Ion beams in radiotherapy - from tracks to treatment planning

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Abstract. Several dozen clinical sites around the world apply beams of fast light ions for radiotherapeutical purposes. Thus there is a vested interest in the various physical and radiobiological processes governing the interaction of ion beams with matter, specifically living systems. We discuss the various modelling steps which lead from basic interactions to the application in actual patient treatment planning. The nano- and microscopic scale is covered by sample calculations with our TRAX code. On the macroscopic scale we feature the TRiP98 treatment planning system, which was clinically used in GSI’s radiotherapy pilot project.

1. Introduction
At present about thirty clinical sites around the world apply beams of fast light ions (protons and/or carbon) for the purpose for radiotherapy, and several more are under construction or planned [1]. A major issue of modern radiotherapy is the delivery of a sufficiently high dose to the target volume whereas the exposure of healthy tissue should be kept at a minimum. Fast light ions offer significant physical and radiobiological advantages over conventional photon radiation to achieve this goal, as evidenced for example in GSI’s pilot project on radiotherapy with carbon ions [2]. However, application of high-LET radiation requires sophisticated and efficient dose calculation and optimization procedures to obtain acceptable patient treatment plans. The various steps to achieve this goal will be described bottom-up. Micro- or even nanoscopic description of energy, or, better yet, damage deposition provides important insights into the basic nature of radiation action at a very low level. Radiobiological modelling, for example, relies to a great extent on a sufficiently accurate description of dose distributions in the sub-micron range. The complexity of biological systems, however, usually prevents complete mechanistic calculations of treatment plans due to the lack of knowledge about important parameters. Therefore, macroscopic descriptions of dose deposition and biological radiation action are currently the methods of choice for radiotherapeutical applications. Various aspects of dose optimization will be discussed and last but not least means of experimental validation will be presented.

2. Ion tracks - first principles
In view of the stochastic nature of the basic ion-matter interactions it is tempting to use nanoscale calculations based on the Monte Carlo method to describe energy - or better: damage deposition at the lowest possible level. Various such attempts exist, for example the code
PARTRAC [3] which is dedicated to describing DNA damage or the GSI grown TRAX [4, 5], suited for general calculations on ion track structure and many more related quantities. These codes apply a set of cross sections for elementary interactions, typically elastic scattering, ionization, excitation, in contrast to traditional approaches relying on "condensed random walk", as introduced already in the 1960s [6]. Figure 1 for example shows simulations of $\delta$-electrons created by ions of various energies. This representation, however, exhibits only the interaction

Figure 1. Paths of $\delta$-electrons created by ions of various energies in water, simulated with TRAX. The dense emission pattern of low energy ions can be seen. The path segments are coloured according to electron energy. Most electrons have very low energies too, below 100eV. The inserted DNA schematics shows the scale of the simulation, i.e. nanometers.

Figure 2. Microscopic dose deposition of low and high-LET radiation. The circle indicates a cell nucleus.

geometry of single tracks in relation to sensitive structures like the DNA. A more realistic
scenario is depicted in figure 2, where the small-scale energy deposition pertaining to the same macroscopic dose ($\approx 1$ Gy) is simulated for radiation of different ionization densities. Low-LET radiation yields an almost homogeneous distribution, whereas stopping particles ($^{12}$C at 15 MeV/u) show track cores with local doses in excess of 10 Gy. Given that biological systems usually respond linear-quadratically as a function of dose, it does not come as a surprise that such high-LET radiation will have an elevated biological effect and thus will be suited as a means for radiotherapy.

With the ability to describe the physical radiation action on the micro- or even nanoscopic level, it might be tempting to describe also the biological action from the first principles. One of the problems of classical microdosimetry, however, is that there is no obvious link from physical dose distributions to resulting biological damage, and this is also true for most if not all models relying on basic physics alone. Figure 3, for example, exhibits a "show stopper": Survival curves after exposure to various kinds of radiation were measured for two widely used cell lines, one being a repair-deficient mutant of the other, so only a few genes are different. That is, the physics is the same, but the biological outcome is entirely different. Nevertheless several groups attempted a mechanistic modelling approach towards a realistic description of biological damage. For an exemplary but incomprehensive list, we refer to a dedicated topical issue [7] as well as to other contributions in the present issue. For example, the complex chemical stage has been included [8] and after reproducing simple plasmid DNA double strand breaks [9] even repair mechanisms [10] have been considered. However, for reaching the predictive power required in the clinical stage, i.e. predicting arbitrary biological endpoints for entire organs a priori, several more years of experimental and modelling efforts would be necessary.

![Figure 3](image-url)

**Figure 3.** Response (cell survival) of repair-deficient XRS-5 vs repair-efficient CHO-K1, for x-rays and $^{12}$C ions with the indicated energies [12].

### 3. Radiobiological modelling in treatment planning

For all ions heavier than protons (and, strictly speaking, even for protons) the inclusion of radiobiological effects, such as survival probabilities and biologically effective dose, into regular treatment planning is indispensable. Figure 4 illustrates the typical response of a cellular system to different types of radiation. Cell survival, $S$, usually is described as a linear quadratic dose response, $-\ln S = \alpha D + \beta D^2$, with coefficients $\alpha, \beta$ depending on cell type, biological endpoint and type of radiation (ion species). The Relative Biological Effectiveness, RBE, is defined as the ratio $RBE = D_x/D_{ion}$ of a reference (i.e. photon) dose, $D_x$, to an ion dose, $D_{ion}$, leading to the same effect. As figure 4 illustrates, RBE is not a fixed property of the respective radiation, but
rather depends on the chosen survival level and hence on the absorbed dose. The target quantity for treatment planning is the RBE-weighted dose, sometimes also called "biological dose", \( D_{\text{bio}} \), connected to the absorbed (or physical) dose via \( D_{\text{bio}} = RBE(D_{\text{abs}}) \times D_{\text{abs}} \). As mentioned,

![Figure 4](image1)

**Figure 4.** Definition of the RBE on the basis of survival curves for CHO cells exposed to different kinds of radiation. The dependence of RBE on survival and dose level is clearly visible.

a full, bottom-up nanoscopic modelling of radiation damage for the purpose of radiotherapy does not appear to be feasible in the near future. Given the dependence on a multitude of parameters, a pragmatic approach like the one taken in the GSI pilot project is to be preferred. In these kinds of approach, nevertheless, the nanoscopic modelling still plays a relevant role, in describing the physics up to a certain scale, to the highest possible detailed level. In fact, a crucial quantity here is the detailed description of dose deposition around an ion path which is represented by radial dose distributions, a collection of which is shown in figure 5 for various ion energies. The complex biological radiation action can be described by the versatile Local Effect model (LEM) \([13, 14]\). It is so far the most successful radiobiological model in clinical use in radiotherapy. Its principles are illustrated in figure 6.

The basic assumptions are that at the local level the radiation damage by sparsely ionizing photon radiation is the same as for ion radiation, and that the cell nucleus is the sensitive target. It should be noted that in its most recent versions, the LEM includes more mechanistic details, such as the spatial distribution of double strand breaks and clustering effects \([11]\).

These assumptions allow us to separate the difficult biological aspect of the problem from the purely physical one. The former is represented by the empirical photon dose response curve, \(-\ln S = \alpha_x D + \beta_x D^2\), the latter by the microscopic radial dose distribution, \(D(r)\). \(\alpha_x, \beta_x\)
usually can be derived from a rich set of experimental data, not only for cell systems in vitro, but also for complete organs in vivo. Combining these main ingredients by integrating the dose response over the cell nucleus yields the response of a cellular system when exposed to ions of a particular type and energy, $-\ln S = \alpha_z D_z + \beta_z D_z^2$, where $D_z$ is the specific energy deposited in the cell nucleus. It should be emphasized that LEM only provides intrinsic $\alpha_z, \beta_z$ for single monoenergetic particle traversals in the first place. Computation of biological effects in complex radiation fields, as they are common in radiation therapy, is the task of the treatment planning system (TPS), such as GSI’s TRiP98 [5, 15]. This task, i.e. to determine the coefficients $\alpha_D, \beta_D$ in $-\ln S = \alpha_D D + \beta_D D^2$ in each voxel of the irradiated tissue, is not trivial, but two solutions exist, a ”classical” one, described in [16], and a much faster approximation in [17]. Once $-\ln S$ is known, all other quantities, including RBE, can be deduced.

\[ -\ln S = \alpha_D D + \beta_D D^2 \]

Figure 6. Illustration of the LEM principles: experimental photon dose response combined with radial dose distributions around an ion track on a cell nucleus yields survival curves.

4. Beam application and dose optimization
Apart from the ion accelerator, the centrepiece of a modern ion beam delivery is a magnetic raster scanner (figure 7), pioneered by the GSI pilot project [18]. These devices provide completely active dose delivery by means of lateral magnetic deflection of pencil beams with a selectable FWHM in the range of 4 to 10 mm. Energy variation of the ion beams by the accelerator allows us to cover penetration depths up to 30cm in water without energy degraders, typically in \( \approx 250 \) steps. A typical single treatment field thus may comprise as many as 50000 individual pencil beam spots organized in \( \approx 50 \) different energy slices. One of the main tasks of treatment planning is to determine the number of particles, $\bar{N}$, within each pencil beam so that the resulting RBE-weighted dose distribution,

\[ D_{bio}(\bar{x}, \bar{N}) = D_{abs}(\bar{x}, \bar{N}) \times RBE(\bar{x}, \bar{N}). \]
matches the medical prescription. Mathematically this can be formulated as a least-squares minimization problem, which reads in simplified form (omitting weight factors):

\[ \chi^2 = \sum_{\vec{x}_{\text{target}}} (D_P(\vec{x}) - D_A(\vec{x}))^2 + \sum_{\vec{x}_{\text{OAR}}} (D_{\text{OAR}}(\vec{x}) - D_A(\vec{x}))^2 \times \theta(D_A(\vec{x}) - D_{\text{OAR}}(\vec{x})) = \text{min.} \quad (2) \]

where \(D_P(\vec{x})\) and \(D_A(\vec{x})\) are the prescribed and actual dose distribution, respectively, and \(D_{\text{OAR}}(\vec{x})\) is the maximum allowed dose level in the Organs at Risk (OAR). \(\theta\) denotes the Heaviside function, its purpose is to impose a penalty if \(D_{\text{OAR}}(\vec{x})\) is exceeded, but to do nothing if the actual dose is below that limit. The sum runs over all voxels in the target and the OAR, respectively. The solution of equation (2) is not trivial due to the nonlinear dependence on \(\vec{N}\) and the constraint term, but can be achieved by appropriate iterative algorithms implemented in the treatment planning system (TRiP98, [19]).

Sample distributions of the resulting particle numbers \(\vec{N}\) are shown in figure 8. They are necessarily inhomogeneous to account for the preirradiation of proximal slices by distal ones.

5. Patient plans and dose verification

Figure 9 shows a resulting patient plan. The high selectivity of carbon ions together with the sophisticated dose optimization procedure allows to cover the tumour volume with the prescribed dose and to spare the OAR to a high degree.

The validity of actual patient plans is usually verified by measuring the absorbed dose distributions in a water phantom [20]. A plan will be accepted if measured and TPS-predicted dose distributions differ by no more than a certain amount, five percent being a typical value.

The ultimate goal of radiotherapy, however, is to achieve a biological effect rather than just delivering an absorbed dose distribution. Thus, it is a good idea to verify the TPS calculations by means of biological dosimetry, i.e. by measuring cell survival distributions after irradiation. Since
this is not possible for each patient in vivo, a so-called Bio-Phantom (figure 10) was developed at GSI which is used to verify typical treatment situations under patient-like conditions.

**Figure 10.** The biophantom device used to measure cell survival distributions. It consists of a vessel with \( \approx 30\text{cm} \) diameter, filled with medium. Cells are deployed on a set of plastic slabs submerged in the medium at well-defined positions, thus serving as a two-dimensional detection system. The whole setup is positioned on the couch and irradiated the same way as a patient.

Figure 11 shows a biodosimetry example for a 2-field optimized plan, a C-shaped target volume wrapping around an assumed OAR. Although CHO cells are not direct surrogates for human tissue, both biological systems follow the same rules as far as radiation damage is concerned, and thus CHO can serve well for the purpose of biological verification of complex irradiation plans.

**Figure 11.** Top view of two-dimensional survival distributions of Chinese hamster ovary (CHO) cells, measured with the Bio-Phantom (left) and calculated with the TRiP98 TPS (right). Comparison by colour shows the agreement between measurement and calculation. The numbers associated with the different colours denote the surviving fraction.

### 6. Conclusion and Outlook

We have described the various steps which lead from a microscopic picture of radiation action to "real life" applications, i.e. patient treatment with ion beams. The described models and methods were successfully applied in the treatment of more than 430 patients from 1997 to 2008 in the GSI pilot project. Follow-up projects like HIT and CNAO are now applying these methods on a larger clinical scale.

TRiP98 and following releases of the TPS are well suited to serve as research prototypes for ion-beam radiotherapy planning, in particular for 4D treatment [21], as well as for so-called "Adaptive Treatment Planning", aimed at the improvement of dose optimization in case of rapid spatio-temporal variation of organ geometry or tumour radiosensitivity. As an example for ongoing research, figure 12 shows model calculations on the so-called Oxygen Enhancement Ratio (OER), which is a measure for the radio-insensitivity of tissue with reduced oxygen content. The TPS is currently enhanced to provide compensation for this "oxygen effect" [22].

At the other end of the scale, the TRAX simulation code will be enhanced towards lower distances, since the track core plays an important role in radiobiological modelling. Figure 13 shows radial dose distributions followed to lower distances in various scenarios [23]. Due to a
lack of experimental data in condensed phase, however, an independent verification currently is difficult.

Lower distances are inevitably related to lower $\delta$—electron energies. Thus we also strive towards better low-energy cross sections and towards target materials other than water, in context with the efforts to measure low-energy electron emission from condensed matter with the GSI Toroid spectrometer [24].

Figure 12. Oxygen enhancement ratio as a function of depth (with relative oxygen content as a parameter) for carbon and oxygen ions delivering the same dose to the entrance tissue. The shaded area indicates a potential target volume. For very high-LET radiation (i.e. stopping oxygen ions) the OER approaches unity, i.e. the oxygen effect vanishes.

Figure 13. Experimental radial dose distribution (in gaseous medium) compared with TRAX simulations (in water) under various assumptions. Accounting for the small-angle elastic scattering of the primary ions results only in small differences to the classic calculations. In contrast, inclusion of radical diffusion, which is present in living systems, significantly affects the radial dose distribution.

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