A PHYSICAL PALETTE FOR ION-BEAM CANCER THERAPY

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For more than ten years, ion-beam cancer therapy has been successfully used clinically in Germany and Japan. Proton-beam therapy is performed in many more centres around the globe. Thousands of patients per year are being treated. These therapies appear to be a more favourable alternative to the conventional photon therapy, also known as radiotherapy [1]. Despite apparent experimental and clinical successes, a comprehensive theoretical description of a physical scenario is missing.

▲ P.21: Man Receiving Electron Radiation Therapy for Skin Cancer over the Eye. ©istockphoto

One reason is that phenomena initiated by an energetic ion incident on tissue happen on many scales in time, distance, and energy. Many thorough papers have been devoted to Monte Carlo simulations of different fragments of the scenario, but they cannot include all scales together because, *e.g.*, time scales for physical processes vary from 10^{-22} s to 1 s. In addition, they do not present the scenario as a hierarchy of phenomena, which is very attractive physically. Our goal is to understand the physics of beam therapy on a microscopic level and, while moving towards this goal, we present a multi-scale approach to the scenario of irradiation with ions.

DNA is disrupted as a result of energy deposition by incident ions, mainly due to ionization of the medium. The secondary electrons formed in this process are considered to be mostly responsible for DNA damage through either direct breaking of DNA strands, or reacting with water molecules producing more active secondaries, or through heating of the medium. In Fig. 1, we depict the schematics of the multi-scale scenario. In our approach, we go through the major phenomena involved in this scenario on different scales.

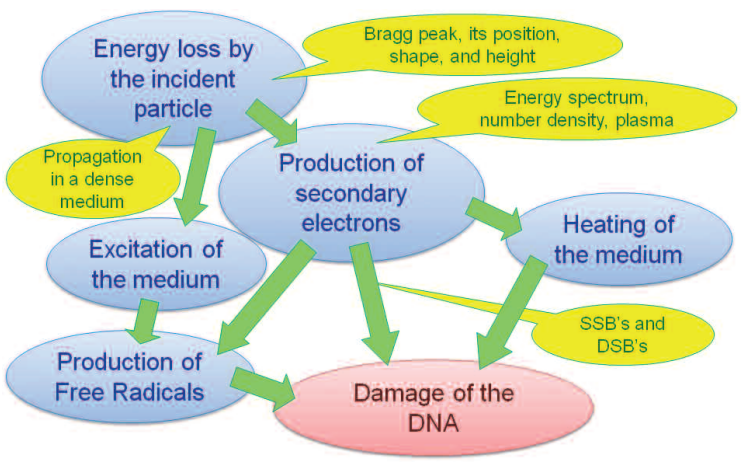
Ion stopping and production of secondary electrons

The advantages of hadron beam therapies are centred on the fundamental difference in energy deposition profile between a massive projectile and a massless photon. The key feature is the Bragg peak: a sharp maximum in the linear energy transfer (LET) of the projectile (see Fig. 2 for an example). This peak results from the fact that the inelastic cross sections sharply increase as the speed of the projectile decreases. It is due to this peak, that the effect of the irradiation on the tissue can be more localized, increasing the efficiency of treatment and reducing side effects.

Position and shape of the Bragg peak are defined by the type of projectile, its initial energy, and properties of the medium. Using information about the cross sections of atomic and nuclear processes as inputs, Monte Carlo simulations [2] predict all characteristics of the Bragg peak. However, their ultimate output is not sufficient since the energy steps are much larger than needed to resolve the microscopic scale.

We have used as an input the singly differentiated cross section (SDCS) of ionization of water molecules (water has been a substitute for the biological tissue) [3,4] and obtained the position of the Bragg peak with a less than 3% discrepancy from both simulations and experiments [3]. In order to achieve this, we corrected a semi-empirical parameterisation of SDCS for relativistic velocities of projectiles and included energy losses due to excitation of the medium. The shape of the Bragg peak is influenced by effects of charge transfer due to picking-off electrons by the initially fully stripped ions (such as $^{12}C^{6+}$) as they slow down, and by projectile scattering. These were included by introducing an effective charge of the projectile and energy straggling (energy spreading due to ion scattering). The resulting shape of our Bragg peak matches the simulated shape if nuclear fragmentation is ignored [3]. Nuclear fragmentation, in the case of carbon ions, is quite substantial and should not be neglected, but so far we have left it for future work. Our calculations [3] are shown in comparison with simulations (ignoring nuclear fragmentation) in Fig. 2.

The SDCS of the energy loss by ions in liquid water taking into account relativistic effects is the cornerstone of ion stopping, the energy spectrum of the secondary electrons, and the production of radicals via excitation of water molecules. The effects represented by the SDCS both define the longest scale related to the ion propagation and provide the initial conditions for the next scale related to the secondaries.



▲ **FIG. 1:** Schematics of the multi-scale approach.

Propagation of secondary electrons and DNA damage

The next scale is defined by secondary electrons. These are produced by ionization of molecules of the medium and by radicals formed as a result of energy loss by the projectile. The maximum energy on this scale hardly exceeds 100 eV and the displacement is of the order of 10-15 nm. The main activity of this scale is diffusion of free electrons and radicals in the medium. Many chemical reactions take place as well; they are also important for estimates of the DNA damage since they

define the agents interacting with the DNA. Again, this aspect has attracted plenty of attention of Monte Carlo simulations adepts [5] who, using various SDCS of ionization (including the effects of the medium [6-9]), trace the electrons and other species through the medium up to their interaction with the DNA. We developed an approach to calculations that can be done on this scale without using Monte Carlo simulations [10,11].

DNA damage, such as a Single Strand Break (SSB), is a result of a sequence of mutually independent events, such as the production of secondary electrons, their diffusion, and the interaction of incident electrons with DNA. We use the energy spectrum of secondary electrons obtained in Ref. [3] and describe their propagation through the medium using a random walk approximation. This is justified since their angular distribution is flat to a first approximation [5]. We also use mean free paths of electrons taken from Ref. [8] and obtain the number of electrons crossing the surface of a cylinder, which represent a single convolution of a DNA molecule. This number multiplied by the probability of a SSB gives the number of SSB's per DNA convolution per ion. The probability of a SSB is taken from experimental data [12], since a complete analysis should include a quantum mechanical treatment of the electron interaction with DNA, which is not feasible at this point. The complete description of this procedure is in Refs. [10,11], and we present some results of this analysis here.

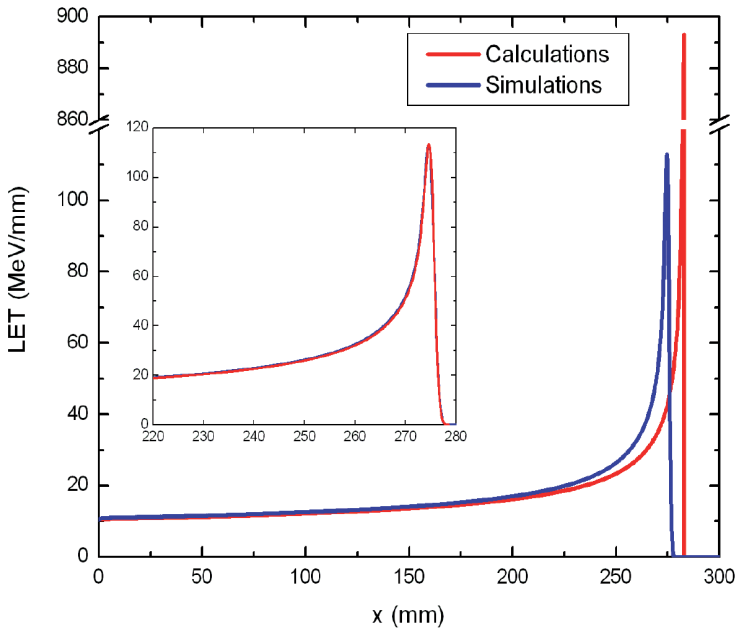
From the most general geometrical configuration presented in Fig. 3 we selected two limiting cases: the DNA convolution being parallel or perpendicular to the ion track. In Fig. 4a, we compare the numbers of SSB's due to the total number of cylinder surface crossings. The difference between the curves is not very significant and all curves due to other possible geometrical situations lie in the shaded area between the curves in this figure. We infer that the geometrical differences are not so important for the final result and that geometrical details of the orientation of DNA segments with respect to the beam may not be so significant.

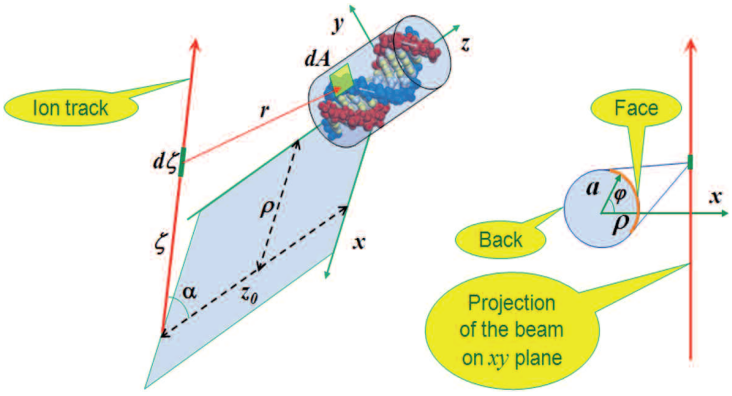
Calculation of the number of Double Strand Breaks (DSB) is more important, since clustered DSB's are irreparable damage. In order to do this calculation, we notice that the measured dependence in Ref. [12] is principally different for more energetic (>5 eV) electrons, for which the probability of a DSB per electron is proportional to the probability of a SSB per electron. This means that most of DSB's are produced by the same electrons or, if an electron breaks a strand, it is much more likely to break another one as well. For less energetic electrons this is unlikely, so the probability of a DSB is proportional to the *square* of the probability of a SSB. This means that the DSB's are produced by different electrons. However, the electron densities used in the experiments of Ref. [12] are about 10^{16} times smaller than those caused by ions in the vicinity of the Bragg peak [3,4]. Therefore we should consider both cases since they may both be important. The results for the DSB's caused by the same electron would be roughly equal to the number of SSB's shown in Fig. 4a divided by a factor of 5. The probabilities of DSB's due to different electrons are shown in Fig. 4b, again for parallel and normal cases. Once again we see that the dependence on geometry may not be so important. Secondaries such as next-generation electrons produced by secondary electrons and free radicals produced by ions after excitation or ionization of the medium can be treated in a similar way.

Complexity of the **geometry of DNA** in **different states** may be **overcome,** because the **geometrical differences** are **insignificant**

Having calculated the probability of a DSB in a convolution located at a certain distance from the beam, we calculate the number of DSB's due to one ion passing through the tissue. In order to do this, we introduce a distribution of cylinders representing convolutions of DNA and sum all their contributions. For our first

▼ **FIG. 2:** The Bragg peak in the Linear Energy Transfer for a single ion, *i.e.*, without scattering, showing discrepancies in depth and height between the calculations and Monte Carlo simulations. In the inset, straggling (but not nuclear fragmentation) is included resulting in excellent agreement between the two.[3].



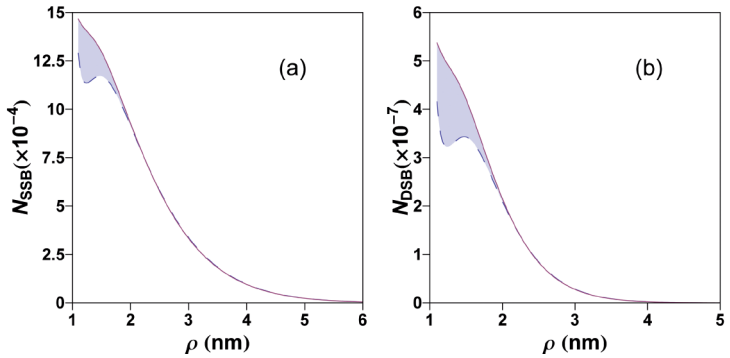


▲ **FIG. 3:** Geometry of the problem. The cylinder represents a single convolution of a DNA molecule, which may have various orientations with respect to the ion track.

estimate, we used the thoroughly studied (experimentally) glial cells, which comprise 90% of the human brain. We have assumed a uniform distribution of DNA inside the cell nuclei in their interphase and calculated that each ion in the vicinity of the Bragg peak passes through about 75 cells causing about 17 DSB's per nucleus. While it is travelling through cell nuclei, it causes 3.3 DSB/μm, comparable to the observations of Jacob *et al.*, [13].

The multi-scale inclusive approach to the physics relevant to ion-beam cancer therapy is aimed at presenting a clear physical picture of the events starting from an ion entering tissue leading to DNA damage. We view this scenario as a palette of different phenomena that happen on different time, energy, and distance scales. From this palette, we choose the major effects that adequately describe the leading scenario and then describe ways to include more details. We think that calculations in this field can be made inclusively without dwelling on a particular scale. Our calculations are time effective and can provide reasonable accuracy. They show that the seemingly insurmountable complexity of the geometry of DNA in different states may be overcome, because the geometrical differences are found to be insignificant. We would like to encourage experimentalists to provide data more relevant to the actual conditions of irradiation, especially on the smallest scales involving DNA damage. This information is vital for further tuning of our approach by selecting and elaborating on the most important aspects of the scenario.

▼ **FIG. 4:** A comparison between the numbers of Single Strand Breaks due to the whole surface of the cylinder **(a)** and Double Strand Breaks caused by separate electrons **(b)** as a function of distance to the DNA convolution in the parallel (blue) and normal (violet) cases, for 20-eV electrons.



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