treated using the Particle-Mesh Ewald algorithm with a box size of 380, 380, and 70 Å along $x$-, $y$-, and $z$-axes, correspondingly. The number of grids in the particle mesh Ewald algorithm was equal to 384, 384, and 96 along $x$, $y$, and $z$ axes, correspondingly. It takes about 15 ps for the shock wave to reach the cylinder boundary for LET= 5000 eV/nm. Therefore, during the first 10 ps after the ion’s passage the effects of scattering of the shock wave from the cylinder’s boundaries can be neglected. In a real cell the volume of the nucleus is densely filled with DNA and protein molecules, and an event of observing only a single nucleosome within the radius of 175 Å form the ion’s track is very unlikely. However, in the present study we investigate the damage of a nucleosome located only 15 Å from the ion’s path. We assume that the presence of other than water molecules in the cell nucleus will have a minor influence on the process of thermomechanical damage.

In this work, we assumed that the deposition of the ion energy into the kinetic energy of water molecules occurs instantaneously. This assumption is applicable in the present work since the characteristic thermalisation time of secondary electrons is smaller than the time needed for the formation of the shock wave being of the order of 50 fs, see reference [20]. We also assumed that most of the ion energy is deposited evenly between water molecules, located not farther than 1 nm from ion trajectory, see [12] for justification of this assumption.

For the simplicity of notations, we will refer to a cylinder (coaxial with the ion trajectory) of radius 1 nm as small cylinder. Then, in order to simulate heating of the medium by the ion, we have increased the velocities of the water molecules in the vicinity of the ion track (see figure 1). The more detailed energy distribution within this hot cylinder would introduce minor corrections to the structure of the shock wave (whose strength was justified in reference [11]) and the energy transferred to the covalent bonds, studied in this paper. Therefore, the heating was modeled by the multiplication of the absolute values of velocities of water molecules in the small cylinder by a certain factor $\alpha$, which was calculated from the following equation:

$$\sum_{i=1}^{N} \frac{(\alpha v_i)^2}{2m_i} = \frac{3}{2} NkT + \int \frac{|dE|}{dx} ,$$  \hspace{1cm} (2)

where $N$ is the total number of atoms in the small cylinder, $v_i$, $m_i$, $k$, and $T$ are the velocity and mass of $i$-th atom, the Boltzmann constant, and the absolute temperature, respectively,
$l$ and $\frac{|dE|}{dx}$ are the length of the cylinder and LET of the ion. In this paper $l = 7$ nm and $\frac{|dE|}{dx} = 900$, 2000 and 5000 eV/nm, which corresponds to the maximum value of the LET for carbon, magnesium and arsenic ions moving in water in the vicinity of the Bragg peak [9], correspondingly.

The molecular dynamics simulations of the heat spike were started using atoms’ coordinates and velocities, recorded after equilibration. The velocities of atoms in the small cylinder were increased by a factor $\alpha$ derived in equation (2). The molecular dynamics simulations were carried out in the NVE microcanonical ensemble using periodic boundary conditions along the $z$-axis of the cylinder. The MD simulations were performed for the first 10 ps after the ion passage using an integration time step of 0.1 fs. We have performed five, three and three independent runs of MD for LET 900, 2000 and 5000 eV/nm, correspondingly.

3. Results and discussion

Let us analyse whether the thermomechanical stress in the DNA fragment caused by the propagation of a shock wave created by an ion can be sufficient to induce the thermomechanical breakage of the covalent bonds in the DNA backbone. The energy of the molecule covalent bonds in the molecular mechanics potential utilized in the present work is described using the following empirical potential, see [19]:

$$U = \sum_{i=1}^{N_b} k^b_i (r_i - r^0_i)^2 + \sum_{i=1}^{N_a} k^a_i (\theta_i - \theta^0_i)^2 + \sum_{i=1}^{N_d} k^d_i [1 + \cos(n_i \phi_i + \delta_i)] + \sum_{i=1}^{N_id} k^id_i (S_i - S^0_i)^2$$

Here the four terms describe the potential energy with respect to variations of distances, angles, dihedral angles and improper dihedral angles between two, three and four neighbouring atoms respectively. The summation in the first term goes over all topologically defined bonds in the system, in the second term over all topologically defined angles, and in the third one - over all topologically defined dihedral angles and in the fourth - over all topologically defined improper dihedral angles.

It is possible to reconstruct the energy of stretching stored in each covalent bond in the system knowing the coordinates of all the atoms as a function of simulation time. This can be achieved using the equation:

$$U_i(t) = k^b_i \left( |\mathbf{r}_1(t) - \mathbf{r}_2(t)| - r^0_i \right)^2,$$

where $\mathbf{r}_1(t)$ and $\mathbf{r}_2(t)$ are the coordinates of two atoms forming the $i$-th covalent bond, $k^b_i$ and $r^0_i$ are the stiffness and equilibrium distance of the $i$-th covalent bond, as defined in equation (4), respectively. Figure 2 shows the energies of stretching of the DNA backbone covalent bonds in the residue closest to the carbon ion trajectory. The results of all independent runs of MD simulations are shown in corresponding graphs of figure 2 simultaneously. The energies are derived from equation (4) and the coordinates obtained from MD simulation. Figure 2 shows that for short periods of time the energy of the covalent bonds stretching in the system can be up to 4.4 eV for LET 5000 eV/nm. The energies of covalent bonds of DNA backbone are $\sim 3.5 \ldots 3.7$ eV, as follows from [21], where the energies of DNA covalent bonds were calculated using density functional theory. One can conclude, that the stress deposited by thermomechanical effects to the DNA backbone is sufficient to break the covalent bonds of the backbone for the case of LET 5000 eV/nm. Note that there is no preferential covalent bond of the DNA backbone to which the energy of the shock wave is deposited. Therefore, it is possible to conclude that the
Figure 2. Energy of stretching of the covalent bonds in the DNA residue closest to the trajectory of carbon ion in the vicinity of the Bragg peak. The notation of different atoms in the residue is shown on the top-left of the graph. The energy of stretching of the bonds is plotted as a function of time calculated from the moment of ion passage. Top-right, low-left and low-center graphs correspond to ions LET 900, 2000 and 5000 eV/nm, respectively. The probability for observing a certain amount of energy in the covalent bonds in the DNA backbone is shown in the low-left graph.

Stresses on the DNA backbone are homogeneously distributed among the bonds being at the same distance from the ion track. The molecular mechanics potential used in the present work does not allow for the breakage of covalent bonds in the system. However, the mean potential energy stored in covalent bonds of DNA backbone during first several picoseconds after ion’s passage is \( \sim 0.19 \text{ eV} \) for the case of LET 5000 eV/nm. Since the energy of the covalent bond is several eV, only a very tiny fraction of the bonds in the molecules can be broken. Therefore, we assume that the effects of bond breakage will have a minor influence on the energy flow in the system, and will address this problem in greater detail in further work.

With the increase of time after the carbon ion passage the fluctuations of the energies of the covalent bonds stretching decrease since the pressure and the temperature in the wake of the wave front are substantially smaller than that at the front of the shock wave. In other words, the most thermomechanical stress to the biomolecule is caused at the moment of passage of the shock wave front through the molecule or directly after it.

In our work we have performed only 5, 3 and 3 simulations for LET 900, 2000 and 5000 eV/nm, correspondingly. For LET 900 and 2000 eV/nm the maximum observed bond energies are \( \sim 0.85 \) and \( \sim 1.6 \text{ eV} \), correspondingly. These values are lower than the DNA covalent bonds energies. However, within single cell nucleus there is a large number of events of ion’s passage close to the DNA molecules. In reference [12], the number of events of ion’s close passage was estimated as being of the order of a few hundreds. It is almost impracticable to perform several hundreds of simulations of heat spikes in order to directly observe the event of bond breakage. However, one can expect that with certain probability one can observe the events of DNA backbone damage by the thermomechanical effects for the cases of LET lower than 5000 eV/nm.
eV/nm [12].

In summary, this paper demonstrates the importance of the thermomechanical mechanism of damage of biomolecules caused by the ion propagation through the biological medium. The reported mechanism of thermomechanical damage should be investigated in greater detail.

4. Conclusions
In this paper we have performed the MD simulation of a shock wave propagating through a nucleosome. The shock wave in the Bragg peak is caused by heating of the water medium during the ion propagation.

We have investigated the cases of LET 900, 2000 and 5000 eV/nm, which correspond to the effective charge of an ion equal to 2.55, 3.8 and 6, respectively.

The results of MD simulations demonstrate that the three-dimensional structure of the nucleosome experiences noticeable deformations. The propagating shock wave 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.

For the case of LET 5000 eV/nm we have observed the events corresponding to deposition of 4.4 eV to certain bonds of the DNA backbone. 4.4 eV is higher than the energy of DNA covalent bonds. Therefore, it is possible to conclude that the DNA molecule cannot sustain such stresses and should be broken. In other words, we observe the event of DNA backbone damage by thermomechanical mechanism.

5. Acknowledgements
A.Y. thanks the Stiftung Polytechnische Gesellschaft Frankfurt am Main for its financial support and appreciates the use of resources at the Frankfurt Center for Scientific Computing. The authors thank the COST Action MP1002 (Nano-IBCT) for the support of the work.

References
[1] Baccarelli I, Gianturco1 F, Scifoni E, Solov’yov A and Surdutovich E 2010 Eur. Phys. J. D 60 1–10
[2] Becker D and Sevilla M 1993 Advances in Radiation Biology vol 17 ed Lett J (Acad. Press) pp 121–180
[3] Becker D, Adhikary A and Sevilla M 2010 Charged Particle and Photon Interactions with Matter Recent Advances, Applications, and Interfaces (Boca Raton: CRC Press, Taylor & Francis)
[4] Sanche L 2005 Eur. Phys. J. D 35 367–390
[5] von Sonntag C 1987 The chemical basis of radiation biology (London: Taylor & Francis)
[6] Adhikary A, Kumar A and Sevilla M 2006 Radiat. Res. 165 479–484
[7] Baccarelli I, Gianturco F, Grandi A, Lucchese R and Sanna N 2007 Adv. Quantum Chem. 52 189
[8] Toulmonde M, Surdutovich E and Solov’yov A 2009 Phys. Rev. E 80 031913
[9] Surdutovich E, Yakubovich A and Solov’yov A 2010 Eur. Phys. J. D 60 101–108
[10] Gerchikov L, Ipatov A, Solov’yov A and Greiner W 2000 J. Phys. B 30 4905–4926
[11] Surdutovich E and Solov’yov A 2010 Phys. Rev. E 82 051915
[12] Yakubovich A, Surdutovich E and Solov’yov A 2011 Nucl. Instr. Meth. B 301 10616/j.nimb.2011.10.069
[13] Barkas W H 1963 Nuclear Research Emulsions I. Techniques and Theory vol 1 (New York, London: Academic Press)
[14] Surdutovich E, Obolensky O, Scifoni E, Pshenichnov I, Mishustin I, Solov’yov A and Greiner W 2009 Eur. Phys. J. D 51 63–71
[15] Surdutovich E, Gallagher D and Solov’yov A 2011 Phys. Rev. E 84 051918
[16] Wu B, Mohideen K, Vasudevan D and Davey C 2010 Structure 18 528
[17] Davey C and Richmond T 2002 Proc. Natl. Acad. Sci. USA 99 11169
[18] Phillips J C et al 2005 J. Comp. Chem. 26 1781–1802
[19] MacKerell A et al 1998 J. Phys. Chem. B 102 3586–3616
[20] Yakubovich A, Surdutovich E and Solov’yov A 2011 Proceedings of the 7th International Conference (ICAMDATA 2010) vol 1344 p 230
[21] Range K, McGrath M and York X L 2004 J. Am. Chem. Soc. 126 1654

7