More Ions for Radiotherapy: About Treatment Planning and Track Simulations

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Abstract. In the recent years, irradiation with swift light ions - from protons up to oxygen - has become an established method in tumour radiotherapy. A prerequisite for successful treatment is the sufficient knowledge of physical and radiobiological processes down to the microscopic or even nanoscopic scale. This report summarizes recent developments. In particular, the application of ions other than protons and carbon will be addressed, as well as modelling approaches on the nanoscale.

Introduction
Most advanced facilities for particle radiotherapy nowadays offer the great advantage of active beam scanning, allowing to implement Intensity Modulated Particle Therapy (IMPT), in analogy to IMRT.

In order to exploit these advantages, specific treatment planning tools are required. GSI's home grown TRiP98 treatment planning system (TPS) matches these requirements, comprising calculation and optimization of absorbed as well as RBE weighted dose distributions. Developed for and clinically used during the GSI carbon ion radiotherapy pilot project [1, 2], it is now used as a research tool within as well as outside GSI. Some of our latest developments will be reported in the following.

More Ions for Radiotherapy
The vast majority of ion beam radiotherapy sites nowadays run proton beam lines. A few of them also offer carbon ion beams, either exclusively or as a viable alternative to protons. There is, however, a growing interest to investigate other light ions. Oxygen ions for example have a somewhat higher LET than carbon in their stopping region, which might be an option to combat hypoxia. This comes, however, at the price of an increased RBE already in the entrance channel. A particularly attractive option would be Helium ions. Their physical and radiobiological properties place them between protons and carbon ions. Compared to protons, they offer a significantly reduced lateral scattering. Compared to carbon ions, their RBE is generally lower, which makes them more suitable for pediatric tumours, where late side effects are a concern. They also generate less nuclear fragmentation when traversing matter. Helium ions are already available for research purposes at HIT (Heidelberg, Germany) and are pondered as a possible replacement for protons there and at other multi-ion sites such as CNAO (Pavia, Italy).
In order to enhance our TPS also for these new modalities, we have incorporated helium as primary ions in our transport model [3]. The most essential inputs are the total nuclear reaction cross sections for the most important target constituents of biological matter, H and O, respectively.

Unfortunately, experimental data so far only exist at very low and at very high energies. In the intermediate range of therapeutical interest, i.e. around 200 MeV/u, no data were available, so one has to rely on semi-empirical nuclear reaction models. We found that the formulae of Tripathi [4] match best the data available at both ends of the energy scale and make reasonable predictions in the therapy range (Figures 1a, 1b). The reaction cross sections were verified by beam attenuation measurements in thick water targets [3]. Beyond the physical validation radiobiological verification is of utmost importance. We use the Local Effect Model version IV [5] to predict radiobiological quantities such as clonogenic survival and RBE. In Figure 2 we report experimental results for our model system, a CHO-K1 cell culture, together with TPS predictions. Comparison of the different contributions, i.e. primary beam exclusively or in combination with the various created nuclear fragments, shows that the most important effect arises from the primary ion. Fragments play only a minor role, at least in the target region.
3. Hypoxia and Radiotherapy

Many tumours have hypoxic regions in their interior. Lack of oxygen supply generally reduces radiosensitivity. A measure for hypoxia is the so called Oxygen Enhancement Ratio (OER), defined in a similar fashion as the RBE, i.e. as the dose ratio for the same survival level for hypoxic and normoxic cells, respectively. For a given dose level hypoxia may cause a significant reduction in tumour control, since malignant cells may not be eradicated fully and subsequently the tumour may recur. A brute force countermeasure would be the escalation of the overall biologically effective dose, however, this is often limited by the tolerance of the healthy tissue. Here high-LET radiation such as ion beams could be a more intelligent countermeasure. This is because it turns out, that the OER as a function of dose-averaged LET decreases with increasing LET and drops to almost unity in the stopping region of ion beams [6]. Figure 3 depicts this dependency. OER can be parametrized as a relatively simple function of dose-averaged LET, which enables us to introduce OER into the dose calculation and optimization engine of our TPS, on top of conventional RBE handling [6].

![Figure 3](image)

**Figure 3.** OER as a function of LET, with the partial oxygen content as a parameter. Symbols represent measurement, curves are model calculations [6]. The shaded areas indicate the range of dose averaged LET for various ions for a typical target depth of 65 to 105mm.

The correctness of this computational procedure has been verified with home grown so called hypoxia chambers, allowing to irradiate cell cultures in medium under controlled oxygenation conditions (Figure 4). Carbon ion irradiations with two opposing fields show, that OER not only can be predicted in effective dose calculation, but also can be used as a driving force to restore the prescribed survival distribution [6]. We thus coined the term "Kill Painting", in analogy to "dose painting" and "LET painting". We believe, however, that our Kill Painting approach is the superior one, since it aims directly at the (non-)survival of the biological system, rather than intermediate quantities like absorbed dose or LET.
4. Track Simulations

Simulations on the microscopic or even nanoscopic scale offer the possibility of a deeper understanding of radiation effects. Our tool for this purpose is the home grown TRAX simulation code, originally developed to describe ion tracks together with the emitted secondary electrons. It follows the usual Monte Carlo principles implementing the single interaction approach rather than condensed random walk [7]. To this end we have enhanced the code with the inclusion of radiation chemistry, i.e. creation, diffusion and recombination of radicals and other chemical species taking place after the initial physical interaction. Special emphasis is on reactive oxygen species, motivated by the similarity of the LET dependency of OER and G-value, respectively.

Dose enhancement by nanoparticles is another currently hot topic. While there is sufficient evidence for biologically efficient enhancement under photon radiation, the picture is less clear for ion radiation. In-vitro survival measurements and in-vivo tumour control results are not always consistent, and seem to depend on a variety of parameters. At least on the physics side TRAX simulations could contribute to the estimation of the magnitude of the effect. To this end we have used our set of metal cross sections to simulate proton-induced creation and escape of secondary and Auger electrons from metallic nanoparticles and their effect on local dose distributions (Figure 5). Apparently dose enhancement by ions is a very local effect, restricted to the close vicinity of the nanoparticle, and much less prevalent than in the photon case.

Figure 4. Upper picture: experimental setup. Lower picture: Survival in a two-field carbon ion plan.
5. References
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