Project co-funded by the European Commission within the FP7 (2007 – 2013)
Grant agreement no.: 228436

ULICE
Union of Light-Ion Centres in Europe

Project type: Combination of CP & CSA
Integrating Activities / e-Infrastructures / Preparatory phase
Start date of project: 1st September 2009 Duration: 48 months

D.JRA 5.3, 5.4, 5.6 – TRiP version including hypoxia – combined report including:
D.JRA 5.3 – TRiP version including spatially variable radio-sensitivity (hypoxia);
D.JRA 5.4 – Protocol for replanning steps due to temporal variation on radio-sensitivity;
D.JRA 5.6 – Table of pre-conditions eligible for multi-ion treatment

Delivery date: M 28 2011/12/31

WP n° and title: WP 5 – Adaptive Treatment Planning for ion radiotherapy
WP leader: Michael Krämer
Reporting period: 2nd

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LIST OF ABBREVIATIONS AND DEFINITIONS

AHF Alper Howard-Flanders model
BED Biological Effective Dose
CHO Chinese Hamster Ovary cells
CT Computer Tomography
DICOM Digital imaging and communications in medicine
DNA Deoxyribonucleic acid
FDG $^{18}$F-Fluorodeoxyglucose
FMISO $^{18}$F-Fluoromisonidazole
GSI Helmholtzzentrum für Schwerionenforschung
GyE Gray-equivalent (unit of biological effective dose)
HRF Hypoxia Reduction Factor
IES Isoenergetic Slice
LEM local effect model
LET linear energy transfer
LQ linear quadratic model
MFO Multiple Field Optimization
OAR organ at risk
OER Oxygen Enhancement Ratio
PET Positron Emitting Tomography
pO2 partial oxygen pressure
RBE Relative Biological Effectiveness
RT Radiotherapy
SFO Single Field Optimization
SOBP Spread out Bragg peak
SUV Standardized Uptake Value
TPS Treatment Planning System
TRiP98 Treatment Planning system for Particles
VOI volume of interest
voxel volumepixel
wepl water equivalent path length
PUBLISHABLE SUMMARY

Hypoxia is one of the most common causes of increased radioresistance in cancer radiotherapy. Even with ion beam irradiation the problem of tumor areas where the oxygen concentration is abnormally low, seems to represent an extremely hard task to overcome. New avenues are now opening for facing this problem, since PET-tracer imaging techniques of different oxygen concentrations are becoming available. Despite present technical limits, these techniques are promising to provide soon an oxygenation map of the target tissue area and consequently will open the door to possible tuning of the treatment accordingly. What is needed now is a way to implement this information, as soon as it will become available in specific ion beam treatment planning.

The present part of the ULICE project is dealing with this task. In the present report, the three deliverables related to OER based TRiP98 implementation have been summarized (5.3, 5.4, 5.6). A simple parametric model is presented, based on an extension of the Alper Howard-Flanders formalism, for getting the two-dimensional dependence of the OER to the LET of the irradiation mean and the oxygen concentration of the tissue. This provides initial OER tables to be input in the code. On the other side, the program is extended in order to handle with OER in the biological dose calculation and to deal with an “isoeffective dose in the presence of hypoxia”. Following the modular structure of TRiP98, the implementation is made in order to allow the input of different OER tables (stemming from different models or experiments) without loss of functionality.

As a result, a first version of TRiP98-OER able to perform forward and inverse planning, including OER-driven optimization, in single and multiple field modality, is presented and comparison to dedicated experiments performed at GSI are reported and discussed. Comparisons with other models for the OER tables generation and their outcome after input in TRiP are also reported and discussed. Furthermore, from the collected results, on the basis of different LET contributions, it is possible to draw preliminary estimates on the outcome of a multi-ion treatment. Finally the software set-up for converting and including clinical PET data is also presented.
CONTENTS AND SPECIFIC DOCUMENT STRUCTURE

1 Introduction

The reduced concentration of oxygen in cells (hypoxia) results in a significant lower cell death rate after irradiation. This situation is often verified in clinical cases and it is related to insufficient blood supply compared to the consumption; it may occur for several reasons in partial areas of a tumor tissue, and according to that may result in different effects. An acute hypoxia is induced by a perfusion limit for a transiently occluded blood vessel, while a chronic hypoxia is generated by a diffusion limit from the vessels walls to the given cells [1]. The microscopic source of this effect is mainly due to the quenching of the DNA damage mechanism mediated by free radicals [2, 3], which are able to fix the biological damage and make it permanent. Since the relative importance of the latter mechanism, compared to the overall damage, is related to the quality of radiation and, in general, to the linear energy transfer (LET), this effect is also LET dependent [4]. This has been explained as a track density effect [5]: in fact, in high density tracks (corresponding to high LET) a recombination process of the generated radicals is likely to occur and it was clearly observed an increase in molecular species yields as well as a corresponding reduction of radical ones [4]. Thence, ion beam irradiation allows, in principle, a drastic reduction of this effect and promises a solution of the hypoxia problem [6].

Hypoxia induced radioresistance is quantified by the parameter oxygen enhancement ratio (OER), defined as the ratio between the radiation dose at a given (reduced) concentration of oxygen and the radiation dose in fully oxygenated conditions (air) that produces the same level of biological effect, i.e.:

\[ \text{OER}_p = \frac{D_p}{D_a} \left|_{\text{same effect}} \right. \]

with \( D_a \), dose in aerobic conditions (characterized by an oxygen partial pressure \( p_a \sim 20\% \)) and \( D_p = D(p) \) isoeffective dose at given hypoxic condition, with \( p < p_a \).

In reality, the conditions sufficient to completely damp this increased radioresistance (down to OER \( \approx 1 \)) are verified only at relatively high LET, i.e. even for ions like carbon, eventually in small portions of a spread out Bragg peak (SOBP) close to the distal end. There is no way at the moment to quantify this dependence, as well as there is no treatment planning system (TPS) for ions equipped with this feature.

1.1 Methods to measure hypoxia

The idea of a “tuned” irradiation of tissues with differently oxygenated areas relies on the possibility to measure this quantity with reasonable spatial and temporal resolution. This issue is at the present time still far to be completely solved.

Cell experiments as the one available at GSI [7], allow a precise conditioning “by construction” (see Section 4 “Experimental verification”) of the target tissue oxygen concentration, while in vivo and patient studies, present of course different limitations.

The golden standard for oxygen pressure measurements in vivo is represented by the Eppendorf probe [8, 9], a polarographic needle which allows a simple electrochemical measurement of the \( \text{O}_2 \) activity of a tissue at the position of its penetration. This provides very precise results [9], but implies obvious counterindications in patient cases because of its invasive nature.

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The major efforts of the imaging community are thus directed to PET tracers. The most used in clinical practice is currently $^{18}$F-Fluoromisonidazole (FMISO), but also $^{18}$F-Fluoroazomycin (FAZA) and $^{64}$Cu-diacetyl methyl-thiosemicarbazone (Cu-ATSM) are object of intensive investigation. For an extensive review see [10–12].

Other imaging possibilities which have been suggested rely on functional magnetic resonance imaging, f-MRI [13], but showed to be too much affected by farmacokinetical models and at the moment are stacked at a very early stage of development.

For PET tracers, one of the key problem is that the relation between uptake and effective oxygen content is not easily retrievable. Some tentative models in this direction have been provided [14] and also calibrations with Eppendorf measurements [15], but are still far to present a reliable correlation. More details on the hypoxia imaging possibilities and related problems are available in deliverable reports D.JRA 3.2-3, and D.JRA 3.5.

### 1.2 Adaptive treatment planning: state of the art

The problem of adapting the treatment to differently oxygenated areas has been tackled from different sides, mainly for IMRT irradiation, and analysing the results in terms of tumor control probability (TCP) [14, 16, 17].

Different methods have been developed, and they are mainly described by Thorwarth et al. [18–20] and Sovik et al. [21–23]: Dose painting by numbers (DPBN) and by contours (DPBC), being respectively a method to define subvolumes of different level of hypoxic condition to be irradiated with different doses, and a pixel by pixel based dose coverage of the irradiated volume.

An alternative method has been suggested very recently as “LET painting” explicitly suited for ion beam irradiation, trying to take advantage of the different LET composition of the extended Bragg peaks of ions [24].

To the best of our knowledge, in any case the two quantities (LET and $pO_2$) have never been considered explicitly simultaneously.

### 2 OER modeling

The first question arising when attempting to model the OER dependence regards the choice of the parameters which have to be considered. A rigorous analysis would lead to the inclusion of several of such parameters: oxygen pressure in the hypoxia, oxygen pressure in the corresponding fully aerated condition, LET, survival level, projectile type, tissue, cell cycle, etc. In our analysis we had to decide at least for the start to reduce at the minimum the number of parameters. Given the modular structure of TRiP, a finer refinement including larger dependence will always be possible. Following a literature survey and fresh GSI measurements [25], it was decided to start with a simple bidimensional parametrization of the OER as a function of LET and $pO_2$ of the hypoxic tissue. Experimental data on OER measurements are quite poor and are either available for photons at several different levels of $pO_2$, either for ions only in fully anoxic conditions ($pO_2 = 0$). A comprehensive collection of these experiments is reported in tables on Refs. [26, 27].
2.1 \( pO_2 \) dependence

The first dependence to be mapped is naturally the \( pO_2 \) one. For that, we decided to extend for every LET level the dependence at asymptotically low LET, i.e. in the case of photon radiation. For this case in the corresponding photon studies [21, 22] it is universally used the parametrization provided by Alper and Howard-Flanders (AHF) [28], who, on the basis of several experiments, describe the relative radiosensitivity \( RR \) at a given concentration of oxygen \( p \), i.e., the ratio of the sensitivities respectively in that condition, \( RS(p) \), and in total absence of oxygen, \( RS(0) \), with the formula

\[
RR(p) = \frac{RS(p)}{RS(0)} = \frac{Mp + K}{K + p} \tag{2}
\]

where \( M \) is a maximum effect (generally found, for different cell lines, to be \( M \sim 3 \)) and \( K \) the concentration corresponding to a half maximum sensitization. Then, considering that \( RS(p) \propto 1/D(p) \), from the eq. 1 the OER may be expressed with a slight approximation in a similar way

\[
OER(p) \approx M/RR(p) = \frac{Mb + p}{b + p} \tag{3}
\]

with \( b = K/M \) (see fig. 1).

We want here to point out that some authors, especially in recent literature (e.g. [27]), prefer to adopt for this quantity the term “Hypoxia reduction Factor” (HRF), giving emphasis to the fact that the varying quantity is the pressure (and thus the required isoeffective dose) of the hypoxic phase with respect to the fixed dose required in full oxygenation, while leaving the term OER to its historical conception and thus to a ratio where the varying dose is in the oxic phase, while the reference is taken as the dose in total anoxic \( (p = 0) \) conditions. To avoid confusion we stress that the quantity which we will deal in this report will be always the one defined in eq. 1.

Figure 1: OER dependence on oxygen concentration derived from AHF model [28].
2.2 Survival level dependence

In principle all OER experimental data are reported as a function of the survival level $S$ (or of the dose $D$), and according to the linear quadratic model (LQ)

$$- \ln S = \alpha D + \beta D^2$$

with $\alpha$, $\beta$ general parameters, the OER dependence should be:

$$OER(S) = D_p(S) / D_a(S) = \sqrt{\alpha_p^2 - 4\beta_p \ln S - \alpha_p \beta_a / \beta_p},$$

thus, in general, dependent on $S$ (or alternatively, the same dependence may be expressed on the dose $D$). It is object of debate from several years if this dependence should play a role or not, since it is known for example that the sensitization effect on $\beta$ is different from that on $\alpha$ and even some studies report a non negligible result [29]. A very recent paper also attempt to systematize these data and to estimate a small correction factor for neglecting this dose dependence in clinical cases [30]. Nevertheless it was clear from most of the literature that if an effect should be accounted, it will be not relevant as for example it happens markedly with RBE. Thus, in first approximation, a dose modifying factor $OER$, at any survival level, could be accounted. E. g. Carlson [31] showed that even if an independent fit of an hypoxic and a normoxic curve will lead in general to a dose dependent OER factor, it is possible to perform a different fit with the additional constraint of imposing a dose modifying factor, i.e.:

$$\begin{cases} - \ln S_a = \alpha_a D_a + \beta_a D_a^2 \\ - \ln S_p = \alpha_p D_p + \beta_p D_p^2 \end{cases}$$

fixing $\alpha_p = \alpha_a / OER$; $\beta_p = \beta_a / OER^2$;

with an almost negligible deviation in the resulting curves compared to the experimental uncertainties (see fig. 2). And substituting the introduced parameters in the eq. 5, one gets of course $OER(S) = OER, \forall S$.

This allows us to safely neglect, at least for the initial input tables, this effect; always keeping the possibility, as mentioned at the start of this section, to reintroduce it in finer tables, or to correct the outcome with the estimation provided in [30].

2.3 LET dependence

As for the LET dependence, we decided to map explicitly its dose averaged value, where the dose averaged LET is defined as

$$\langle LET \rangle_D = \frac{\sum_i LET_i D_i}{\sum_i D_i} = \frac{\sum_i LET_i^2 F_i}{\sum_i LET_i F_i}$$

while the track averaged LET is a simpler average on the fragments’ respective fluences $F_i$.

$$\langle LET \rangle_T = \frac{\sum_i LET_i F_i}{\sum_i F_i}$$
It was shown that dose averaged LET is a better descriptive quantity of the radiobiological effect of an ion which is producing a mixed beam [32].

Firstly the other asymptotic condition was considered, i.e. $p_{O2} = 0$. This condition (pure anoxia) is not really interesting in clinical practice, since is mostly related to already dying cells, while the “hypoxic fraction” at intermediate levels of oxygen is most dangerous. Nevertheless it is useful to describe the maximum effect, and it is also the condition where most experiments are available. For our purposes, then, we used the large Japanese dataset published in 2000 [33], with several OER measurements e.g. for the V79 tissue and where it is shown a very slight dependence on the ion type (more pronounced for the lighter ones). In fact results for ions as different as carbon and neon lead to a difference which is quite small as compared to the experimental spread of the data. Moreover the tissue dependence has also been shown to be relatively small, and this allows us to take as a primer the current table also for modeling different cell types.

Then the OER data at $p_{O2} = 0$, for 10% survival as a function of LET were fitted with a form similar to the AHF one but where, in order to reproduce the steeper fall-off towards higher LET, we introduced an additional parameter $\gamma$:

$$OER_0(LET) = \frac{M_0a + LET^\gamma}{LET^\gamma + a}$$

with fitting parameters found to be $a = 8.27 \cdot 10^5$ and $\gamma = 3.0$.

A further confirmation of the validity of the dose modifying approximation arises from the analysis of these data and specifically comparing the fit obtained on the 10% survival data with the other data reported in that collection [33] (see fig. 3).

Other intensive experiments of heavy ions with hypoxia were reported by the Berkeley group [37] and Rijswyk/London [38] but since data reported are vs. track averaged LET and not dose averaged, a comparison is not straightforward and too sensitive to experimental errors.

**Figure 2:** Survival dependence of OER: left panel, independent fit of aerobic and anoxic data (solid curves) and simultaneous fit (dashed lines) with the dose modifying constraint (eq. 6); right panel, corresponding OER values. (Experimental points not shown for clearness. Redrawn and adapted from Ref. [31]).
Figure 3: LET dependence of OER obtainable from Japanese experiments [33]: left panel, OER resulting data at different survival levels and compared to the fit provided in this work and performed using only the 10% values; right panel, survival dependence of observed OER at different LET levels.

Finally the extension in the full two-dimensional plane was obtained combining the two asymptotic relations by assuming a similar LET dependence at any $p_{O_2}$ [36], and thus substituting to $M_0$ in eq. 9 a maximum value dependent on $p_{O_2}, M_p$ coming from eq. 3:

$$OER(LET, p_{O_2}) = \frac{b(aM + LET^3)/(a + LET^3) + p_{O_2}}{b + p_{O_2}}$$

with $M = 3$ and $b = 0.25\%$.

The complete surface is shown in fig. 5. Independent measurements performed at GSI, with the techniques described in following Section 4 “Experimental verification”, confirmed the behaviour of the fully anoxic curve, and additionally gave some insights of the partial hypoxic conditions with a set of measurements at $p_{O_2} = 0.5\%$, for a single LET value, which resulted, after averaging on the 3 performed experiments, in very good agreement with the corresponding computed curve. The

Figure 4: Survival curves measured at GSI [34, 35] for carbon at $LET = 100$ keV/µm and different hypoxic conditions ($p_{O_2} = 21\%$; $0.5\%$ and $0\%$, respectively, left) and several ions in fully anoxic conditions (right).
Figure 5: OER dependence on LET and oxygen concentration, in the parametric description provided in this work [36] and, in the lower panel, selected surface cuts compared to independent experimental data [34, 35]. The number of performed experiments is also shown close to the corresponding average point, see text for details.
complete original experimental data [34, 35] are shown in fig. 4, while the extracted OER values are summarized in fig. 5 and superimposed to our independent fit. There the numbers close to the points correspond to the number of experiments performed; and when only a single experiment was possible, mean and standard deviation are derived from the colonies counts. These data also confirmed the almost negligible dependence on ion type, once the dose average LET is considered.

The complete lack of experimental points (excluding the single one reported) at intermediate values of $p_{O_2}$ and LET, is a serious limit of the present and any other model, especially since these are the most relevant conditions for treatment planning. In order to let improve the model and fill the experimental gap, as an additional outcome of this work, a collaboration with NIRS in Japan has been established in the context of the International Open Laboratory (http://www.gsi.de/forschung/bio/nirsiol.html) and a HIMAC beamtime has been already approved for performing several experiments with different ions in 2012, in order to cover different ranges of LET, exactly at the intermediate $p_{O_2}$ values which are needed [35].

3 TRiP implementation

TRiP98 (Treatment planning for particles) [40–42] is a code born in connection with the pilot project at GSI and is now, after more than 10 years, developed in several directions, including moving targets handling, different beam modeling, several ions, etc. Present status is summarized in [39]. After serving the pilot project at GSI [43], TRiP98 is presently experiencing a second life as a research prototype for the growing facilities preparing to use heavy ions. Furthermore, for its modular structure, is especially suited to be expanded to account for different effects and it is then the ideal candidate to be implemented towards the hypoxia handling approach. The core part of the program is in the optimization (see fig. 6), now available also for multiple fields [42] and based on biological effect,
but where the biological effects are presently accounted only through the RBE. The key quantity in the optimization process is the objective function $\chi$ which should be minimized as a function of the particle numbers

$$\chi^2(\vec{N}) = \sum_{i \in \text{Target}} \frac{(D_{\text{pre}}^i - D_{\text{act}}^i(\vec{N}))^2}{\Delta D_{\text{pre}}^2} + \sum_{i \in \text{OAR}} \frac{(D_{\text{max}}^i - D_{\text{act}}^i(\vec{N}))^2}{\Delta D_{\text{max}}^2} \cdot \Theta(D_{\text{act}}^i(\vec{N}) - D_{\text{max}}^i),$$

where $\vec{N}$ is a vector of particle numbers in each raster point, $D_{\text{pre}}^i$, $D_{\text{act}}^i$ and $D_{\text{max}}^i$ are respectively the prescribed dose, the actual one and the maximum acceptable one at the voxel $i$ and the $\Delta D$ are weight factors.

The computed doses, in case of biological optimization are corresponding to the biological dose, which is presently related to the physical one by the relation

$$D_{\text{Bio}}^i(\vec{N})[\text{GyE}] = D_{\text{Phys}}^i(\vec{N}) \cdot RBE^i(\vec{N}),$$

and where for carbon ions it is valid

$$RBE^i(\vec{N}) \geq 1 \forall i.$$

Our purpose was then to include in the biological effect also the OER. For the explicit calculation of the biological dose, a straightforward simplification which has been introduced recently is the low dose approximation [44]

$$D_{\text{Bio}}^i(\vec{N})[\text{GyE}] = \sqrt{\frac{\alpha_i \cdot (\vec{c}_T^i \cdot \vec{N}) + \beta_i \cdot (\vec{c}_T^i \cdot \vec{N})^2}{\beta_i}} + \left(\frac{\alpha_i}{2\beta_i}\right)^2 - \frac{\alpha_i}{2\beta_i},$$

where $\alpha_i$, $\beta_i$ are photon parameters, $\alpha_i$, $\beta_i$ the ion parameters in the mixed field resulting at voxel $i$ and $\vec{c}_T^i$ the corresponding row of the dose correlation matrix [39], representing the magnitude of the contribution of all raster spots to the voxel $i$. The OER, thanks to its dose modifying feature, may then be easily included in eq. 14 by substituting the ion parameters by

$$\alpha_i^\prime(\text{LET}_i, p_i) = \alpha_i / \text{OER}(\text{LET}_i, p_i)$$

and

$$\beta_i^\prime(\text{LET}_i, p_i) = \beta_i / \text{OER}(\text{LET}_i, p_i)$$

and the “isoeffective dose in the presence of hypoxia” may be computed and consequently the resulting survival.

The code is then implemented to deal with provided external tables for a given tissue, with the possibility to provide different entries also for every ion type. However, for the start, for the reasons mentioned in the previous section, the latter dependence is used as dummy, with all the particles resulting on the same OER dependence. The largest approximation affects the accounting of the lighter fragments which probably will give a consistent deviation. The use of the dose averaged LET, as seen, mitigates this deviation, but does not eliminate completely the problem and a better description of – especially – proton and helium fragments would be necessary in further developments.

The OER tables are imported and then at any voxel, according to the present $p_{O2}$ and the computed LET resulting from the local mixed field, an interpolation returns a value to be passed to the biological effect routines mentioned above.
3.1 Expected survival calculations

The quantity immediately retrievable from this model and from the LET resulting at any point of the irradiated target is the OER as a function of ion penetration depth. This analysis is shown for several $p_{O_2}$ values and for 2 different primary ions on fig. 7. The effect of stopping particles, dominating at the distal end of the target volume, in suppressing the radioresistance effect is clearly evident, especially for the more drastic (lower) $p_{O_2}$ conditions. But it is also evident how this LET “counter-effect” plays a role, especially for carbon ions, only in a relatively small region of the extended Bragg peak.

This allows already to draw some estimates of an expectable clinical advantage of the use of different ions as the ones available, e.g., in the Heidelberg facility. In fact, while one may appreciate the overall effect of a carbon ion, it is remarkable how an oxygen ion irradiation, with a prescribed dose chosen in order to maintain the same dose in the entrance channel, may drastically further reduce the effect in the intermediate $p$ values corresponding to relevant clinical hypoxia.

For a more detailed comparative analysis see tables 1 and 2. In tab. 1 a similar situation as the one plotted in fig. 7 is shown, for different extensions of the tumor target (and then of the SOBP) along the penetration depth dimension $z$. The effect of the two ions, delivering the same dose to the entrance channel are explored at the proximal end and in the central point of the extended volume. From the relative reduction ($R_{O/C} = (OER_C - OER_O)/OER_O$) it is quite visible how the effect of the higher

![Figure 7: Comparison of the computed OER along a SOBP, for carbon (black curves) and oxygen (red curves) at different $p_{O_2}$ levels. The hatched areas represent the clinical interesting regions for hypoxia (0.15% < $p_{O_2}$ < 0.5%).](image-url)
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<td>15</td>
<td>11</td>
</tr>
<tr>
<td>6.0</td>
<td>OER$_C$</td>
<td>2.8</td>
<td>2.2</td>
<td>1.6</td>
</tr>
<tr>
<td></td>
<td>OER$_O$</td>
<td>2.6</td>
<td>2.0</td>
<td>1.5</td>
</tr>
<tr>
<td></td>
<td>$R_{O/C}(%)$</td>
<td>10</td>
<td>9</td>
<td>6</td>
</tr>
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</table>

**Table 1:** OER for carbon and oxygen and relative reduction ($R_{O/C}$) for a tumor of different sizes (extension along $z$), centered at a depth of 8.3 cm wepl, computed at different positions within the extended volume. Data for 4 cm size correspond to fig. 7.

<table>
<thead>
<tr>
<th>tumor depth (cm)</th>
<th>$p_{O_2}$</th>
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<th>0.15%</th>
<th>0.5%</th>
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<td>2.0</td>
<td>1.5</td>
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<td>23</td>
<td>16</td>
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<tr>
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<td>1.9</td>
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<td></td>
<td>$R_{O/C}(%)$</td>
<td>19</td>
<td>16</td>
<td>12</td>
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</tbody>
</table>

**Table 2:** OER for carbon and oxygen and relative reduction ($R_{O/C}$) for a 4 cm wepl extended tumor centered at different depths, computed at different positions within the extended volume. 8.3 cm depth correspond to fig. 7.
LET ion is especially advantageous in small tumors, highly hypoxic, reaching a value of 30%. In tab. 2 the same analysis is done for tumors of the same extension (4 cm along z) placed at different depth, i.e. where the isocenter is placed respectively at 6.3, 8.3 (as in fig. 7) and 10.3 cm in water equivalent path length (wepl) from the tissue entrance. In this case a clear trend as a function of depth seems not evident at least as compared to the uncertainties due to the oscillations of the dose averaged LET profile, and the improvement appear to be almost constant for more deep seated tumors as compared to the ones closer to the surface. A similar comparative analysis for protons and carbon ions, but just for a single irradiation configuration, is reported in Ref. [26].

This kind of analysis may help to lay the basis for the conditions which drive the choice for a multi-ion treatment [45]; a point which will be further developed in tight connection with the TRiP multi-ion development (see Deliverable report D.JRA 5.7).

Then, accounting for the survival calculations implemented as explained above, it is possible to perform forward planning calculations returning the corresponding survival level, assuming an homogeneous target at different $p_{O2}$ states (fig. 8). One can now appreciate in terms of actual survival level along the irradiated extended volume, how the combined role of oxygen concentration and dose averaged LET drastically affect the biological outcome, as shown for an exemplary tissue of CHO cells ($\alpha_x = 0.22 \text{ Gy}^{-1}, \beta_x = 0.02 \text{ Gy}^{-2}$)

A refined tissue model can also be considered, as shown in fig. 9, where the oxygenation level is spatially inhomogeneous (as in the interesting clinical cases) and the code is shown to correctly deal with changes of $p_{O2}$ values from one voxel to the other.

![Figure 8: TRiP98 recomputed survival curves along a carbon ion SOBP, for different oxygenation levels of the target (CHO cells), after optimization on a corresponding aerobic tissue.](image-url)
3.2 Optimization and dose compensation

After exploiting the possibility of TRiP98 to predict the survival along a spreadout Bragg peak, attempts of dose compensation and inverse planning have been performed. In the first version, the RBE effect accounting for OER is computed directly in each iteration step, while the gradients calculations are not altered.

Results are plotted in fig. 10. As it is visible, in case of an homogeneous hypoxic tissue (left panels), dose compensation is able to restore the required survival level. Also in the case of a composed tissue, even if with slight fluctuations, the dose compensation in the tissue is successful, but the price to pay is a larger damage in the entrance channel which needs to be prevented. The effect of the correction is clearly visible in the resulting physical dose, which, as evident in the composed tissue case, may consequently also have discontinuous shapes in correspondence to abrupt changes in tissue sensitivity. Another technical point that is arising from this data is that as long as a strong sensitivity variation is along the \( z \) axis, it is technically not problematic to adjust the dose delivery accordingly, but when it occurs within the same isoenergetic slice (IES), an abrupt jump in fluence might be required to the ion scanning system that is not always feasible. This point might require the design of specific irradiation geometries in order to minimize the gradient in the \( x, y \) directions. A two-dimensional view of the survival profile in a similar, slightly more complex, model tissue is shown in fig. 11, and there it is proofed that the uniformity of the dose coverage is assured also in the lateral dimensions.

The normal tissue can be much better spared adopting an additional field and performing a multiple field optimization (MFO), i.e. optimizing at the same time the contributions from both fields to the overall effective dose. This means that the vector \( \vec{N} \) in eq. 11 is containing as many components as all the raster spots of all the fields, and the minimization of the \( \chi^2 \) function is performed on this full space at once. This method has been already shown to be convenient in RBE-weighted dose optimization, especially of complex target geometries [42]. In this specific case, where hypoxia is additionally included, considering the OER dependence on LET it is especially advantageous the use of several fields, since the differently oxygenated regions can be irradiated using the best LET components of
Figure 10: TRiP optimized plan for an homogeneous target tissue at $p_{O_2} = 0.5\%$ (left) and for a composed target (aerobic, 0.5%, 0%). Upper figures, survival rates, lower figures physical doses (in units of $D_{pre}/1000$) resulting from the full biological optimization. Results with dose compensation shown in dashed lines and compared to a normoxic target plan (solid lines).

Figure 11: TRiP98 bidimensional computed survival profiles, without (left) and with (right) taking into account the non uniform oxygen concentration of the target tissue into the optimization.

the two fields, as also found in Ref. [24]. In fig. 12 it is evident how the overall survival has a more convenient profile, as well as the contributions from different fields to the physical dose, show how the program selects the beams accordingly.
Figure 12: TRiP optimized plan for an inhomogeneous target as in fig. 10, with multiple field optimization as compared to single field. First panel survival level, second panel, physical dose contributions.

4 Experimental verification

Dedicated plans were produced for three beamtimes occurred at GSI in order to test the predictive features of the code and the reliability of the semiempirical OER model used. For that, a dedicated exposure chamber has been used, which has been developed and patented at GSI [7]. CHO cell lines
were grown on a 4.5 cm$^2$ area on gas permeable foil supported on a PVC-ring. This allowed to gas the chamber for several hours with standard gas mixtures: 95% N$_2$, 5% CO$_2$ for anoxic condition and 94.5% N$_2$, 5% CO$_2$, 0.5% O$_2$ for hypoxic condition. The chamber wall for the beam entrance has a thickness of 1 mm (see fig. 13) and the gas flow was measured with a thermal mass flow meter calibrated for nitrogen.

4.1 Composed tissue

In the first beamtime (April 2011), a tumor tissue with 3 different concentrations of oxygen has been simulated. A 4 cm water equivalent length target centered at 8.1 cm from the beam entrance was planned, divided in a first region (from the proximal end) of 13 mm of normoxia, a second layer of 13 mm of hypoxia ($p_{O2} = 0.5\%$), and a last one of complete anoxia ($p_{O2} = 0\%$), 14 mm. Three chambers, each one containing 3 rings gased at the corresponding concentration, where then placed in a corresponding position after accounting for the path length conversion factors. Additionally two, normoxic single chambers where placed in the entrance channel as a further control. The plan was prepared in order to have a 10% survival in the target in a normoxic case. In order to assure uniformity in the dose coverage, the target was chosen as a broad parallelepiped, with $\Delta x = 6$ cm and $\Delta y = 10$ cm.

The results (fig. 14) show an overall qualitative agreement between measured survival and the TPS predictions and suggested refined insights for a second experiment. In fact, apart for an overall scaling factor, which may be induced to a collective increased radioresistance of all the cells, the most puzzling fact was the total absence of any kind of LET effect at the distal end of the peak.

4.2 A closer look to the LET effect

In the second beamtime (July 2011)), the last part of the spread out Bragg peak has been analyzed in total anoxic conditions; and, in order to check the consistency, an identical configuration with normoxic cells was irradiated too.

Three triple chamber, then, were prepared in oxic conditions and another three at $p_{O2} = 0$. In order to increase the number of sampling points within the target volume, every triple chamber, for every oxygenation state was placed on a threadmill perpendicular to the beam, with respectively 0, 1 and 2
Figure 14: TRiP computed (line) and measured (points) survival for differently oxygenated regions along a spread out Bragg peak (see text for details).

Figure 15: TRiP computed (lines) and measured (points) survival for normoxic (green) and fully anoxic (black) target cells along the distal end of a spread out Bragg peak. The red dotted line correspond to an expected survival for an hypothetical partial oxygenation ($p_{O_2} = 0.5\%$).
slices of material inducing a shit of 1.2 mm each. In this way the last 8 mm of the extended Bragg peak, where the LET effect is supposed to be larger, have been sampled uniformly and fairly densely.

These results were affected by a possible additional uncertainty due to an occurred technical accident at the accelerator’s outlet, which caused a slight overdosage, which being energy dependent affected asymmetrically the extended Bragg peak. Nevertheless it was possible to estimate the energy dependent correction factor to the delivered physical dose, and some preliminary indications may anyhow be extracted from the corrected data shown in fig. 15.

While the normoxic data show a good agreement, the anoxic data are presenting a quite different behaviour from the predicted curve. A possible explanation for that is that the actual oxygenation level has been altered and a non zero content of oxygen was present in the chamber at the time of irradiation, reducing and “flattening” the corresponding response curve as a function of the depth. The red curve in fig. 15 represents this hypothesis, but it is still not fully able to explain the experimental behaviour.

Alternatively, these results allow to consider the possibility that the present OER model overestimates the gradient of the OER fall-off versus LET, which may be less steep than predicted, and as a consequence, result in a less pronounced decrease of the survival level as a function of depth.

Surprisingly, at the same occasion a survival curve at intermediate oxygen concentration ($p_{O_2} = 0.5\%$) at a fixed LET value (100 MeV/mm) was performed to test the introduced model for generating the OER tables in a crucial region, confirming the point plotted in fig. 5.

**Figure 16:** TRiP computed (lines) and measured (points) survival for differently oxygenated target cells along the distal end of a spread out Bragg peak resulting from the last experiment performed at GSI. The open symbols correspond to the original data, the closed ones are corrected for a 2 mm shift retrieved after dosimetric measurements. Green normoxic, black anoxic.
The same experiment was repeated in October with better conditions and finally a reasonable set of results has been collected. In this case, the resulting data showed a much better agreement with the prediction as visible in fig. 16, where they are plotted together with the bar of errors resulting from the colonies counts. The agreement is even larger if one accounts for an overall range shift of 2 mm which could be easily verified due to spatial deformation of the rings, for gravity, and thus inducing an increased path length that was measured with dosimetric films. This is also confirmed from the analogous effect in displacing the distal end, both in the oxic as in the anoxic set of cells.

A publication collecting the code update and the experimental results is in course of preparation [46].

5 Comparison with other models

After performing our first test with our own parameterization we were informed of a similar modeling of OER$(p, \text{LET})$ just published from the Munich group [26]. After contacting the group, we performed several comparisons, in order to evaluate the effect of the different OER tables. In their paper Wenzl and Wilkens show a parameterization which stems from a slightly different approach. In their case an AHF-like behaviour is assumed on each of two LQ parameters for the $p$ dependence, while a linear dependence with respect to the LET is also included for the $\alpha$ parameter:

\begin{align}
\alpha(L, p) &= \frac{(a_1 + a_2 L)p + (a_3 + a_4 L)K}{p + K} \\
\sqrt{\beta}(p) &= \frac{b_1 p + b_2 K}{p + K}
\end{align}

these values are then inserted in eq. 5 and, fixing $K$ to an experimental value and assuming always $S = 0.1$, the parameters $a_i, b_i$ are obtained.

The result is sensibly different from our approach as visible in fig. 17. In their approach much more experiments are taken into account, while the parameterization is extracted considering all the points in full anoxic conditions and then the other parameters are derived. For details see Ref. [26]. They show different results for in vitro data and in vivo data, where also the fully oxygenated state is different, and thus the parameter $p_a$ was taken differently and corresponding to 4%. A comparison of the bidimensional dependence is shown in fig. 17. The most evident feature is that the overall gradient of LET dependence is much less steep.

Then, the TRiP-OER extension was shown to be able to handle successfully also these alternative tables, and the results for an irradiation configuration similar to what described in the previous section are shown in fig. 18. In the same figure we report, as an example, the experimental data from the two last reported experiments, respectively on left panel those of fig. 15 and on right panel those of fig. 16. It is shown that even with this different formalism the flat behaviour seen in the first experiment (left panel) cannot be explained, while for an assumed larger content of oxygen in the experimental anoxic set-up, a better agreement could be verified. On the other hand, a comparison with the most reliable data (those of last experiment, right panel) shows a slightly better agreement with our proposed model.

In a subsequent, just published work of the same group [30] the tables are expanded accounting for a dose dependence. The correction has been shown to be relatively small and we do not analyse here, for the moment, this issue.

A parametric approach very similar to ours was presented, again during this year, from Brahme [17]. In this work also the dose modifying approximation is used and the same $p_{O_2}$ dependence as we did,
while the LET dependence is described according to an exponential formula:

\[
OER(p, LET) = 1 + (M(p) - 1) \exp\left[-(\frac{LET}{LET_0})^2\right]
\]  

A very small deviation is observable from our model (an even steeper gradient in LET fall-off), which can be considered negligible when propagated to the treatment plans.

Finally, another interesting model of the same bidimensional dependence has been provided very recently by the Carlson group [27]. In this case the approach is substantially different and for the first

Figure 17: Comparison of OER surface cuts from the present work (black lines) with those from Ref. [26] (blue lines). Different linestyles for both sets of curves refer to the corresponding \( p_{O2} \) values shown in the legend.

Figure 18: Comparison of expected survival computed importing OER tables from the present work (black lines) with those from Ref. [26] (blue lines). Different linestyles for both sets of curves refer to the corresponding \( p_{O2} \) values shown in the legend; points are data from experiment 2 (left) and 3 (right).
time a partially mechanistic explanation has been attempted. The model stems from a Monte Carlo simulation of the probability of the damage fixation mechanism to occur as a function of radiation quality (there simply taken from the ratio of the primary ion relativistic velocity, $\beta$, and effective charge, $Z_{\text{eff}}$) and oxygen concentration. Then the OER (HRF) of the double strand break induction obtained from the model is matched to that one of clonogenic survival from the experiments, in the same asymptotic cases as we considered. The resulting function has the same dependence in the $p_{O_2}$ variable, as we used (eq. 3), while the maximum value $M$ therein is modulated from the LET dependence as a parametric function of $Z_{\text{eff}}/\beta$ (see Ref. [27] for details).

Implementations of OER tables resulting from this alternative model in TRiP98 is also feasible and straightforward.

6 Towards clinical applications

After testing the code in simple geometrical distributions of $p_{O_2}$, which we can consider as a simulated PET, our attention was naturally focused to allow TRiP to receive real clinical data and to test its efficiency in dealing with them.

Figure 19: PET-CT exemplary data imported from WP 3 (courtesy from Alina Santiago, see Deliverable report DJRA 3.5 for details). Upper figures FDG, lower figures FMISO.

An exemplary set of FMISO PET data from one anonimized patient case was received from WP 3 (see fig. 19), for this purpose. This has helped to develop accordingly the conversion tools in order to be read by TRiP98. In collaboration with Milan partners, a series of tools (PTX-TOOL) has been developed to convert the DICOM PET uptake data in the native TRiP format, as a PET cube (analogous to the CT cube) to be imported in the program [47]. A scheme of the full implementation is shown on fig. 20. The PET uptake data are loaded as DICOM files together with the corresponding CT slices and RT structures. Then, if necessary, a registration is performed to align the PET with the CT slices and a conversion from DICOM to the TRiP98 input format VoxelPlan. The standardized uptake value (SUV) is computed and every CT voxel of the gross tumor volume is labeled with this value, later transformed in $p_{O_2}$. This value, finally, is passed to the TRiP98 code and processed as explained in Section 3 “TRiP implementation”.
Unfortunately the low uptake-to-noise ratio and the peculiar spatial distribution of the signal of this single patient case (see fig. 21) did not allow so far to use it in planning, while some attempts of smoothing the signal are currently in play. Other examples are going to be exchanged with WP 3 through the Dresden group, as well as contacts have been established with other medical partners (AUH, MUW, ETOILE), who are already preparing or are supposed to be able to provide similar data. Tests of the complete version of the code with other patient cases are then under way.

7 Temporal variation

As also mentioned in the previous section on clinical data, and shown in the detailed report on FMISO data DJRA 3.5, the temporal instability of hypoxia poses a big additional problem. For example in figures 22 and 23, it is shown how within a week from the treatment start the FMISO signal is drastically changed within the structures of interests, leaving several complications to the treatment plan purposes. In fact fractionated treatments will require an “online” tuning of the plan accounting for the new distribution of $p_{O_2}$ in the target volume, fraction by fraction. This problem and its outcome in treatment planning, especially in the case of FMISO acquisitions, has been discussed in detail in recent times for example in Ref. [48].

This online tuning is in principle feasible with the new versatile TriP98 version, which does not require huge computational costs, but it is bound to the possibility to provide reliable PET imaging data sets for each fraction. The way to adapt the clinical data of the day, already implemented in the conversion tool PTX-tool, is shown in detail in fig. 24: the PET and CT daily acquisitions, already
Figure 21: Detail of the uptake values inside the gross tumour volume (GTV) contours (blue) from the FMISO-PET data of fig. 19.

Figure 22: FMISO signal superimposed to the GTV structures, contoured from the FDG signal at the planning moment (g) and after a week (h). See Deliverable report DJRA 3.5 for details.

Figure 23: FMISO acquisitions (same patient of fig. 22) of the first three weeks superimposed to the CT taken on the second week.
registered within each other, are mapped on the planning CT, giving a PET registered to the planning dataset that can be “masked” on the GTV planning contours extracting the corresponding new uptake data sent to TRiP98. Of course in ordinary clinical practice, a too dense replanning schedule would be not feasible for the complexity and length of the verification procedure.

According to that system, a replanning becomes necessary as soon as the pixel values within the GTV change over a given threshold. A quantitative assessment will be, then, immediately feasible, as soon as a comprehensive set of daily acquisitions could be provided.

In outlook, an alternative way to interpret the PET data, which are often imprecise, might be to model the spatio-temporal evolution of the oxygen concentration following a partial irradiation and considering the tumor growth, and match the result to the following imaging acquisitions. In this regard a collaboration has already set in play with a Braunschweig group who recently suggested an agent based model on tumor spheroid dynamical growth versus irradiation [49] (see fig. 25).

An initial, indicative result is the simulation of the reoxygenation mechanism in combination to growth in a small tumor model which can be supposed to represent a region close by a vessel (see fig. 26). It is shown how the reoxygenation occur within minutes after the irradiation, while the growth restore along a couple of days the anoxic status of the given region [50]. This kind of dynamics might be checked with Eppendorf probe measurements of small tumor models.
**Figure 26:** Oxygen level at the center of a small tumor model (1 mm diameter) versus time, including a typical fraction irradiation event [50].

Another related option would be to explore the variation of the hypoxic fraction as a function of vascular density, as proposed by the Stockholm (KI) partner [17].
CONCLUSIONS

It has been shown that it is possible and straightforward to improve the TRiP98 TPS in order to account for spatially inhomogeneous sensitivity due to hypoxia.

- A working version has been tested and now it is possible to provide OER tables in addition to RBE tables to the code.
- A semiempirical map of OER dependence on LET (dose averaged) and $p_{O_2}$ has been provided and loaded into the program. The simple model used has been verified with independent experiments.
- The enhanced TPS version is able to return survival prediction on a given irradiation configuration as well as to preliminary compensate the required dose to obtain homogeneous coverage in the target.
- The latter dose compensation has been shown to work correctly also with multiple field optimization, opening the possibility to tune the LET components of simultaneous fields accordingly.
- Qualitative agreement with extended volume ion beam irradiation experiments has been shown.
- The input of clinical data (PET) of oxygen concentration into the program has been made possible, in addition to the simulated ones.

Additionally, indications have been provided to the use of several ions in treatment.

The remarkable effect in the resulting survival profiles of different tables coming from different OER modeling (see Section 5 “Comparison with other models”), suggests to further investigate on modeling as well to further perform experiments, especially for intermediate levels of oxygen pressure (0.15% to 0.5%) and for intermediate levels of LET. In this connection, an additional outcome of this work was also to initiate actions in both directions: on the experimental side, a collaboration between GSI and NIRS has been established resulting in an accepted proposal for beamtime at HIMAC (Japan) for specific measurements of OER at the above mentioned conditions [35]; on the modeling side, dissemination to the nanoscale radiation damage modeling community (a contribution on the present work presented at the nano-IBCT conference: http://nano-ibct.sciencesconf.org) resulted in the submission of a new EU training network proposal (ARGENT) with one project focused on mechanistic modeling of the oxygen effect. All these efforts will be crucial to better understand and improve the efficiency of LET-aided reduction of hypoxia resistance, and will provide the perfect complement to the ULICE adaptive treatment planning project.

On the other hand, the work in progress in the context of this ULICE project, which will eventually turn out in an update of the present deliverable, will focus on the clinical implementation and includes:

- plans on real clinical cases (FMISO, FAZA);
- improved optimization approaches;
- dose and LET painting approaches in collaboration with AUH partner;
- merging of the TRiP-OER version with the multi-ion one (see report DJRA 5.7) towards a fully optimizable, multi-ion hypoxia-driven treatment planning, perfect tool for the new multi-ion irradiation perspective available at HIT.
REFERENCES


