DISS. ETH No. 24768

PROTON RANGE PROBE AS A TOOL FOR IMAGE GUIDED PROTON THERAPY

A thesis submitted to attain the degree of DOCTOR OF SCIENCES of ETH ZURICH (Dr. sc. ETH Zurich)

Presented by
Abdelkhalek Hammi

MSc in Applied Physics
Carl von Ossietzky University Oldenburg

born on 08.03.1981

citizen of
Morocco

accepted on the recommendation of
Prof. Dr. Antony John Lomax
Prof. Dr. Andreas Vaterlaus
Prof. Dr. Nigel Allinson

2017
Abstract

Proton therapy has become a highly effective tumour treatment modality, since it makes use of the physical characteristics of protons to deposit highly localized, cytotoxic energy that kills cancerous cells. A fundamental advantage of this therapy concept, over other types of external radiation therapy, is the characteristically sharp dose fall-off at the distal edge allowing for substantial sparing of adjacent normal tissues. However, the success of proton therapy hinges on the accuracy with which the pencil beams can be delivered to the target volume. To fully exploit the potential of this modality, innovative imaging techniques to monitor the patient and the proton in-vivo range are required.

In the first part of this work, we have performed an investigation into the feasibility of performing in vivo range measurements with what we call the Range Probe (RP). This consists of transmission imaging with proton pencil-beams at radiographic energies in combination with a range telescope as detector to measure the residual proton range. The set-up for the simulated radiography was characterized in terms of proton beam parameters and image reconstruction. The potential of a large field RP to monitor patients was also presented.

The second part of this thesis proposes innovative solutions for online, image-guided proton therapy for clinical implementation using the RP approach. The technique was further developed for fast online positioning of head and neck patients treated with particle therapy, which makes use of a small number of pencil beams to detect patient misalignments. The retrospective clinical study has shown that translational patient misalignments can be detected with an accuracy below 1 mm and using only 3 three range probes, while the semi-experimental study using the anthropomorphformic phantom has demonstrated that this approach could potentially predict rotational errors to $\leq 1^\circ$ using only five RPs positions and from one single direction. The Proof-of-concept experimental investigation of the approach has been performed using an in-house developed Multi-Leaf-Ionisation-Chamber and the head phantom and dedicated rotational jig. This experimental study demonstrates that using only two, carefully selected RPs, translations and rotation errors could be detected with an accuracy of 1 mm and $1^\circ$ respectively. In addition, two online tracking techniques were presented to localize moving targets and to mitigate uncertainties arising from tumour motion. The first technique is a full imaging approach, which attempts to suppress radiographic image features in order to increase tumour visibility especially in mediolateral projections. This method was inspired by X-ray digital subtracted radiography. The results have shown that the contrast has increased by at least 70% and with a maximum enhancement of more than 330%. The second technique is based on the identification of internal anatomical structures, visible in RPRR type images, which can be correlated to motion of the tumour. The results have shown that tumour location can be
predicted with a high accuracy using only a few single RP positions, with a 2D average deviation in predicted tumour position of lower than 1.2 mm being achieved.

Furthermore, the potential of RP-computed tomography was investigated as a means to directly measure the relative stopping powers and range changes that may occur over the course of fractionated proton therapy. We have also developed a technique that uses only two radiographic projections and pre-knowledge of the patient’s anatomy to reconstruct and localize geometrical changes inside the patient. The retrospective clinical study has shown that the approach can reconstruct water equivalent range changes with an acceptable accuracy and using only two radiographic projections. Although further developments and measurements are still required before the RP is clinically applicable, the findings of this thesis affirm the potential of the RP approach for patient set-up and for reducing range uncertainties in its future clinical use.
**Zusammenfassung**


Im ersten Teil dieser Arbeit wird die Range Probe (RP) Methode angewandt, um die Protonenreichweite im Patienten abzuschätzen. Die RP-Methode ist ein Bildgebungsverfahren welches auf hoch energetisch gebündelte Protonenstrahlung und einem Reichweite-Fernrohr (Detektor) basiert, durch welches die Reichweite der Protonen gemessen wird. Der Aufbau für die modellierte Protonen Radiographie wird in Bezug auf die Protonen Strahlparameter und Bildrekonstruktion charakterisiert. Um Patienten überwachen zu können wird die RP-Methode zudem auf grosse Stahlen-Felder in der Protonen Radiographie angewandt.

Auch wenn noch weitere Entwicklungen und Messungen erforderlich sein werden, zeigen die Ergebnisse dieser Arbeit, dass die Unsicherheiten der Protonen Reichweite in zukünftigen klinischen Anwendungen durch die RP-Methode verringert werden.
Acknowledgements

Pursuing and finishing this PhD work was a life changing experience for me and I would like to thank the people who have helped me over the last four years to make this thesis possible.

Firstly, I would like to express my sincere gratitude to my supervisors Prof. Tony Lomax for giving me the opportunity to join the family of Center Proton Therapy and for giving me the freedom to pursue my own ideas and research interests. Your patience, motivation and guidance were invaluable in my work.

I would also like to thank Sairos Safai for his administrative supervision and for the discussion about the proton scattering. Special thanks go to Stefan König for the discussion and suggestion concerning the measurement and detector technology.

I am indebted to all my colleagues, student, PhD’s and the Post-doc who have provided help and have shared knowledge and funny moments with me. Special thank have to go to my office mate Fabian for his always positive attitude. He never fails to make me smile. I enjoyed our academic and nonacademic conversations.

Last but not the least, I would like to express my deepest gratitude to my parents. There are not enough words to describe how thankful I am to them for always supporting me and for being there for me.
Aims and outline of this thesis

The aim of this work is to investigate the feasibility of the use of proton Range Probes (RP) for imaging, positioning and patient monitoring in proton therapy. A proton range probe is a single, narrow proton pencil beam, delivered to the patient with sufficient energy that it passes completely through, and such that it’s range can be measured on exit from the patient. The potential for both individual RP and scanned grids of RP (providing a simple form of proton radiography, RPPR) have been investigated. Whilst most of the reported work is simulation based, with RP and RPPR being calculated using Monte Carlo (MC) tools, some first experimental results with RP are also reported.

The thesis is structured as follows:

In Chapter 1, the theory of proton interactions with matter, together with the clinical rational and technology of proton therapy are discussed. Chapter 2 then provides a brief review of current imaging and range verification tools for particle therapy, together with an introduction to the proton range probe concept. The RP concept is further expanded on in chapter 3, which describes the concept of proton range probe radiography (RPPR) and presents some first examples of RPPR simulations and applications calculated based on clinical CT data, including a method for estimating and quantifying average range and range dilution for degraded Bragg peaks (e.g. after passing through complex density heterogeneities). Chapters 4, 5 and 6 then present three different studies into potential clinical applications of RP and RPPR. Chapter 4 demonstrates how just a few (3 - 5) well selected RP, all delivered from the same incident direction, can be used for determining translational or rotational patient misalignments. Chapter 5 then looks into the potential of RP radiographs for tumour imaging and whether well-defined structures in these images can be used as surrogates for predicting tumour motion, whilst chapter 6 reports on RP based tomographic reconstruction methods. Finally, in chapter 7, we present some first experimental results for RP.
Contents

Abstract ................................................................................................................................. iii

Zusammenfassung ................................................................................................................ v

Acknowledgements ............................................................................................................. vii

Aims and outline of this thesis ............................................................................................ ix

1. Introduction ...................................................................................................................... 3

1.1 Physical rationale for proton therapy ........................................................................... 4

1.1.1. Electromagnetic energy losses for charged particles .............................................. 6

1.1.2. Range of proton ....................................................................................................... 7

1.1.3. Multiple Coulomb scattering .................................................................................. 9

1.1.4. Nuclear interactions ................................................................................................. 10

1.1.5. Water equivalent thickness (WET) ......................................................................... 11

1.1.6. Features of pristine Bragg curves (BC) .................................................................. 12

1.1.7. Radio-biological rationale for ion beam therapy ................................................... 13

1.2 Delivery ......................................................................................................................... 15

1.2.1 Accelerator ................................................................................................................ 15

1.2.2 Passive scattering (PS) ............................................................................................. 16

1.2.3 Pencil beam scanning ............................................................................................... 17

1.2.4 Planning CT ................................................................................................................. 18

1.3 Range uncertainty ......................................................................................................... 18

2. Imaging techniques in particle therapy ........................................................................... 20

2.1 PET imaging ................................................................................................................ 21

2.2 Prompt gamma radiation ............................................................................................. 24

2.3 Particle radiography and computed tomography ......................................................... 26

2.3.1 Proton radiography .................................................................................................. 27

2.3.2 Paul Scherrer Institute experience ......................................................................... 29

2.3.3 Loma Linda University Medical Center experience ............................................. 31

2.3.4 Other techniques ..................................................................................................... 32
2.3.5 Integrating systems ...........................................................................................................32
  2.3.5.1 Commercial flat-panel detector ......................................................................................33
  2.3.5.2 Time-resolved dose measurements using single detectors ........................................33
  2.3.5.3 Proton-counting radiography based on CMOS APS technology ............................34
  2.3.5.4 Charge-Coupled Device based transmission imaging ................................................36
  2.3.5.5 Transmission imaging based on scanning beams ......................................................37
  2.3.5.6 Proton Range Probe ....................................................................................................38
3. Grid based range probe proton radiography (RPPR) .................................................................40
  3.1 Grid based range probe radiography ....................................................................................41
  3.2 Simulation tool ..................................................................................................................41
  3.3 Calculating residual WET’s for RPPR ..............................................................................43
  3.4 Preliminary applications of RP proton radiography .............................................................45
    3.4.1 RPPR’s for positioning and detection of anatomical changes ........................................47
    3.4.2 RPPR’s as direct measurements of patient specific WET ...........................................49
    3.4.3 Energy dependence of RPPR .......................................................................................52
      3.4.3.1 Results ..................................................................................................................52
      3.4.4 Discussion ................................................................................................................54
4. Patient positioning using range probes ....................................................................................56
  4.1 Methods ..............................................................................................................................57
    4.1.1 Determination of optimal RP locations and database generation ..................................59
    4.1.2 Determining translational offsets – a patient study .......................................................60
    4.1.3 RP location selection and data base generation ............................................................60
    4.1.4 Simulation of daily RP positioning measurements ........................................................61
    4.1.5 Determining rotational offsets – a phantom study .......................................................62
  4.2 Results ................................................................................................................................63
    4.2.1 Determining translational offsets – a patient study .......................................................63
    4.2.2 Determining rotational offsets – a phantom study .......................................................65
  4.3 Discussion ...........................................................................................................................68
  4.4 Appendix – An analytical model of proton range probes ....................................................70
1. Introduction

The exploitation of ionizing radiation for therapeutic oncology began with the discovery of X-rays by Röntgen in 1895 (Röntgen, 1898). Since then, radiation therapy has undergone a big development. The introduction of $^{60}$Co in the early 1950s enabled the use of high energy photons for treatment. In the 1960s, medical linear accelerator (LINAC) were then invented. This new technique enabled the use of higher photon energies than possible with Cobalt machines and thus the treatment of more deep located tumours. In 1975 the first computed tomography (CT), allowing for three-dimensional (3D) imaging of internal anatomical structures, was born. The new imaging modality made it possible on one hand to better demarcate and localize both tumours and healthy tissue regions, and on the other hand provided attenuation coefficients for more accurate planning of the treatment. In modern photon-based radiotherapy, new technologies based on sophisticated optimization and dose calculation are now applied. Three-dimensional conformal radiation therapy (3D-CRT) delivers conformal fields to the shape of the target, allowing to spare healthy adjacent tissue. In addition, intensity modulated radiation therapy (IMRT) allows for highly homogeneous and conformal radiation of the tumour by modulating the individual intensity of multiple fields. This technique allows to deliver higher radiation dose to the volume of the tumour while reducing the dose to neighbouring vital organs (Erjona et al., 2013).

Nowadays, radiotherapy based on x-rays is the most common form of external beam therapy and radiotherapy is one of the main modalities to treat patients with cancer. This modality is based on delivering external ionizing radiation and is delivered as a primary or complementary therapy in combination with other modalities such as surgery or chemotherapy. The aim of radiation therapy is to maximize the damage of tumour cells, while minimizing side effects for healthy tissue. In addition, tumour control probability (TCP) and normal tissue complication probability (NTCP) can be used to evaluate radiotherapy treatment plans. These sigmoidal based curves provide probability quantities as a function of the delivered dose and are based on biological information as well as clinical outcomes of both tumours and healthy tissues. Due to their steep dose response, radiotherapy research attempts to broaden the so called ‘therapeutic window’, which results from the difference between both curves and which can be achieved by increasing dose conformity to tumour regions while reducing dose to healthy tissue.
Due to the lack of an electric charge, and for therapeutic energies up to 20 MeV, the Compton process is the most dominant interaction for energy absorption of photons within patient tissues. The photons transfer their energy to free-electrons which will generate short-range secondaries along their path which are absorbed locally. Photon attenuation is described by the Beer-Lambert law (1.1), resulting in an exponential decrease of deposited dose (Figure 1-2 (a)). As such, the integral depth dose (IDD) is characterized by a buildup region at the surface, which is caused by secondaries and depends on the initial energy.

\[
\Phi(z) = \Phi_0 \exp\left(\int_0^z \mu(E(z)) \, dz\right)
\]  

(1.1)

Figure 1-1: TCP and NTCP curves as a function of dose. The resulting therapeutic window is the dose range where the probability to control tumour is high with less normal tissue complication.

1.1 Physical rationale for proton therapy

Wilson (Wilson, 1946) proposed to use accelerated proton beams for radiotherapy as an alternative technology to conventional X-ray therapy. Protons lose their energy progressively along their track, resulting in a different depth dose curve as the one obtained by high energy photons (Figure 1-2 (a)). This profile is characterized with a low dose at the entrance “plateau region” which rises with increasing depth. The most energy is deposited at the end of the proton range, followed by a sharp fall-off of the dose resulting in the characteristic “Bragg
curve” (BC). The depth of this Bragg peak can be tuned by selecting the initial energy of the proton beam. Therefore proton therapy allows for a highly conformal dose to the target. Figure 1-2 (b) shows a side by side comparison between an IMRT and an intensity modulated proton therapy (IMPT) (Lomax, 1999) dose distribution of a treatment plan. It is obvious that this technique results in a lower integral depth dose to healthy tissue and better sparing of organs at risk (OAR) (Miralbell et al., 2000).

Protons interact with matter through different processes, which determine the dose distribution of a beam. In the following, we briefly review these processes. In this section we review the interaction processes of protons with matter and will focus only on interactions of protons with maximal kinetic energy up to 250 MeV. This proton kinetic energy corresponds to a nominal range 380 mm in water (Berger et al., 2005) and it is currently the most applicable maximal energy in proton therapy centers. The relative velocity to the velocity of protons of any energy can be calculated by:

\[ \beta = \frac{v}{c} = \frac{\sqrt{E_T^2 - m_0^2 c^4}}{E_c + m_0 c^2} \]  \hspace{1cm} (1.2)
where $c$ is speed of light, $v$, $E_c$ and $E_T$ are velocity, kinetic and total energy of the projectile. For a proton with mass $m_0 = 938$ MeV/c$^2$ and energy of 250 MeV, $\beta = 0.61$. In this range of energy, the protons lose their energy predominantly by Coulomb interaction with electrons and through nuclear reactions.

1.1.1. **Electromagnetic energy losses for charged particles**

Charged particles transfer most of their energy by non-elastic collision with the atomic electrons of the traversed matter. This energy loss results in atomic ionization and is described by the Bethe-Bloch equation (Ziegler, 1999)

$$\frac{-\partial E}{\partial x} = 4\pi r_e^2 m_e c^2 \frac{Z_p^2 Z_t}{\beta^2 A_t} \left[ \frac{1}{2} \ln \left( \frac{2m_e c^2 \beta^2 \gamma^2 W_m}{l^2} \right) - \beta^2 - \frac{C}{Z_t} - \frac{\delta}{2} \right]$$

(1.3)

where $r_e = e^2 / 4\pi \varepsilon_0 m_e c^2$ is the classical electron radius, $e$ and $m_e$ are the electric charge and the mass of electron, $\varepsilon_0$ is the permittivity of the vacuum, $N_{av}$ is Avogadro’s number, $Z_t$, $A_t$ and $l$ are the atomic number and atomic mass and the average excitation potential of the target atom, $Z_p$ is the effective charge of the particle, $\gamma = 1 / \sqrt{1 - 1/\beta^2}$ and $W_m$ is the maximum energy loss of the proton in a single collision with a free electron. $C$ is the shell correction, which plays a role only at low velocities compared to the velocities of the bound atomic electrons in the target atom. $\delta$ is the density effect correction term. The maximum energy loss to a free electron is described by

$$W_m = \frac{2m_e c^2 \beta^2 \gamma^2}{1 + 2\gamma m_e \frac{m_e}{m} + \left( \frac{m_e}{m} \right)^2}$$

(1.4)

The deposited energy in water as a function of proton kinetic energy is shown in Figure 1-3. It can be seen that electronic stopping power contributes mostly to energy loss, whereas the contribution of nuclear stopping power is very small in comparison. It is clear from the equation (1.3)) that the energy dependence can be approximated by $\frac{\partial E}{\partial x} \approx \frac{1}{\beta^2}$ at non relativistic particle energies. As such, the rate of the transferred energy increases when the velocity of the proton decreases along the penetration direction in the medium, resulting in a rapid rise at low energies, explaining the typical shape of the Bragg peak curve.
1.1.2. Range of proton

The mean range of protons $R$ impinging on a medium is defined as the depth where the proton fluence drops to half of its initial fluence. This is due to the statistical fluctuations of the energy loss processes of individual protons. As a result, mono-energetic protons don’t have identical range, implying that the range of a proton beam is intrinsically an averaged value. This longitudinal smearing of the range is known as range straggling. The range can be numerically computed by integrating the inverse of the total stopping power function from an initial energy $E_0$ to a small final kinetic energy $E_f$ (the so-called Continuous Slowing Down Approximation proton range (CSDA)) (Berger et al., 2005), which however, ignores scattering and range straggling effects

$$R(E_0) = R(E_f) + \int_{E_f}^{E_0} \left( \frac{1}{\rho \frac{dE}{dx}} \right)^{-1} dE \left[ \frac{g}{cm^2} \right]$$

(1.5)

$R(E_f)$ is the residual path length ($E_f = 10 \text{ eV}$ and $R(E_f) = 0$) (Jani, 1982). A relationship between kinetic energy of the proton beam and the corresponding range in water can also be analytically approximated using a power law known as the Bragg–Kleeman rule (ICRU 49, 1993);
\[ R_0 = \alpha E_0^p \]  
(1.6)

where, \( E_0 \) is kinetic energy in MeV, \( \alpha \) is an absorbing medium constant which is proportional to the square root of the effective atomic mass and to the inverse density of the medium (Bortfeld, 1997). \( p \) is an exponent. Figure 1-4 shows the range energy relationship where \( p \approx 1.737 \) and \( \alpha \approx 0.00269 \ \text{cm MeV}^{-1} \). In clinical practice, integral depth dose measurements are used to approximate the proton range, where the proton range in the stopping medium corresponds to the distal 80% point of the Bragg peak.

Range straggling increases with increasing depth of protons due to the accumulation of the small fluctuations of the energy loss processes. This means that the dose deposited at the end of the range is smeared for higher energy protons, which results in a reduced magnitude of the peak than for lower energies (see Figure 3-2 (c)). For monoenergetic protons, the distribution of the path can be approximated as a Gaussian (Berger et al., 2005);

\[ R(z) = \frac{1}{\sqrt{2\pi\sigma_z}} e^{-\frac{(z-R_0)^2}{2\sigma_z^2}} \]  
(1.7)

where \( z \) is the penetration direction and \( \sigma_z \) the standard deviation, and depends on the inverse of the square root of the particle mass. This dependence explains why a Bragg peak resulting from heavy ions has a sharper peak than protons. \( \sigma_z \) can be approximated by a power law of proton range (Tobias et al., 1980):

\[ \sigma_z = 0.012R^{0.951}\sqrt{A}^{-1} \]  
(1.8)

Figure 1-4: The projected mean range of a proton beam in water (CSDA) (blue) and (red dashed) is the corresponding approximation using Kleemann rule and PSI data of gantry 2.
1.1.3. **Multiple Coulomb scattering**

Protons, passing near to an atomic nucleus, will interact also with the Coulomb field of the nucleus. Due to the small mass of protons in comparison to the mass of the nuclei, the transferred energy is negligible and thus the trajectory deflection is negligible. After many of these interactions however, a single proton will be scattered with a net angular deviation from its initial incident direction (Multiple Coulomb Scattering (MCS)). The divergence of proton beams crossing a medium is characterized by the scattering power, which is the differential of the mean square scattering angle of the particles in the depth $z$ of the material:

$$s = \frac{d\bar{\theta}^2}{dz} \quad (1.9)$$

For large scattering angles, the probability distribution is approximated by Rutherford scattering and has a larger tail than a Gaussian distribution. For small scattering angles, Moliere (Molière, 1948) has approximated the distribution function by a three-term power series. For very small angles, the first- and second order term can be neglected, resulting in a Gaussian distribution.

$$f(\theta)\,d\theta = \frac{1}{\sqrt{2\pi}\bar{\theta}} \exp\left[-\frac{\theta^2}{2\bar{\theta}^2}\right] \,d\theta \quad (1.10)$$

where $\theta$ is the angle between the proton direction and the longitudinal axis and $\bar{\theta}$ is a characteristic angle and which can be calculated as follows:

$$\bar{\theta}^2(z,E_0) = C_1^2 \left(1 + C_2 \frac{Z}{L_R} \right)^2 \frac{1}{L_R} \int_0^z \frac{1}{4E^2(z')} \,dz' \quad (1.11)$$

where $E_0$ is the proton initial energy, and the constants $C_1 = 13.6\,MeV$ and $C_2 = 0.038$ (Lynch and Dahl, 1991), $E(z')$ is the residual energy at the depth $z'$ and $L_R$ is the mean radiation length and depends on the chemical composition of the medium. It can be approximated by:

$$L_R = \frac{716.4A}{Z(Z+1)\ln(287/\sqrt{Z})} \quad (1.12)$$

where $Z$ and $A$ are the atomic and the mass numbers of the scattering material respectively (Tsai, 1974). For composite materials, the radiation length can be approximated by:

$$\frac{1}{L_R} = \sum_{i=1}^{n} \frac{w_i}{L_{R,i}} \quad (1.13)$$
where \( n \) is the number of components, \( w_i \) and \( L_{R,i} \) are the fraction by weight and the radiation length of the element, respectively. A convenient formula to calculate \( \theta_0 \) was presented by Highland (Highland, 1975):

\[
\theta_0 = \frac{14.16\text{MeV}}{\beta c p} z_p \sqrt{\frac{z}{L_R}} [1 + 0.038 \ln(z/L_R)]
\]  

(1.14)

The MCS is relevant for clinical dosimetry as it extends the transversal dose coverage. The material and the energy dependence of this latter necessitate the differentiation between the contributions of the scattering before the patient’s surface (e.g., monitor chamber, air gap) and the scattering within the patient’s tissue. Figure 1-5 demonstrates lateral broadening as a function of the traversed distance in water for four energies for two different particles (Pedroni \textit{et al.}, 2005).

1.1.4. \textbf{Nuclear interactions}

The probability that protons react with the nucleus increases with the kinetic energy of the proton energy (equation (1.5)). Since the residual energy of protons has to be much higher than the Coulomb-barrier of the target nuclei, the threshold for nuclear reactions through protons of the most biological materials is of the order of 8 MeV (ICRU 63, 2000). In the inelastic interaction the nucleus will break into different fragments. Possible secondaries at therapy energies are protons, neutrons, heavy fragments such as alphas and recoiling residual nucleus. As a rule of thumb, protons undergo nuclear reactions at the rate of 1.2\% (g/cm\(^2\)) in water, resulting into that approximately 20% of the primaries will undergo nuclear reactions over the clinical energy range. This primary fluence reduction and the long range resulting
neutrals impact the dose distribution. The proton fluence can then be described by the following formula:

\[
\Phi(z) = \Phi_0 \exp \left( \int_0^z \rho_t \sigma_t(E(z)) \, dz \right)
\] (1.15)

where \( \Phi_0 = \Phi(z = 0) \) is the initial fluence, \( \rho_t \) is the corresponding density of the target and \( \sigma_t(E(z)) \) the total nuclear absorption cross section that depends on the energy.

1.1.5. **Water equivalent thickness (WET)**

In proton therapy, the physical properties of the human soft tissues for energy loss, scattering and nuclear interactions resemble the one of water (Newhauser and Zhang, 2015). As such, water is used as a reference absorber material in dosimetry and range measurements. In clinical routine, the proton range in water is used as a surrogate for the human body and also for all objects crossing the beam path (e.g. proton beam monitor, patient’s immobilization system etc.). This allows to quantify the beam energy needed for the treatment just by adding the stopping power of the equivalent thickness in water of those materials. Water-equivalent thickness (WET) describes the amount of water \( t_w \) that results in the same proton range as a given material with a thickness \( t_m \) and density \( \rho_m \). The measurement concept is shown in Figure 1-6.

\[
WET = t_m \frac{R_w}{R_m}
\] (1.16)

where \( \frac{R_w}{R_m} \) is the ratio of proton range in water to the one in material. This approximation is only correct for stopping length media (Newhauser and Zhang, 2015). For thin targets, the WET is equal to the integral of the water equivalent path length (WEPL) along the beam path

\[
WET = \int_0^l WEPL \, dl
\] (1.17)

The WEPL can be thus approximated (Telsemeyer et al., 2012):

\[
WEPL \propto \frac{\rho_m^{\text{eq}}}{\rho_w^{\text{eq}}} \frac{\ln \left( \frac{2m_e c^2 \beta^2 y^2}{I_m} \right) - \beta^2}{\ln \left( \frac{2m_e c^2 \beta^2 y^2}{I_w} \right) - \beta^2}
\] (1.18)

since the mean ionization energy of typical tissue like materials are comparable to that of water, \( I_m \) is usually set to \( I_m \approx I_w \). Also the relative stopping power of a material to water can be approximated as constant for energies in the range \([10 – 1000]\) MeV (Köhler et al., 1965).
The WEPL for thin material can be calculated:

\[ \text{WEPL} = \frac{\rho_m \bar{S}_m}{\rho_w \bar{S}_w} \]  

where \( \bar{S}_m \) and \( \bar{S}_w \) are the mean stopping power of the medium and water respectively as a function of energy:

\[ \bar{S} = \frac{\int S dE}{\int dE} \]  

Zhang and Newhauser (Zhang and Newhauser, 2009) have used the Bragg–Kleeman rule (1.6), instead of the mean stopping power, and have computed values for \( \alpha \) and \( \beta \) for the WEPL for several materials.

\[ \text{WEPL} = t_w = t_m \frac{\rho_m}{\rho_w} \frac{S_m}{S_w} = t_m \frac{\alpha_w p_w}{\alpha_m p_m} E^{p_w-p_m} \]  

For very low energies (10 MeV) and for high Z materials (e.g. metal implanters, cortical bones, etc.) the relative stopping power (RSP) exhibits a dependence on energy that has to be considered in clinical practice (Newhauser and Zhang, 2009).

Figure 1-6: Schematic illustration of the principle of measuring the Water Equivalent Path Length (WEPL) of a target \( m \) by using the shift of the depth dose curve in the water tank. The target \( m \) is assumed to be denser than water what will results in a WET value greater than 1.

1.1.6. Features of pristine Bragg curves (BC)

A pristine BC is the depth dose curve that is obtained from a monoenergetic proton beam impinging on an absorber. As already explained above (section 1.1.1), the depth dose of protons is characterized by a low dose entrance and a sharp drop of the dose when the protons
reach their range. Different physical processes (e.g. electronic-, protonic buildup, MCS etc.) affect different depth regions of the depth dose curve. Due to MCS, the peak of the depth dose of small proton beams is suppressed as compared with that of a broad beam (see Figure 1-7). Close to the central beam axis of a broad beam, the removed fluence caused by lateral scattering is compensated by scattering towards it, resulting in an equilibrium state. However, this state is not the case when the size of the beam becomes smaller than the size of the scattering power due to MCS (Newhauser and Zhang, 2015). As a result, the energy fluence deposited at the deeper part of the Bragg curve is smeared out laterally much more than that in the plateau region. For this reason, proton beams with small size are not suitable to treat small and deep situated targets (Goitein, 2008). At the entrance of the absorber medium, charged secondaries are generated from non-elastic nuclear reactions and will deposit their energy deeper in the medium, resulting in a build-up effect. Since the composition of secondaries doesn’t vary much with increasing depth, electronic equilibrium is reached in a depth of about 4g/cm² (Goitein, 2008).

![Figure 1-7: Depth dose curve at the central-axis of proton beam of varying sizes. Figure courtesy of (Preston and Koehler, 1968).](image)

1.1.7. **Radio-biological rationale for ion beam therapy**

The response of biological tissue to ionization doesn’t depend only on the deposited dose, but also on the density of ionization accruing. This latter depends on the rate of the energy transfer per distance:
\[ \text{LET} = \frac{dE}{dx} \]  

(1.22)

Compared to photons, protons show an increased effect on biological target material which depends on the local ionization density. For protons, the linear energy transfer (LET) in the plateau region is small, resulting in a low ionization density. Only in the peak region, where LET is high, is the ionization density high. This leads to an increased biological effect.

The relation between dose and cell damage is determined on the basis of cell culture experiments. The results are mathematically described by the linear-quadratic model or \( \alpha-\beta \)-model:

\[
LQ = -\ln \left( \frac{N}{N_0} \right) = \alpha D + \beta D^2
\]  

(1.23)

Where the dose is defined as the total energy absorbed per unit mass:

\[
D(\vec{x}) = \frac{\partial E}{\partial m}(\vec{x}), \quad (1\text{Gy} \equiv J/Kg)
\]  

(1.24)

\( N \) and \( N_0 \) are the surviving and the initial number of cells irradiated with the dose \( D \). \( \alpha \) is the parameter that describes the linear component of the survivor curves, while \( \beta \) refers to the quadratic portion of the curve. The relative biological effectiveness (RBE) is used in order to compare two different radiation processes. Proton RBE is then defined as the quotient of a reference photon dose \( D_{\text{photon}} \) (typically \( ^{60}\text{Co} \)) to proton dose \( D_{\text{proton}} \) leading to the same biological effect:

\[
RBE_{p^+} = \frac{D_{\text{photon}}}{D_{\text{proton}}}
\]  

(1.25)

If we use formulas (1.23) and (1.25) we can then defined \( RBE_{p^+} \)

\[
RBE_{p^+}(\alpha_x, \beta_x, \alpha, \beta, D) = \frac{\sqrt{\alpha_x^2 + 4\beta_x(\alpha_pD + \beta_pD^2) - \alpha_x} - \alpha_x}{2\beta_x D}
\]  

(1.26)

where \( \alpha_x, \beta_x \) are parameters of the reference radiation and \( \alpha_p, \beta_p \) are parameters of proton radiation (Wilkens and Oelfke, 2004). Figure 1-8 show an example of two survival curves for cells irradiated by densely (high LET) and sparsely ionizing radiation (low LET) beams. The large shoulder of the photon curve indicates that a lot of repairs occur in the cells after the irradiation. However, densely ionizing radiation exhibits a cell survival curve that is almost a straight line i.e. almost no repair is possible in the cells irradiated with the same dose delivered by heavy ions.
INTRODUCTION

Figure 1-8: Survival curves for cells irradiated with X-rays (Cobalt source) and with protons. Densely particles cause more damage to the cells, which can only be repaired to a very limited degree. Figure courtesy of (Wouters et al., 2015)

1.2 Delivery

In general, tumours have a bigger size dimension than the dimension of a single mono energetic pencil beam. Therefore, in order to be able to deliver a homogeneous high dose to all the tumour volume, an accelerator and beam-line system is used to accelerate protons with a required intensity and several methods are applied to enable a full coverage of the target.

1.2.1 Accelerator

A cyclotron consists of two semi-circular dipole magnets placed side by side. The dipole magnets are designed to generate uniform magnetic fields and are separated by a gap in which an electric field is induced by an alternating voltage. Particles are then injected into the middle of the cyclotron and make use of the magnetic force to bend till they reach the gap where they are accelerated through the electric field. Particles will thus follow a path with larger radius as they gain energy. In the meantime, the electric field is alternated to allow for further accelerating. Due to the energy gain, the increase of speed of the particles compensates for the increased path length traversed. The frequency to reach the gap is constant and is called the cyclotron frequency.

\[ \omega_{\text{cyclotron}} = \frac{qB}{m} \sqrt{1 - \frac{v^2}{c^2}} \]  \hfill (1.27)
INTRODUCTION

Cyclotrons for proton therapy can deliver a beam with a nominal energy of up to about 250 MeV. This maximal energy corresponds to a range in tissue of over 30 cm and allows to treat deep situated tumours. In order to be able to treat tumours situated elsewhere in the human body, an energy degrader system is used in the beamline.

An alternative accelerator type for therapy is the synchrotron. A synchrotron is a circular ring in which particles are accelerated through interaction with externally applied electromagnetic fields. As opposed to the cyclotron, the circular path of the particles in the synchrotron is constant; therefore the magnetic force $\vec{B}$ required to bend the energetic particles must be increased in synchronization with each rotated loop. For this accelerator, no degrader system is necessary, as the energy of the protons can be varied pulse by pulse. However synchrotrons are much bigger than cyclotrons and provide only pulsed beams.

1.2.2 Passive scattering (PS)

Passive scattering (Koehler et al., 1975) and (Koehler et al., 1977) is the most common modulation technique in proton therapy. In this approach, the entire target volume is irradiated with a uniform field until the prescribed dose is applied. The beam is scattered laterally using sophisticated scatter foils to cover the cross section of the target volume. Then a rotating modulator wheel is used to spread the proton flux longitudinally (Chu et al., 1993). A spread-out Bragg peak (SOBP) is generated by superimposing single BPs of different range and different weights, resulting in a uniform dose in depth. This consists of many range shifters with different thickness. The lateral field is then collimated and the distal field is shaped to fit the distal edge of the tumour using a patient-specific range compensator. In order to minimize the scattering, the compensators are made of low-Z material. PS suffers from the drawbacks of requiring individual patient-specific hardware and also from unnecessarily high dose at the proximal side of the target volume. Furthermore the collimation and compensator hardware causes a decrease of intensity and also increased dose due to secondaries such as neutrons.
1.2.3 Pencil beam scanning

Active scanning in proton therapy (Kanai et al., 1980), (Haberer et al., 1993) and (Pedroni et al., 1995) is based on delivering the prescribed dose using a sequence of single spots, with the lateral coverage of the target volume being achieved by deflecting the positions of proton pencil beam spots using sweeper magnets. Longitudinal adjustment is then achieved either by varying the nominal energy or by introducing a range shifter with a defined WET in the beam path. The dose is controlled by the time of the delivery of the spot and by the beam current. This technique allows for more conformal dose distributions at the proximal side to the target volume in comparison to the passive scattering technique (see Figure 1-9). In addition the use of patient specific hardware is no longer required, which reduces the time cost of the quality assurance and also the dose due to neutron contamination. On the other hand, the delivered dose is sensitive to the accuracy of the raster locations of the spots, keeping in mind that a field is composed of a temporally delivered sequence of single spots. As such, the technique is prone to interplay effects when non static target volumes are treated (Phillips et al., 1992) and (Bert et al., 2008).
1.2.4 Planning CT

Generally in proton therapy, a single-energy X-ray CT (planning CT) of the patient is acquired. This provides precise information about 3D anatomical locations for diagnosis and so allows for delineating targets structures and organs at risk (OAR). In order to increase contrast and information of anatomical structures, the CT images are registered with other imaging modalities, such as Magnetic Resonance Imaging (MRI) or Positron Emission Tomography (PET) to increase the soft tissue contrast and metabolic functionality respectively (Schiepers and Dahlbom, 2011).

The CT provides 3D maps of photon attenuation within the patient. As photon attenuation and proton stopping power are both a function of the electron density (Schaffner, 1997), it allows to calculate the proton range and so the planned dose delivery. However at low photons energies, as used in CT imaging, or in high density tissue, not only Compton scattering but also photoelectric effect and coherent scattering contribute to photon attenuation. While the first one is proportional to Z, photoelectric and coherent scattering are proportional to higher orders of Z. Protons however depend on tissue density and the chemical composition of the material (see equation (1.13)). The conversion from CT number to WEPL is based on the proportionality between the relative stopping power ratio and the relative electron density which correlates to the attenuation coefficient (Schaffner, 1997).

In clinical practice, this can be achieved based on calibration measurements using tissue substitute materials of known elemental composition which have the same radiological properties of body tissues. Their relative stopping power is measured using a proton beam. The most advanced method to perform this calibration was presented by Schneider (Schneider et al., 1996). This stoichiometric method makes use of both the chemical composition of biological tissues and the measured CT-number of tissue substitute materials to derive CT-numbers of human tissues.

1.3 Range uncertainty

As already mentioned (section 1.1), the rationale for the clinical use of particle beams is the feasibility of delivering higher doses to the tumour while sparing surrounding healthy tissue, leading to a reduced treatment volume and a lower integral dose (Kraft, 2000). The efficiency of the treatment can be improved by 3D modulation and optimized weighting of individual pencil beams (Scheib and Pedroni, 1992) and (Lomax, 1999). However this superiority is based on the accuracy with which the intended dose can be delivered to the target volume. Several sources of uncertainties could accrue throughout the fractionated treatment. Such
uncertainties may provoke a shift in location of the distal dose falloff, which could cause under-dose in the target location or overdose in healthy tissues or in the worst case in OAR that could result in a serious clinical failure (Lomax, 2008). Some of these uncertainties have a random character, and therefore would diminish over the whole fractionated resultant deviations decrease by the root mean square of the number of fractions (e.g. daily deviation of positioning of the patient). On the other hand, some of these can be systematic and will be proportional to the range of the applied beam and would last over the whole treatment.

Paganetti (Paganetti, 2012) has reported that several sources of errors are related to inferring the WER value from the patient planning CT data. The mean excitation potential required to convert CT number to RSP has deviations of the order of 10–15% (Andreo, 2009) which could lead to a range error of about 1.1% for soft tissue and 1.8% for bone (Schaffner and Pedroni, 1998). Uncertainties in attenuation values, such as beam hardening, motion and high-Z material artifact, also affect the range calculation (Chvetsov and Paige, 2010). In addition, the resolution of images can impact the resulting proton range (España and Paganetti, 2011). The total resulting deviation is assumed to be about 2.5% of the applied proton range, to which a 1mm random error should be added. However, since the prescribed dose is delivered over several weeks, anatomical changes may occur due to change of the weight of the patient, variations in the filling of cavities and pathologically-triggered changes in tumour tissue, due to tumour cell kill as a result of the radiation treatment. In addition, functional anatomical variation has to be taken in account, such as tumour motion due to breathing, variable filling of the bladder and rectum. To compensate for these uncertainties, the planning target volume (PTV) needs to be expanded by applying adequate safety margins. The applied magnitude of this latter reflects the clinical accuracy of the treatment and leads to increases the volume of surrounding organs receiving high dose while reducing the therapeutic ratio (Marks et al., 1974).
2. Imaging techniques in particle therapy

In order to exploit the superiority of high precision proton therapy, in-vivo range verification and a high accuracy with which the intended dose is delivered to the target volume are required. This is particularly true as the patient’s tissues are highly inhomogeneous in density and chemical composition, and the Bragg Curve (BC) position is extremely sensitive to variations of the material crossing the beam path. Knopf (Knopf and Lomax, 2013) have reported the currently available tools for in-vivo range verification and have categorized the monitoring approaches in three stages:

Measurement technique:

- Direct: proton range is measured directly
- Indirect: proton range is induced from other phenomena and signals

Timing:

- Online: monitoring can be performed pre- or during the treatment delivery
- Offline: monitoring performed after completion of the treatment

Dimension:

- 1D/2D/3D: the geometrical information obtained from the measurement

Seco and Spadea (2015) have also reviewed the state of the art and the tools under development for imaging in both proton and ion therapy. The authors however have categorized the approaches in three stages which depend on the timing and thus the importance of the impact of the monitoring on the quality of the treatment.

This chapter provides a brief review on the current range verification modalities in particle therapy, and will focus on Positron Emission Tomography (PET), prompt photons and proton transmission imaging (PTI) with the latter modality being the focus of this thesis.
2.1 PET imaging

Figure 2-1: Double head positron camera installed in the treatment site at GSI Darmstadt. Figure courtesy of (Enghardt et al., 2004a).

In-vivo range verification techniques are based on detecting secondary particles resulting from nuclear interactions between the particles and the nuclei of the target in patient. The emitted secondary depends on the particle and on its energy. Table 2-1 lists few $\beta^+$ emitters, their half-life and the threshold energy of incident protons for the interaction in the human body (Kraan, 2015). The emitted positron annihilates, after a small distance, with an electron of the surrounding tissue, into a pair of high-energy photons of 511 keV, which can be detected using a PET coincidence detector and the position of the electron-$\beta^+$ annihilation can be reconstructed, what allows for the reconstruction of the activity along the beam path (see Figure 2-2).

<table>
<thead>
<tr>
<th>$\beta^+$ emitter</th>
<th>Half-life (min)</th>
<th>Reaction channel</th>
<th>Threshold (MeV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{15}$O</td>
<td>2.037</td>
<td>$^{16}$O(p, pn)$^{15}$O</td>
<td>16.79</td>
</tr>
<tr>
<td>$^{11}$C</td>
<td>20.385</td>
<td>$^{12}$C(p, pn)$^{11}$C</td>
<td>20.61</td>
</tr>
<tr>
<td>$^{13}$N</td>
<td>9.965</td>
<td>$^{16}$O(p, 2p, 2n)$^{13}$N</td>
<td>5.66</td>
</tr>
<tr>
<td>$^{14}$N</td>
<td></td>
<td>$^{14}$N(p, pn)$^{13}$N</td>
<td>11.44</td>
</tr>
<tr>
<td>$^{30}$P</td>
<td>2.498</td>
<td>$^{31}$P(p, pn)$^{30}$P</td>
<td>19.7</td>
</tr>
<tr>
<td>$^{38}$K</td>
<td>7.636</td>
<td>$^{40}$Ca(p, 2p, 2n)$^{38}$K</td>
<td>21.2</td>
</tr>
</tbody>
</table>

Table 2-1: Frequent nuclear reaction producing positron emitter production in proton therapy. Adapted from (Kraan, 2015)

For irradiation with carbon ions (Figure 2-2 (left)), the profile of the induced activity shows a flat plateau and a peak of the activity localized proximal to the Bragg peak. This is due to the fact, that the kinetic energy of the positron emitting residual projectile (e.g. $^{10}$C and $^{11}$C) is the
roughly the same as the primary fluence and therefore roughly identical range, which can be explained by the proportionality dependence of the mass radiative stopping power to $Z^2/A$ (Rinaldi, 2011). On the hand the activation in proton beams however is caused mainly by the reaction with the matter and there is no projectile activation, the $\beta^+$ activation doesn’t correlate with the proton depth-dose curve, rather it depends only on the on the elemental composition of the matter in the beam path (Figure 2-2 (right)), rather it depends only on the target activation and so on the elemental composition of the material in the beam path (Parodi et al., 2002). The higher activity yield of the proton beam in comparison with heavy ions is caused by the high primary fluence of the protons applied to reach the same physical effect as carbon ions (Kraft, 2000) and (Rinaldi, 2011) The fall-off profile for protons of the activity is however shifted against the depth dose curve. The early drop of the activity of protons in comparison to the BC is explained by the energy threshold required for interaction (Oelfke et al., 1996) and (Knopf and Lomax, 2013).

Figure 2-1 depicts the integrated in-beam PET at Gesellschaft für Schwerionenforschung Darmstadt (GSI) for in-vivo range verification. The data acquisition is performed during the beam delivery which allows for a verification immediately after the beam delivery (Enghardt et al., 2004b), (Parodi, 2004), (Crespo et al., 2006) and (Nishio et al., 2010). This approach allows monitoring of the activity contribution produced by short half-life positron emitters (see Table 2-1) and avoids the washout of the biological signal (Parodi et al., 2007b). In addition the verification of individual treatment fields is possible and the monitoring can by performed without moving the patient. On the other hand, the clinical integration of such arc system could limit treatment coverage of the beam line. In addition it suffers from low signal to noise ratio due to very short half-lives random events produced through nuclear reactions and $\beta^+$ emitter fragments (Enghardt, 2004a).

Figure 2-2: Comparison of depth profile of measured $\beta^+$activity (solid line) and the depth dose curve (dotted) in PMMA. (a) For carbon ions beam of 260 MeV/u and (b) for 140 MeV proton beam. Figure courtesy of (Enghardt et al., 2004b).
The integrated in-beam PET scanner at GSI consists of a limited angle two opposite positron detectors. The detectors are composite of 42 x 21 cm$^2$ active windows. Each camera consists of 8 x 4 position-sensitive scintillation detectors of bismuth germinate (BGO) with a size of 54 x 54 x 20 The blocks are further subdivided into 8 x 8 small crystals resulting in 2048 x 2048 array of response within the detector Field of View mm$^3$ (Casey and Nutt, 1986) and (Enghardt et al., 2004a).

Post-treatment activity monitoring on the other hand typically uses commercial PET (Parodi et al., 2007). This provides a better spatial resolution than the previous cited system since it allows to exploit the full ring detector. On the other hand, the monitoring is performed in a different patient set-up as in the treatment. In addition this modality measures the integral dose and can’t resolve individual fields and it suffers from washout of the signal.

In-vivo Range verification using PET activity has some promising results PET (Parodi et al., 2007). However the monitoring could be performed only during or after the treatment since the secondaries activity results only by the treatment beam. In addition the modality suffers from the low accuracy of the spatial reconstruction due to the diffusion process within the biological tissues. These factors render this technique not yet suitable for direct range verification. On the other hand this method is suitable for post-treatment dose verification. Studies have shown, that comparison of the measured PET activity distribution with MC calculated activity, based on prescribed dose distribution, provides a method for verification of treatment delivery (see Figure 2-3) (Parodi et al., 2008).

Figure 2-3: The on-line dose monitoring using PET system implemented at GSI. Left: The planned dose distribution superposed on a CT slice. The OAR (brain stem) is bordered in red. Middle: the corresponding Monte Carlo pre-calculated positron activity. Right: the measured positron activity as iso-dose. Figure courtesy of (Enghardt et al., 2004a)
2.2 Prompt gamma radiation

Prompt gamma imaging has also been investigated as an on-line approach for range verification for particle therapy (Min et al., 2006). Prompt gammas are produced from the decay of nuclei exited due to the non-elastic nuclear interaction along the path of the incident protons with the target nuclei. The longitudinal correlation between the emitted prompt gamma profiles along the beam path and the location of the residual depth dose can be used to monitor the range of the particle on-line (Min et al., 2006). Such monitoring is performed through the time correlation between the detected $\gamma$-rays and the impinging beam. Furthermore, the detected rays have to be discriminated from $\gamma$-rays emitted from decays happening in the surrounding tissue due to scattering and also from Compton-scattered $\gamma$-rays and those resulting from interactions of elastically scattered neutrons. The energy spectrum of the emission is in the range (0-10 MeV) (Kraan, 2015). In comparison with the $\beta^+$ imaging technique, the main advantage of prompt gammas is that the measurements are not limited due to washout effects and diffusion in biological tissue since they are emitted instantly (first $10^{-11}$ seconds after the collision) and are emitted where the reaction occurred.

Min et al., (2006) analyzed the spectrum of gammas detected from an angle of 90° to the beam axis. A scintillator detector (CsI) was used with an appropriate collimation in order to shield moderated fast neutrons and un-collimated gammas. The results of a 100 MeV proton beam in a phantom have confirmed the correlation between the location of the Bragg peak the peak of the prompt $\gamma$ distributions within 1-2 mm. However this correlation deteriorates at higher proton energies due to neutron background.

![Figure 2-4](image-url): (a) schematic detector system used to measure the prompt gamma. The detector is aligned perpendicular to the beam axis. A collimation system based on high-Z material, paraffin and B4C powder is used to shield for neutrons and scattered photons. (b) The measured spectra of prompt gamma scans compared to depth dose curve measured using the same beams and ionization chamber. Figure courtesy of (Min et al., 2006).
Bom V. et al., (2011) proposed the principle of using a gamma camera and a knife-edge-shaped slit placed perpendicular to the beam direction. The results of the MC calculations have shown that this technique increases the collection efficiency in comparison with a pinhole camera. This concept has been experimentally validated using a homogeneous Polymethylmeth acrylate (PMMA) target and a range verification with a 1σ accuracy of 1-2 mm has been reported (Smeets et al., 2012). Investigations have demonstrated that the approach is more suitable for scanned proton beam therapy (Polf et al., 2009) and (Kurosawa et al., 2012). To overcome the detection challenges, time of flight (TOF) and energy discrimination techniques have been proposed in order to better discriminate between prompt gammas and background radiation (Testa et al., 2010) and (Richard et al., 2010). Monte Carlo simulations and measurements resulting from irradiation of PMMA targets with 73 MeV/u 13C and 12C ions have been performed and have shown that the cross sections of non-elastic collisions is within 5-10% and results in 2 photons and three neutrons for each single interaction (Testa et al., 2008). The energy spectrum of the resulting photons and the velocity of the neutrons, which range between the speed of the impinging projectiles and zero, allow to distinguish between the signals of the γ-rays and the signal of the neutrons. On the other hand, there was no correlation between prompt neutron and the carbon ion range.

A first clinical application of in vivo range verification based on prompt γ-rays has been reported (Richter et al., 2016). Prompt gamma imaging was performed using a prototype of a knife-edge shaped slit camera consisting of 40 individual scintillation units arrayed in two columns and adjusted to detect emission spectrum of the prompt gammas in the range of MeV (3–6 MeV) (Smeets et al., 2012) and (Perali et al., 2014). In vivo measurements were performed for patients treated with passive scattered proton beams. Monitoring this treatment modality however introduces a drawback of higher neutron contamination and single Bragg peak locations can’t be resolved as the entire tumour volume is irradiated at once. As such, the authors filtered the noisy signals by subtracting the neutron induced gamma background, with the background quantification of each field being separately performed by measuring identical treatments through closing the collimator slit of the camera. To avoid the uncertainties that can be caused by the interfractional anatomical changes, background signal quantification was performed during treatment and in a homogeneous water phantom. (Testa et al., 2014) have proposed to make use of the time-resolved analysis of the prompt gamma signal to resolve the energy spectra resulting from the modulation wheel in passive scattering and results have shown that this technique could detect inter-fractional range deviations of 2 mm. The authors report also that these results are in agreement with range verification performed using control CTs (Richter et al., 2016).
2.3 Particle radiography and computed tomography

Due to the fact that diagnostic CTs are performed with X-ray energies of about 120 keV, the derivation of proton stopping power necessitates a semi-empirical calibration curve, resulting in water equivalent range (WER) uncertainties (1 sigma) of 1.1% and 1.8% in soft tissue and bone respectively (Schaffner and Pedroni, 1998) and 5.0% in lung tissues (Yang et al., 2012). The resulting conversion uncertainty consists of the quadratic sum of the parameterization of stoichiometric method, mean excitation potential and the variation of composition of the human tissue and other sources (Poludniowski et al., 2015). As such, a direct measurement of proton stopping power would be of great clinical value.

Proton imaging is based on the transmission of low fluence, high energy protons through the scanned object, so that the intensity of penetrating radiation can be detected downstream of the patient (Koehler, 1968), (Hanson et al., 1982), (Schneider and Pedroni, 1995), (Schulte et al., 2004) and (Shinoda et al., 2006). High energy proton imaging provides the potential to reduce the uncertainties correlated to X-ray based conversion calibrations, since the source of errors cited above do not contribute to the measured RSP (Schneider et al., 1996) and (Poludniowski et al., 2015). Such improvement in accuracy will potentially allow to reduce clinical safety margins, and expand the scope of possible treatment beam directions.

Incident charged hadrons lose energy primarily by inelastic Coulomb collisions with the atomic electrons, while the rate of energy lost due to hard-collision with the nuclei is minor
This can be explained by the mass of protons in comparison to the one of nuclei, since the energy loss of the incident projectile is proportional to the inverse of the mass of particles of the matter (see section 1.1.1). As such, integral stopping power is characterized mainly by the properties of the target medium and the incident energy. For typical proton energies used in therapy (ranges of 70 to 250 MeV) and for human tissue (low-Z medium), the stopping power ratio however exhibits a weak dependence on the incident energy and on the thickness of the object (Janni, 1982), (Yang et al., 2012), and (Newhauser and Zhang, 2015). This approximation provides enough clinical accuracy that proton radiography, measured at beam qualities that do not differ significantly from therapeutic ones, could be used to improve the accuracy of the calibration curve applied in the dose calculation (Schneider et al., 1996) and (Doolan et al., 2015). However, and as will be discussed in this thesis, proton imaging could also be performed during pre-treatment to decrease positioning errors since the transmitted images are provided with the same geometrical conditions as used during treatment. Furthermore, proton imaging could be used to directly verify anatomical changes and motion in the beam path, due to the higher sensitivity to density variations compared to X-ray radiography. In addition, proton radiography has the advantage of reduced imaging dose compared with X-ray monitoring system (Schneider and Pedroni, 1995) and (Schulte et al., 2004). Finally, if several projections of residual energy or range are acquired by rotating the proton gantry about the patient, proton CT (pCT) information can be further processed to reconstruct a 3D WEPL that could potentially be used for proton treatment planning (see section 6.2.1).

Poludniowski (Poludniowski et al., 2015) have reported on more modern developments of proton- radiography and -CT. The goal of proton imaging is to recover the true water equivalent thickness within the patient which is equivalent to the integral of RSP along the proton track. A rational requirement of such a system therefore is to achieve a density resolution of 1%, a spatial resolution of 1 mm, an imaging time (including acquisition and reconstruction time) of less than 20 min and a dose exposure of less than 20 mGy for a head scan (Schulte et al., 2004).

### 2.3.1 Proton radiography

In the 1960s, Koehler (Koehler, 1968) from Harvard reported on the first experimental work of proton radiography (PR). He suggested to use the statistical fluctuations of the stopping depth (Range straggling) of the proton fluence with a given initial energy (see section 1.1.2) to produce residual fluence maps measured with a photographic film. Since the range straggling is approximately proportional (1-2%) to the nominal range, even a finite variation of the thickness of the object (up to 2%) will result in a substantial (up to 100%) change in the
residual fluence. Placing a photographic film at the end of the proton range, this approach has been found to measure even a 0.2% density variation in a homogeneous media with high contrast while using only low radiation dose radiographs compared to X-ray radiography. On the other hand, the PR images were found to be rather blurred due to Coulomb multiple scattering of protons. In addition, the proposed approach was limited to thin and homogeneous samples.

Figure 2-6: (a) First published proton radiograph based on measuring proton intensity at the end of proton range. (b) First proton computer tomography performed at Los Alamos using a pencil beam of 240 MeV. The scanned object consists of PMMA cylinder with inserts of multi geometrical forms and density. (a) Figure (a) courtesy of (Koehler, 1968) and figure (b) courtesy of (Hanson et al., 1978).

Hanson et al. at the Los Alamos Laboratory (Los Alamos, NM), have developed the first pCT concept (Hanson et al., 1978) and (Hanson, 1979), and have also investigated the application of different detector modules (Hanson et al., 1981). The authors also performed the first human specimen scans (Hanson et al., 1982). In order to provide a high quality beam, a vacuum box has been used to extend the vacuum up to the target in order to avoid MCS effects of the primary particle resulting from the air gap between the nozzle and object. The pencil beam size was determined by the slit size and was 1 mm Full Width at Half Maximum (FWHM) in the horizontal and 10 mm in vertical direction, while the divergence was 6 milliradians at the entrance of the object. Two energies of 224 MeV and 236 MeV were used with energy spreads of 0.4% FWHM. The phantoms were PMMA cylinders with aluminium inputs. In order to reduce the energy dynamic required from the detector, the phantom was placed in a water bath of 266 mm. Two gas filled multi-wire proportional chambers (MWPC) were placed 50 mm behind the object to track each proton’s position. The gas filling of the MWPC consisted of (75% argon, 1% freon (13B-1), 24% isobutane, and 0.4% l-propanol) and operated in event trigger mode. The active wires were operated in the vertical mode which, together with the beam collimation, allowed to restrict the vertical scattering accepted by the system. It was found that up to 29% of the primary protons end up outside the vertical wires,
reducing the efficiency of the system. The residual energy-range detection was performed using a stack of 32 counters NE102 scintillator of 51 x 81 x 31.8 mm$^3$ with the first two counters being operated as event triggers. The root mean square deviation of the range was observed to be $1.54 \pm 0.10$ mg cm$^{-2}$ with fluctuations in range being caused by scattering, variations of thickness of the water tank and also the SPR dependence from the initial energy (Janni, 1982). 360 projections were performed with a 0.5° angular resolution and pencil beam positions of 1 mm. The position of the events at the exit of the water bath were then used to track the protons which were assumed to have traversed the water bath in straight lines. Finally, tomographic reconstruction was performed using standard filtered back-projection methods. This work proved the dosimetric advantage of pCT compared to X-ray CT, but also highlighted the poor spatial resolution due to MCS, and the restricted efficiency of the system due to a limited event collection rate (10 kHz).

2.3.2 Paul Scherrer Institute experience

Experience in proton radiography at the Paul Scherrer Institute (PSI) was first based on a gantry integrated radiographic system (Pedroni et al., 1995). The proton-tracking detector (Pemler et al., 1999) consisted of two position sensitive scintillating fiber hodoscopes (see Figure 2-7), a photomultiplier and fast readout logics allowing event rates of 1 MHz. The scintillating hodoscopes (Bicron BCF 12; square fibers, decay time, 3.2 ns, and maximum emission $\lambda = 435$ nm) were placed both in front of and behind the scanned object, to enable measurements in coincidence of the entrance and the exit coordinates of each event. Residual range was detected with a range telescope consisting of a stack of 64 closely packed and optically isolated plastic scintillator tiles, each with a thickness of 3mm (Bicron BC404, decay 1.7ns and maximum emission $\lambda = 408$ nm). This density resolution results from the range straggling of the applied beam energy and the uncertainties of the detector, and is close to the combined range uncertainty of a 170 MeV proton beam with a momentum band of $\Delta p/p \approx 0.4\%$ (2.5 mm). The accuracy of the system, based on measurements using homogeneous water and 214 MeV, was better than 0.6 mm. For lateral positions measurements, the fiber hodoscopes had a sensitive area of 220 x 32 mm$^2$ and a width of 2 mm. For each coordinate, two layers of fibers were shifted against each other by half of a fiber width, resulting in a spatial resolution of 1mm. This approach has been found to double the light yield efficiency over that of a single 1 mm fiber (Pemler et al., 1999). Wavelength-shifting fibers were used to collect the scintillation light and guide them to the photomultiplier-channel.

The authors have also measured the broadening of the range spectrum to create range dilution images. These images reflect the scatter power of the impinged region and thus it could
demarcate inhomogeneous locations. The broadening of the range spectrum was obtained by integrating the range distribution of each measured proton in each single pixel and determining the range located between 31% and 69% values of the cumulative range distribution.

Figure 2-7: Schematic presentation of the PR system used at PSI. The coordinates of incident protons are measured with the mean of two pairs of hodoscopes are placed in front of and behind scanned object. Each pair of consists of two laterally shifted hodoscopes to increase the spatial resolution. Figure courtesy of (Schneider et al., 2004).

Figure 2-8: PR Images of the dog patient treated at PSI. The images were reconstructed in different depth in the object. (up) density range images, (below) range dilution images. The images were reconstructed at 5% (left), 30% (middle) and 50% (right) of the integral thickness of the animal. Figure courtesy of (Schneider et al., 2004).
2.3.3 Loma Linda University Medical Center experience

![Proton computer tomography set-up](image)

Figure 2-9: Proton computer tomography set-up (Phase-II) using a fixed proton beam line. The rotated object is placed between silicon micro-strip sensors which measure the coordinates and the entrance angle of protons. The residual energy is measured by the mean of a stack of scintillator detector. Figure courtesy of (Sadrozinski et al., 2016)

The Loma Linda University Medical Center (LLUMC) has also developed a proton CT head scanner (Schulte et al., 2004). In their system, in order to improve spatial resolution of the reconstructed water equivalent path length, tracker systems were used to measure the entrance and exit proton coordinates and angles before and after the scanned object. This allows for the tracing of the ‘Most Likely Path’ (MLP) that protons undergo through the object (Williams, 2004). The tracker consists of silicon micro-strip sensors (SSD) which were originally developed for high energy physics. These comprise of two single-sided sensors, one each with horizontal and vertical strips. The thickness of the SSD has been chosen to be small (228 µm) as MCS could affect the accuracy of the MLP within the object. The range detector consists of multi-stage plastic scintillators with a read-out rate of up to 2 MHz. Their investigations have shown that reconstruction of objects require at least 100 events per cubic millimeter of the detectors in order to compensate for losses due to nuclear interactions and the uncertainties to determine the residual energy at the detector. A pCT of a head phantom was performed using 90 planar projections of 180° angular range in 2° steps. The scans were completed within 6 min due to the fast readout rate. The resulting integral dose corresponds to 1.4 mGy which is much lower than that delivered using conventional CT.

Using the same set-up, Plautz (Plautz et al., 2014) have also suggested to perform proton scattering radiograph, as this is very sensitive to energy variation, since the mean lateral scattering angle is proportional to the inverse of its energy and is a function of the radiation length of the irradiated object (see equation (1.14)). For each pixel, the horizontal and vertical mean scattering over the events were measured, which are equal to the net angular scattering of the impinging event and the beam axis. The resulting scattering was added in quadrature to
generate the lateral scattering angle (equation (1.19)). The energy-loss radiograph was then derived analytically using equation (1.11)) for proton scattering (Lynch and Dahl, 1991). These promising results have demonstrated that scattering radiographs of thin objects have the potential to provide higher density resolution than energy-loss radiographs.

2.3.4 Other techniques

The TERA Foundation (Amaldi et al., 2010) has also built a system previously designated to speed up and improve quality assurance at the National Center for Oncological Hadron therapy (CNAO) in Pavia. The detector system is based on a set of position sensitive Gas Electron Multipliers (GEM) and a range telescope consisting of plastic scintillators of 28.3 mm thickness. The system makes use of two scintillators at the entrance windows as a trigger for the readout. The Gaussian fitting of the plate locations with the highest signal increase the nominal accuracy to 1.4 mm.

Alternatively, the SWAN project suggested a novel system based on nuclear emulsion film detectors (Braccinia et al., 2010). This kind of detector consists of a layer of silver bromide (AgBr) crystals and ionizations generated after a particle passes through produce tracks which can be visualized using optical systems. Such a detector was built from two layers of 44 µm nuclear emulsions separated with a 205 µm thick triacetate base. Plastic plates were used as range shifters and each plate was wrapped with two nuclear emulsions. Even though this system doesn’t detect the entrance direction of the particles, it can record however this downstream of the object and can locate where the protons stop. Experiments on a rod phantom, consisting of PMMA and Aluminum, were performed using a low intensity beam and an energy of 138 MeV, and demonstrated a range accuracy below 1.4 mm.

2.3.5 Integrating systems

An alternative approach to proton radiography to the single event tracking systems are those that work on integrated detection of residual proton beams. In integrating systems, the signal deposited in the detector is an average over all residual protons of a narrow proton beam after it has traversed the irradiated object (Poludniowski et al., 2015). For this reason, this mode requires calibration between the deposited signal and information about the traversed density as a function of the incident energy and fluence.
2.3.5.1 Commercial flat-panel detector

Telsemeyer et al. (2012) have used a commercial flat-panel to perform proton radiography based on heavy ions. The detector consists of a Lanex fast back phosphor screen coupled to an amorphous silicon matrix originally used in clinical imaging of photons (Antonuk, 2002). The WET of the irradiated object is then determined by varying the energy of the beam dynamically and locating the maximum transmission signal. Due to the limited energy resolution of incriminations of the accelerator, a nominal accuracy of 1 mm and 1.5 mm WET for low and high beam energies were determined respectively. To accelerate the imaging time for tomography measurements, a passive energy scanning was applied instead of active energy variation. This was arranged by placing a PMMA wedge of 19.57° downstream the object and in front of the detector. Using an interpolation of the drop of the signal allows to determine the signal corresponding to 80% of the signal maximum and has been found to enhance the density resolution to 0.5 WET. The tomographic imaging of a plastic cylindrical phantom was done using 80 planar projections of 2.25° angular steps, with the WEPL being reconstructed using back projection algorithms. This approach demonstrated a density resolution of 1% WEPL and a lateral resolution of 0.8×0.8 mm². Further investigations were performed to measure the WET of an anthropomorphic phantom using an active energy scan ranging between 247 and 303 MeV/u and a density resolution of 1 mm WET. The obtained radiographs were compared with the calculated WET from the treatment planning system, resulting in a relative ratio of 1.004 ± 0.022 (mean ± 1σ) and 94% of the relative values agreeing to within 5%.

2.3.5.2 Time-resolved dose measurements using single detectors

The exploitation of point dose measurements for in-vivo proton range verifications for passive scattering treatment using range-modulated fields has been investigated by (Lu, 2008). This is based on detecting, at a single point, the time pattern of the deposited dose, since the dose rate of such a modulated beam has a periodic dependence on the rotation frequency of the modulation wheel. When de-convoluting the dose rate signal using the RC time constant of the detector, the temporal characteristic of the dose rate as a function (DRF) (see Figure 2-10) can be resolved (Lu and Kooy, 2006). When comparing the measured DRF with a database of DRF which are measured at known WEPL the residual range of the proton beam traversing the phantom could be determined using pattern matching (Testa et al., 2013) or the root mean square width technique (Gottschalk et al., 2011). This approach has shown a millimeter accuracy of the WET when the measured locations are situated on the plateau of the SOBP (Bentefour et al., 2012). It has also been proposed that this technique could be expanded to an imaging approach by using a 2D octagonal matrix of semiconductor diodes. This detector
consists of 249 semiconductor diodes with fast time sampling (2 ms), a lateral resolution of 7.07 mm and a horizontal and vertical spacing of 10 mm of diodes on the same line. The nominal density resolution is defined by the sampling and the scope of the database of DRF, which is 1 mm WEPL and ranged between 5.5 cm to 20 cm (see Figure 2-10 (b)).

The results of the radiographic images of the plastic phantom were very promising and delivered doses for a single radiograph were as low as 7 mGy. However, the results of a step-like and anthropomorphic phantom have shown the high sensitivity of the approach to range mixing caused by MCS and which is amplified by density heterogeneities as measured DRF at the interfaces of density heterogeneities can’t be matched in a database derived from measurements made through homogeneous materials. As such, up to 30% of the measured points were incorrect. The short time required to perform a single radiographic image however (100 ms) perhaps would allow for monitoring of a moving target.

![Figure 2-10: (a) Experimental set-up to perform transmission imaging of a cylindrical phantom based on 2D-diode-array detector. (b) Database of dose rate functions for proton WET. Figure courtesy of (Testa et al., 2013).](image)

### 2.3.5.3 Proton-counting radiography based on CMOS APS technology

The use of a complementary metal-oxide-semiconductor (CMOS) active pixel sensor (APS) has also been investigated to perform proton radiographic imaging (Seco and Depauw, 2011). CMOS detectors can provide the deposited energy of the protons impinging on the detector in the form of a voltage difference, from which the residual stopping power can be determined using an appropriate calibration. Primary radiographic imaging has been performed using a matrix of 40 x 40 µm² pixel and a double scattering beam of 117 MeV with the first results showing the potential of this detector. Due to MCS of the beam traversing the irradiated object
however, the integrated signal in the pixel exhibit a dependence on the distance between the object and the location of the sensor.

Other extensive investigations have been performed using a Dynamic range Adjustable for Medical Imaging Technology (DynAMITe) large area CMOS APS (see Figure 2-11 (a)). This detector \((12.8 \times 12.8 \text{ cm}^2)\) incorporates two different geometrical arrangements of diodes within each pixel, allowing for two different spatial resolutions \((50 \, \mu\text{m} \text{ and } 100 \, \mu\text{m} \text{ pitch})\) \((\text{Esposito et al.}, 2011)\). The high spatial resolution mode provides a better signal-to-noise ratio performance and enhances the potential for resolving single events \((\text{Poludniowski et al.}, 2014)\). First measurements were performed using a 36 MeV proton beam with diameter of 50 mm. Subsequently, the authors investigated the performance of the DynAMITe device to perform PTI. A contrast phantom based on a 8 mm PMMA thick block (see Figure 2-11 (b)) was scanned using a therapeutic proton beam of \(100 \times 100 \, \text{mm}^2\) with energies from 30 to 240 mm. The results demonstrated the potential of high spatial resolution proton radiographic imaging due to the small pixel dimension. Nevertheless the contour regions of the object were blurred and halo effects were observed, due to the fact that the detected signal was a combination of primary and scattered protons.

![Figure 2-11](image)

Figure 2-11: (a) The CMOS APS wide area sensor with dynamic geometrical resolution (DynAMITe). (b) Contrast phantom used for transmission experiment. The phantom is based on PMMA material containing different thickness levels and different material forms. (c) Proton based transmission images using DynAMITe detector and a proton beam with a range-energy of 30 mm. Figure courtesy of \((\text{Poludniowski et al.}, 2014)\)

Further experiments have been performed by means of two connected DynAMITe detectors \((\text{Poludniowski et al.}, 2014)\), with the two layers being triggered to simultaneously count single proton events. To test this, a 36 MeV proton beam was collimated using a pinhole set-up of 2.3 mm diameter prior to the upstream sensor. This allowed to focus the majority of the primary beam on to a finite row of the reconstructed image. To resolve single events occurring in the two detectors, a clustering algorithm based on thresholding was developed to analyze
the contrast images with the threshold set as to equal the collective charge of 1500 electrons with a 3.6 eV potential per electron-hole pair and energy transfer of 5.4 keV. The threshold was found to provide balance between reducing the dynamic temporal noise and small enough to distinguish real coincidences. The selected threshold values were also confirmed using MC simulations of the set-up. This technique has demonstrated the ability to discriminate between signal contributions from energy loss and from fluence scattering (Poludniowski et al., 2014).

CMOS single detectors have been also used to estimate the range of patient treatments in the clinical environment. This approach is based on the dose ratio curves of the proximal side of the analytically approximated BC of two energies (Doolan et al., 2015). A Look up table was developed to correlate uncertainty in the dose ratio with uncertainty of the WET. The validation using the CMOS APS demonstrated a range resolution of 1.6 mm ± 1.2% (rms error ± 1σ).

2.3.5.4 Charge-Coupled Device based transmission imaging

Zygmanski et al. (2000) have used a Gd2O2S:Tb X-ray intensifying screen and Charge-Coupled Device (CCD) camera to perform proton CT. The measured intensity of light in the beam path is converted to a residual proton range using a calibration performed using an ionization chamber in a water tank. The transmission experiments were made using a beam energy modulator, a 160 MeV proton beam and a cylindrical contrast phantom. The cylinder was filled with water and contained a smaller cylinder of different medium and tissue like materials. The pCT was reconstructed from 100, equally spaced projections by means of the Feldkamp–Davis–Kress (FDK) algorithm for cone-beam CT (Feldkamp et al., 1984). The results of the WEPL show a good agreement with literature values and ones measured using a multi-layer faraday cup. In order to minimize the effects of MCS, an identical approach to the one developed by (Zygmanski et al., 2000) has also been used to perform ion CT (Muraishi et al., 2009). The projections in this case were done using helium and carbon beams of 230 MeV/u and 400 MeV/u respectively with projections being acquired over 360° with 1.4° angular steps. The results have shown an improvement of the spatial resolution of the reconstructed images and a reduction of the blurring due to MCS.
Figure 2-12: Reconstructed pCT using different phantoms: (a) contrast phantom contains different media and artificial tissue like material, (b) resolution phantom. Figure courtesy of (Zygmanski et al., 2000)

2.3.5.5 Transmission imaging based on scanning beams

As explained in section 2.3.5.4, heavy ions suffer less scattering than protons. For this reason, ion radiography provides the potential of better spatial resolution than proton imaging (Muraishi et al., 2009). This has been exploited at the Heidelberg Ion-Beam Therapy Center (HIT). The experiments were done by measuring directly the ion residual range using a parallel plate ionization chamber detector (Rinaldi et al., 2013). This detector consists of 61 single ionization chambers which are filled with air and separated with 3 mm PMMA slabs serving as range shifters. The range telescope has a large opening of 300 x 300 mm² allowing for 250 x 250 mm² effective field size. The density resolution of the detector is determined by the WET of the slab which corresponds to 3.495 mm. The residual ion range has been considered to correspond to the maximum of the depth dose which is estimated from the ionization chamber measuring the maximum current (Rinaldi et al., 2013).

Using this system, a planar radiograph was made using a raster pattern of single ion pencil beams and the range telescope was synchronized with the controlling system of the accelerator, such that the measured current for each pencil beam could be located within the time series of the raster point’s signals. As such, the spatial position of the grid point corresponds to the coordinate from the monitor unit. The nominal density resolution of the detector was improved using data processing methods to increase the range resolution, called (MIRR) (Rinaldi et al., 2014). A resolution of 0.8 mm WET was reported through refining the localization of the measured maximum signal. This method is based on comparing the ratio of the signals of the adjacent ionization chambers with the one obtained from a pristine Bragg
peak simulated by Monte Carlo. The results have shown a promising potential to perform radiographic and tomographic imaging using the range telescope and $^{12}$C 396.29 MeV/u monoenergetic pencil beams and a beam cross section of 3.5 mm FWHM. For these tests, raster scanning was performed using a horizontal and vertical spot to spot spacing of 1 mm. Measurements on an anthropomorphic phantom indicated that about 87% of measured WET’s agreed within a 3% relative error and with a distance to agreement of 3 mm (Rinaldi et al., 2014).

### 2.3.5.6 Proton Range Probe

An alternative approach to in-vivo range verification is the concept of the ‘Range Probe’ (RP) (Mumot et al., 2010). A RP is a narrow, mono-energetic and low-dose proton pencil beam of sufficient energy such that it traverses completely through the object and can be detected downstream (Romero et al., 1994) and (Watts et al., 2009). The residual integral depth dose (RIDD) can then be measured using a range telescope or multi-layer ionization chamber (MLIC) such that the residual depth dose can be completely detected, adding the potential of evaluating the distal fall-off of the BC (see Figure 2-13 (b)). By comparing the measured residual depth dose with one simulated previously (e.g. based on Monte Carlo methods) on the planning CT of the patient, such a probe can provide useful information on in-vivo range.

To study the feasibility of the approach, a preliminary Monte Carlo (MC) study on a patient CT has been previously performed (Mumot et al., 2010). For this, a single 177 MeV proton pencil beam was simulated laterally through the CT and simulated to stop in a water-like range telescope downstream of the patient. The residual depth dose curve in the detector was reconstructed by integrating the dose over the plane parallel to the detector at different depths in the detector. Such range probes were modeled in different patient locations with variable density heterogeneities, and the residual integral depth dose assessed for different assumed density resolutions of the detector. For simplification, the 90% to 10% distal gradient of the Bragg peak was approximated to be linear and was used to determine a single figure for the residual range in the detector. These preliminary results demonstrated the potential to detect two different sources of information. First, range could be verified by measuring through a relatively homogeneous region of the patient with an accuracy of 0.5%, with plate thicknesses of up to 4.4 mm WET being found to provide sufficient range resolution to measure 1 mm and 1% range errors in homogeneous material. Second, by deliberately delivering pencil beams through more heterogeneous regions of the patient, a potential patient misalignment can be verified, such that relatively small position changes of the patient could result in a substantial degradation of the shape of the residual depth dose curve in the detector (range degradation). This feasibility study indicated that this method could be easily implemented in any clinical...
environment, since it requires only the ability to deliver a narrow, mono-energetic pencil beam and to position a range telescope behind the patient (see Figure 2-13(a)). Subsequently, a multiple-leaf-ionisation-chamber (MLIC) system has been used to perform a first experimental validation of this approach (see chapter 7). The MLIC used is a stack of single ionization chambers (IC) filled with air and was developed to measure integral depth dose curves of proton pencil beams for fast quality assurance (Lin et al., 2009). A MWPC placed at the entrance enables to monitor the beam profile. The MLIC has an active area of \(100 \times 100 \text{ mm}^2\) and consists of 128 plane parallel IC with each IC consisting of 1 mm plate of Aluminum. Each plate this also serves as a range shifter. The Alu-plates (anode) are coated with 100 \(\mu\)m isolated Mylar foil and a 0.1 \(\mu\)m layer of copper (cathode) covers the surface of Mylar for signal collection. The cavity between the anode and cathode is 1 mm wide. The nominal density resolution of a single IC is \(2.27 \text{ mm} \pm 0.003 \text{ mm WET}\) and the total WET is \(290.6 \text{ mm} \pm 0.003 \text{ mm}\). Thus, complete depth doses for proton beam energies up to 200 MeV can be measured. For proton beams with energies higher than 200 MeV, PMMA plates should be laid in front of the MLIC. The collected charge in each IC is then transformed to a water equivalent residual integral depth dose by substituting the thickness of the plates with their effective WET. The energy dependence of the SPR is considered to be negligible (Köhler et al., 1965), (Janni, 1982).

![MLIC](image)

**Figure 2-13:** (a) Experimental set-up of the range probe: in the center the anthropomorphic phantom is positioned on the patient couch. The MLIC is deposed on the right side of the phantom. (b) Comparison of the RIDD from MLIC measured and MC pre-calculated RPs.

Based on the preliminary study of Mumot, in this thesis, we further investigate the potential of proton range probes range and positioning validation in proton therapy. Although most of the presented work is simulation based, in chapter 7 we return to the MLIC based experimental validation of the approach.
As a starting point for this thesis, in this chapter we present some first investigations into the potential of grid based, range probe proton radiography (RPPR) as a tool for on-line imaging of patients. Two applications of this technique will be briefly described. In addition, this chapter presents the methods for performing and reconstructing proton range maps (RM) which are employed for other applications presented in this thesis.

The first part of this chapter is dedicated to the use of MC tools for simulating range robes and optimization of the beam model in order that the modeled beam fits the experimental data. In the second part, we discuss some initial applications of RPPR as a potential tool for patient set-ups and in-vivo range verifications, followed by an evaluation of the potential accuracy of RPPR for predicting WET of patients by comparing the values predicted by RPPR with ground truth values calculated directly from calibrated X-ray CT data. Finally, the dependency of the accuracy of WET data measured by RPPR will be assessed as a function of RP energy and beam width.

Figure 3-1: Sketch of the active raster scanning principle at PSI used to simulate proton radiographs based on MC simulation and phase space data.
3.1 Grid based range probe radiography

The concept of RPPR is simple, and is an extension of the Range Probe (RP) concept described in chapter 2. Instead of individual ‘probes’ being applied in order to determine total WET through a patient or sample at individual points, in RPPR, many such RP’s are delivered and detected in a grid pattern with a pre-defined regular spacing. By measuring the range of the residual integral depth dose (RIDD) curve of each RP of the grid in a wide-area, integrating detector, a range image through the patient can be acquired with a lateral spatial resolution determined by the applied grid spacing. Here, simulated RPPR for a number of cases have been generated using patient CT data and MC simulations based on clinical proton beam data from Gantry 2 at PSI.

3.2 Simulation tool

All RP based radiography simulations in this chapter, and in the thesis, have been calculated using the Monte Carlo tool VMCP. VMCP is a MC package for proton transport processes based on a proton beam algorithm which segments a large proton field into individual protons and transports them through the media individually (Kawrakow et al., 1996), (Fippel and Soukup, 2004) and (Gardner et al., 2007). Electromagnetic, nuclear elastic scattering and inelastic reactions are all implemented (Soukup et al., 2005). VMCP converts the HU of the patient CT data set to a mass density. However, as the attenuation coefficient depends on the X-ray energy spectrum and the characteristics of the CT scanner, an appropriate and scanner specific CT calibration curve is required to perform an accurate conversion between HU and the mass density. The stopping power ratio of the media is calculated as energy and mass density dependence (ICRU 46, 1992), (ICRU 49, 1993) and (Berger et al., 2005). The function for the lateral and angular displacements of protons was incorporated using (Rossi and Greisen, 1941). The beam model of the MC was adapted to fit the features of the experimental pencil beam of PSI in order to acquire reliable simulated PR. To match VMCP to clinical data, mono-energetic pencil beams were modeled in a water tank, without modeling the beamline. The resulting integral depth dose curves were compared to experimental data obtained using a water range telescope and over 57 energies ranging from 73.95 MeV to 228.12 MeV with a WEPL incrementation equal to 5 mm. We compared the width of the pristine peaks which corresponds to the width between the proximal- and the distal 80% depth. The parameters $\alpha$ and $p$ have been adapted by fitting the Bragg-Kleeman equation (1.16) to PSI experimental data (Figure 3-2 (c)) for $R_{total}$ in mm and found $\alpha = 0.0268\ mm/MeV$ and $p = 1.731$. A second calibration was performed to correct for the dose reduction by increasing...
the depth due to range straggling and reduction of the fluence. An approximation to the differential fluence has been used which is derived from the power-law relationship (Lee et al., 1993) and is roughly proportional to the proton range (Bortfeld, 1997). The following approximation was found to provide improved fitting results.

\[ \phi(z) = \phi_0 \left( \beta' + \frac{\beta''}{\log(R_0)} \right) \]  

(3.1)

where \( z \) is the depth, \( \beta' = -6.565 \) and \( \beta'' = 54.021 \log(mm) \). These beam parameters were used to parametrize the generated proton pencil beams. The files of the phase space of the beam field contain the kinetic energy, momentum band, pencil beam coordinates and their direction cosine. depicts a schematic illustration of a range probe field composed from a grid of single proton pencil beams with horizontal and vertical spacing. To define the beam origin of the radiographic spots as extracted from the beam nozzle, the patient coordinate system has to be considered together with the origin of the coordinates of the table. For this, the patient coordinate system is aligned with the origin of the CT matrix such that the lateral direction corresponds to the x-axis, the anterior posterior direction corresponds to y-axis and the inferior superior direction corresponds to z-axis. All MC based RP’s and RPPR’s in this thesis have been calculated using the above described model, with the ‘detector’ (on the exit side of the sample or patient) being modelled as a simple water block with its relative stopping power being corrected as necessary for the residual energy of the protons depositing energy in the detector.
Figure 3-2: (a) Range-energy dependence of experimental data of PSI based on the range-energy equation. (b) Dose reduction as function of the proton range of experimental data of PSI. (c) Integral depth dose curves for several monoenergetic proton energies [70 MeV – 230 MeV]. The effect of the range straggling can be observed by peak to plateau ratio and the broadening of the peak region at the end of the proton range.

3.3 Calculating residual WET’s for RPPR

The spatial resolution of a RPPR is given by the lateral spacing of the applied, high energy RP, while a pixel in a RP radiograph has a value corresponding to some estimation of the
WET along the beam path of that RP through the imaged objects. Knowing that the residual energy of protons exiting the imaged object will be deposited in the detector, the WET can be expressed as:

\[
WET = R_{total} - R_d - R_m
\]

(3.2)

where \( R_{total} \) is the CSDA proton range, \( R_d \) is the range of the residual beam energy inside the detector and \( R_m \) is the WET of other components in the beam path.

However, as already discussed, when protons traverse along a region with strong heterogeneity interfaces, the protons will scatter through different densities, resulting in a degradation of the RIDD (see Figure 2-13 (b)), (Schaffner and Pedroni, 1998). Thus, for substantially degraded RIDD (e.g. for those RP which have traversed regions of large density heterogeneities) there is no clear definition of range, especially when using a plane parallel (integrating) detector (see chapter 7) which averages the detected signal over the whole area of the scattered pencil beam. As such, we have defined WET here as the weighted average of the residual ranges of a set of range shifted, pristine Bragg peaks, weighted such that their resultant cumulative RIDD matches that of the MC simulated RIDD. By this approach, we can account for the different range changes experienced by protons in the finite beam when passing through heterogeneous media. This approach is essentially a superposition problem, which can be solved by de-convolving the degraded RIDD with the pristine Bragg curve of the applied RP. This deconvolution step has been performed numerically based on the Nelder–Mead method (Nelder and Mead, 1965) as this optimization doesn’t require derivatives for the objective function. The cost function to be minimized is based on the square of the difference between the predicted and the measured RIDD. For the deconvolution, an appropriate pristine BC is simulated based on MC simulation \( BC(R_0) \) and \( R_0 \) is the corresponding nominal proton range in water.

\[
BC(\bar{r}) = \sum_{i=1}^{n} \omega_i \ast BC(R_0 - wet_i)
\]

(3.3)

where \( i \) is the index of the corresponding sub-BC, \( \omega_i \) is the weighting contribution of the fluence, \( wet_i \) and \( n \) are the equivalent thicknesses and the count of the corresponding sub-spectral protons. Figure 3-3 shows an example of this deconvolution process for a MC simulated RIDD after passing through a patient CT (Figure 3-3 (a)), together with the extracted set of weighted, pristine Bragg peaks which best match this curve. From these, the weighted mean of the range of the RIDD can be calculated. We will return to this deconvolution technique in chapters 4 and 7.
Figure 3-3: RIDDC (diamond) measured using MLIC in head phantom. The range spectra (dashed lines) resulting from the de-convolution of the RIDDC. The resulting integral of the range spectra (orange solid line)

3.4 Preliminary applications of RP proton radiography

This part of the work focuses on investigating some first potential clinical applications of the RPPR concept. The simulations were performed using CT data sets of patients treated for skull-base tumours at PSI, and for which at least one repeat CT, acquired immediately prior to treatment, was available. All patients were part of an institutional protocol to check possible anatomical changes (see e.g. (Placidi et al., 2016)). This group of patients allowed us to investigate the clinical potential of RPPR to detect both inter-fractional anatomical variations accruing during the fractionated treatment, as well as positional errors. The slice thickness of the CTs was 2 mm and the lateral resolution ranged from 1.41 x 1.41 mm\(^2\) to 1.95 x 1.95 mm\(^2\).
Figure 3-4: Dose maps of grid of RPs resolved in depth propagated through CT geometry into the “ideal detector” (water slab) in x (right-to-left).

An example line, and its predicted distribution in the ‘detector’, for a RPPR is shown in Figure 3-4. All RPs have been modelled using a mono-energetic proton beam of initial energy 200 MeV and a momentum band of 0.6%. Beam width in-air was 7 mm FWHM for all cases and the FOV was chosen to cover the head of the patient. The number of modeled RPs is given by the grid spacing, which was chosen to be between 1 - 5 mm, depending on the case. All radiographs were modeled as a sequence of many RPs and the RIDD of exiting pencil beams were scored in an ideal ‘detector’. Each simulated RP is saved separately, which enables to connect each registered signal to the spot location from the phase space file. The detector has been modelled as a water-like block of material positioned beyond the exit point of the RP from the patient CT, with the WEPL resolution of the detector being given by the pixel size of the CT. The active area was wide enough to detect each positioned RP within the FOV, also allowing for scattering. The MC simulations were performed using $10^6$ histories for each RP which was found to produce accurate results in comparison with the experimental data (see chapter 7). The RPPR maps were then reconstructed as a function of WET and compared to the WET calculated for an idealized digitally reconstructed proton radiograph, which we take to represent the ground truth (GT). This idealized WET DRR is obtained from the patient CT using simple linear projections through the data and converting from HU-to-RSP using the same calibration curve used to commission the VMCpro MC engine.
GRID BASED RANGE PROBE PROTON RADIOGRAPHY (RPPR)

Figure 3-5: (a) and (b) Radiography images based on a proton pencil beam of energy 200 MeV and a grid spacing of 1 mm in horizontal and vertical axes. (a) Topographic representation. (b) Proton range map converted to WET. The fine grid distance results into high spatial resolution RPPR. (c) and (d) are radiography performed with same phase space as (b) with uniform spacing of 2 mm and 5 mm.

An example proton RPPR is shown in Figure 3-5 (a) and (b). This was calculated with a spot-to-spot spacing of $\Delta x = \Delta y = 1$ mm. With such spacing, a quite high spatial resolution radiograph can be obtained. On the other hand, this is inherently inversely dependent on the dose delivered to the patient and the time required to perform the monitoring. Figure 3-5 (c) and (d) therefore show RPPR’s for the same patient with spot-to-spot spacings of 2 mm and 5 mm, from which it is obvious that the lateral resolution depends strongly on the grid spacing.

### 3.4.1 RPPR’s for positioning and detection of anatomical changes

Figure 3-6 (a-b) and (c-d) depict lateral and A-P RPPR’s for a patient based on different CT’s of the same patient acquired on different treatment days. The pixel values are expressed in WET (mm) as calculated using the deconvolution approach described above. Anatomical regions of high density heterogeneity such as the sinus-, nasal cavities and trachea can all be resolved, demonstrating the advantage of the density sensitivity of RPPR. As the two RPPR are performed using the same scanning pattern of the proton beams, a pixel by pixel differentiation (RPPR$_1$ – RPPR$_2$) (Figure 3-6 (e) and (f)) could detect anatomical changes or patient misalignment between the two CT’s. For instance in this case, RPPR$_2$ could be the treatment specific measurement and RPPR$_1$ the reference which could be either measured at the day of treatment planning or reconstructed based on the planning CT. Interestingly, small shifts of a mm or so are clearly visible (despite the relatively coarse spatial resolution), and there is a clearly visible change in anatomical thickness in the neck area as seen in the lateral RPPR’s.
Figure 3-6: (Upper) MC simulated pRPPR based on planning CT (a) and (b) correspond to AP and lateral projection; (Middle) MC simulated rRPPR performed through pre-treatment CT for the same patient and same direction (case 3). The RPPR are converted to WET in mm; (e and f panels) are the pixel by pixel subtraction of the corresponding proton radiograph (WET difference) in two projections, superimposed on pRPPR and showing a density shrinking in the neck.

In order to investigate the potential of RP grid radiography for detecting such positioning errors in more detail, we have used a normalized cross-correlation method to detect rigid
position variations between fractions based on these simulated RPPR (Figure 3-7). The technique has shown the possibility to detect small position variations between the treatment fractions and even smaller than the nominal spatial resolution of the RPPR (Table 3-1). We will return to the issue of patient positioning using individual range probes in chapter 4.

![Figure 3-7: Patient positioning using MC calculated WET maps. (a) Planning position. (b) and (c) are AP and SI two translation error occurring during the fractionated treatment.](image)

<table>
<thead>
<tr>
<th>Simulated error [mm]</th>
<th>Detected error [mm]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 1</td>
<td>0, 0, -1</td>
</tr>
<tr>
<td>Case 2</td>
<td>0, 1, 0</td>
</tr>
</tbody>
</table>

Table 3-1: Results of shift study. The values are given in x, y and z coordinates system.

### 3.4.2 RPPR’s as direct measurements of patient specific WET

Comparisons of the RPPR and reference WEPL maps (DRR) are visualized in Figure 3-8, with the pixel size of the RPPR images having been resampled to fit the resolution of the WEPL map, as given by the CT data set resolution. The brain region exhibits good agreement between the RPPR and WEPL. On the other hand, deviations are found around the cavities and regions that border on interfaces with high WET contrast (skull, palate etc.). The major cause for the observation is the range mixing and the spatial spacing used to perform RPPR. Furthermore the deviation has been found to be depends on the grid spacing.
A direct assessment of the RPPR as a measurement technique for evaluating range changes has been performed by comparing the measured WET change for all cases with the WEPL DRR. For four patients, the maximal deviation was found to be lower than 1 mm. However, the RPPR seems to overestimate the measured WET change, which is caused by proton range degradation at density interfaces, especially in cavity regions and interfaces of the patient surface with air.
Finally, Figure 3-10 shows the result of a sensitivity, specificity, precision and accuracy estimation (Olson and Dursun, 2008) of detecting changes of WET of more than 1mm. These have been found to be greater than 0.8 in all cases, affirming the potential efficacy of this tool for detecting and localizing intra-fractional changes in WET. Case 1 and case 3 seem to reach the largest values of sensitivity and accuracy, where density changes were localized in nasal cavities and the neck region respectively. However, for cases 2, 4, 5 and 6, the cavities were found to be only partially filled and such a high degree of heterogeneity appears to deterministically affect the sensitivity of this tool.
3.4.3 Energy dependence of RPPR

As a final part of this chapter, the dependence on RPPR WET measurements on RP beam width and energy has been performed. The major range uncertainty of the measured mean residual range is dominated by the inherent range straggling accumulated along the path of the beam heading to the entrance window of the detector and the precision of assessment of the residual range (Bashkirov et al., 2016). The former factor is approximated to 1.2% of the nominal proton range $R_0$ (Janni, 1982), while the second one is assumed to be systematic and corresponds to the half thickness of the single IC. Both uncertainties depend on the impinging particle energy. Thus, it is important to quantify the impact of both parameters on the extracted energy loss proton range maps, especially when a compact MLIC and modulated RP energy are applied. As such, RPPR’s with different nominal energies have been modeled in this part of the work. For these simulations, the FOV was selected large enough to cover the whole head of patient 4 with a spot spacing of 2 mm in both the lateral and vertical directions. RPPR’s were then calculated for different energies from 190 MeV and 245 MeV in equal steps of 5 MeV. To investigate dependence on beam size, two different pencil beam sizes ($\sigma$ in air) were used $B_1 = 3$ mm and $B_2 = 2.3$ mm. To avoid the potential biases of range errors resulting from scattering in the air, the distances between the source, reference of patient and position of range telescope were kept invariant for all simulations. For each parameter, the corresponding RIDD obtained with the lowest energy (190 MeV) being considered as reference and the deviations in average WET between the RPPR calculated for each energy and this reference computed. Similar deviations to the DRR have also been calculated.

3.4.3.1 Results

Figure 3-11 shows the results of this analysis. It can be seen that the energy selection doesn’t impact the quality of the RPPR performed using 3 mm sigma transversal beam size ($B_1$) (Figure 3-11 (a)). The mean error is located around the value zero. The corresponding 95% confidence interval (CI) fluctuates slightly and reaches a maximal value of ±1.8 at the energy of 245 MeV (shaded areas). This low variation demonstrates independence from energy selection. As would be expected, the narrower beam ($B_2$) shows a smaller 95% CI in comparison to $B_1$ due to the reduction of range mixing at high density interfaces. On the other hand, the 95% CI increases with increasing energy, which can be explained by corruption of the measured residual range toward the larger ranges, caused by RP located outside the projected patient geometry.
Figure 3-11: The dependence of nominal energy and transversal beam size on energy loss radiographs measured using a range telescope. (a) Effect of range straggling and SPR-to-energy dependence on measured mean residual range using two spot sizes (FWHM (B1) = 7.1 mm and FWHM (B2) = 5.4 mm). (b) Deviation between proton DRR and energy loss radiograph as function of RP energy.

Deviations of RPPR with proton DRR are depicted in Figure 3-11 (b). For the different beam widths mean deviations of 0.64 mm + 0.11 mm (B1) and 0.18 mm + 0.08 mm (B2) (+1σ) have been found. For the narrow beam RPPR (B2) the 95% CI reaches a maximal value of [-1.16, 1.23] in comparison to values of [-3.18, 4.21] for B1. Finally, Figure 3-12 shows maps of WET deviation in relation to the ‘ground truth’ WEPL DRR for RPPR simulated with set-up B1 and for energies of 195, 200, 230 and 240 MeV. A clearly increasing inaccuracy in determining WET can be seen as the energy increases, once again a result that is due mainly to increasing energy straggling with increasing energy.
In this chapter, a preliminary study into the potential for range probe proton radiography (RPPR) has been described. This approach would use a grid of high energy proton pencil beams (range probes) for generating proton radiographs, which could then be compared to virtual radiographs obtained from the patient planning CT for validating proton range *in-vivo*, as well as patient set-up. Although there are clear limitations in the spatial resolution of this approach compared to other proton radiographic techniques, we believe the method described here could be relatively easily implemented in the clinical environment of proton therapy facilities based on pencil beam scanning, as it would only require some form of range telescope after the patient to detect the integral residual depth dose on exit of the patient. By applying a raster scan of multiple RPs, proton RMs of large FOV can be produced for various applications. Indeed, this technique is a real beams eye view (BEV) approach, since it makes use of the same geometrical arrangement of the beam used during the treatment, overcoming the uncertainty of the geometrical calibration between the CT and the gantry coordinate system.

The MC settings used here have been calibrated based on experimental set-ups performed at PSI using several beam energies with a range spacing of 5 mm and a wide area multi-layer detector and MC simulated proton radiographs. A range spectra analysis has also been applied to augment the density resolution of proton radiographies acquired with such an integrating system. Using this approach, only small range errors were observed in comparison to reference WEPL maps of the patient in homogeneous regions, with larger discrepancies being detected in the region of large density interfaces. However, the best agreements have been
found for the lowest possible energies (i.e. those that have enough energy to just pass through the head and produce a useful RIDD in the detector) and, perhaps unsurprisingly, for RP with narrower beam widths.

The proposed patient monitoring system has also shown its potential to detect inter-fractional anatomical changes (investigated further in chapter 6) and also patient positioning errors with magnitudes less than the grid spacing of the radiograph, a result that will be further explored in the following chapter. The accuracy of the simulations performed here however depends on how the Bragg peak of the RP would actually be measured on exit from the patient. In this work, we have assumed that some form of wide area, multi-layer ionization chamber (MLIC) is available. Such detectors have been developed at our institute (Lin et al., 2009) for daily QA measurements of range and energy, and are also available as commercial devices (e.g. IBA Giraffe, De.Tect.Or). Indeed, an experimental validation of the RP concept will be presented in chapter 7. However, such devices are typically large, as they have been designed to measure depth-dose curves for energies of 200 MeV or more. Although such devices can certainly be used for range probe type measurements, a detector for routine clinical RP measurements would certainly need to be optimized.
4. Patient positioning using range probes

In the previous chapter, the potential of 2D grid based RPPR to verify patient set-up was introduced. It implies using low fluence transmission proton images to evaluate the positioning of the patient and thus to avoid discrepancies between the planned and the delivered dose. Currently, the majority of proton facilities still set-up patients using orthogonal kilo-voltage (kV) X-rays. Two projection radiographs (e.g. AP and lateral) are fused to reference DRR, calculated from the CT. The residual setup error is then quantified as the magnitude of the 3D vectors, derived from orthogonal, 2D translations deduced from the matching of orthogonal X-ray pairs with the DRRs. Such registrations are typically performed by detecting the coordinates of fiducial markers, anatomic landmarks and/or bony-structures (Bel et al., 1996), (Pisani et al., 2000), (Verellen et al., 2003) and (Bolsi et al., 2008). The limitations of using this approach are that 3D patient misalignments are only deduced from 2D projections of these landmarks, with the restriction that the detection of non-translational patient set up errors, such as rotations, is difficult if not impossible (Siyong et al., 2009). As such, and more recently, cone beam computed tomography (CBCT) has been introduced into conventional radiotherapy, and is now slowly being introduced into proton therapy (Park et al., 2009). This modality allows for the acquisition of 3D volumetric patient data inside the treatment room, providing an opportunity for the detection of both 3D translational and rotational setup errors (Meyer et al., 2007). However the low contrast-noise-ratio of the images, due to the high scatter-to-primary ratio (Siewerdsen and Jaffray, 2001), limits the clinical use of this modality. In addition, the use of in-room diagnostic CTs for 3D imaging is also being proposed and introduced for proton therapy (Pedroni et al., 2004).

The aim of this chapter is to instead investigate the potential of individual Range Probes (RP), as opposed to RPPR, as a tool for online 3D positioning of head and neck patients treated with particle therapy. Since any change of patient orientation in relation to these beams will result in changes of the density heterogeneities through which they pass, our hypothesis is that patient misalignments can be deduced from measured changes in the resulting Bragg Curve (BC) degradation and range. As such, their locations need to be carefully selected in order to have optimal prediction power for detecting misalignments. In other words, the aim is to find RP where the measured RIDD will change significantly as a function of small patient orientation misalignments. This change in RIDD shape as a function of density heterogeneities and patient misalignments we call the ‘RP fingerprint’.

---

1 This chapter, without the appendix, is currently under review for publication in Physics in Medicine and Biology
In this chapter, we have simulated the use of RPs for positioning under two different scenarios. To reproduce more realistic cases, and to investigate the sensitivity of this technique, we have used an anthropomorphic phantom to simulate RPs in random, but well defined orientations under controlled conditions. In addition, we have also verified the reliability of this approach under real clinical treatment conditions, by simulating RPs through re-planning CT data of four patients treated at PSI. Finally, we also develop an analytical approximation of RP propagation through patients as a fast method of generating the RIDD data bases necessary for the methods described in this work.

4.1 Methods

A flow chart showing the methodology for the RP concept, and that followed in this work, is shown in Figure 4-1. It is our hypothesis that 3D patient positioning can be directly deduced from the measurement of the RIDD of a small number of RP’s, selected such that they have maximal prediction power for patient misalignments. As such, daily RP measurements would be acquired through the patient, and the measured RIDD then compared to a pre-calculated database of simulated RIDD, calculated through systematically misaligned instances of the original planning CT (so-called ‘error scenarios’). By finding the CT ‘error-scenario’ which provides the best match of the measured RIDDs to those in the database, the patient’s positioning error can be directly deduced. Such a matching can be quickly performed based on minimizing least-square differences between the 1D measured and pre-calculated data. As such, these error scenarios (and therefore the pre-calculated database) should take into account many potential combinations of patient translations along, or rotations around, each spatial axis away from the reference position of the patient.
Figure 4-1: Flow Chart of the RP positioning procedure. All the processes, outside the dashed orange rectangle, are pretreatment. The dashed orange rectangle contains steps performed during the treatment: The purple dashed rectangle corresponds to patient measurement. In our MC simulation study this step has been substituted by RP MC calculation based on repeat CT (green dashed rectangle).
4.1.1 Determination of optimal RP locations and database generation

A key element of the proposed approach is to be able to find the optimal RP positions through the patient which are associated with the largest changes in RIDD shape. This translates into a problem of determining the impact of the displacement of the anatomical base line on the proton range spectra of RP. As such, changes of both average range and range dilution (as a result of density heterogeneities encountered along the beam path through the patient) have been used as predictors of optimal RP locations for determination of patient misalignments. The complementary information provided by both range and range dilution is demonstrated in Figure 4-2. This shows a side-by-side comparison of MC calculated RP proton radiographs (generated using a 2D grid of RPs, with spacing of 2 x 2 mm and 200 MeV and beam widths of 3 mm sigma) generated through a patient planning CT. By combining both average range (Figure 4-2 (a)) and range dilution (Figure 4-2 (b)), a radiograph with improved contrast of organ interfaces and edges, indicating degradations of the RIDD for RPs traversing these locations, can be generated (Figure 4-2 (c)). Range dilution in this context is defined as the equivalent thicknesses between the proximal and deepest pristine Bragg peaks obtained from the range spectra analysis (equation (3.3)).

Thus, the enhanced information provided by the combination of range and range dilution should be a good indicator for the selection of the optimal locations for RP for measurements. Once these RP positions have been found (for details, see below), the data base of potential RIDD under each error scenario, and for each selected RP location, can be calculated using Monte Carlo methods. As a proof-of-principle of the approach, simulated RP measurements have been applied to two different misalignment scenarios. In the first, they have been applied to retrospectively determine daily translational offsets in four patients treated at our institute, for which at least one repeat CT during treatment was available. In the second, the potential of a small number of RPs, all incident from a single direction, for determining 3D rotational misalignments has been investigated under laboratory conditions.
4.1.2 Determining translational offsets – a patient study

In this first study, we investigate the ability of the above described RP concept to detect translational patient misalignments under real clinical conditions. This study has been performed retrospectively on four, randomly-chosen patients treated for skull-base tumours at PSI, and for which at least one repeat CT, acquired immediately prior to treatment, was available. For each, translational offsets had been determined clinically using our standard daily positioning procedure, based on the acquisition of orthogonal planar X-ray images and bony landmarks registration. In our centre however, such images are acquired using a diagnostic CT in topogram mode see (Bolsi et al., 2008). Thus, given that the repeat CT’s were acquired on the same CT directly after positioning and with the same CT protocol, these daily determined translational offsets can be considered to provide the ‘ground-truth’ positioning misalignment for each repeat CT. A total of seven set-up scenarios have been retrospectively analyzed using simulated RP measurements, based on repeat CT’s (two each for three patients and one for the remaining four).

4.1.3 RP location selection and data base generation

For each patient, the original planning CT was used to locate candidate RP locations that could best detect translations along each major anatomical axis (L-R, A-P and S-I corresponding to x-, y- and z-axis in the coordinate system used in this work) in the following way. For both lateral and AP directions, simple proton range DRR were first generated by converting the CT-number into RSP (Schneider et al., 1996) and then integrating along the beam direction. The anatomical structures that may vary day-to-day (e.g. cavity fillings) were segmented and masked out. Density heterogeneities within the patient were then quantified by applying a 2D derivative operator to these DRRs, followed by a rectangular to polar conversion of the resulting partial derivatives (see e.g. (Parker, 1997)). From this, a normal vector can be derived which represents the magnitude and direction of the local WET changes projected along the proton beam. Thus, a relative change in position of the patient along this normal vector should cause a range mixing and/or degradation of the RIDD resulting from a RP applied at this location. Using these first, analytically derived vectors (see e.g. Figure 4-3), a sparse set of potential RP candidate locations can be obtained that correspond to those locations where the largest changes in measured RIDD shape and position are expected for patient misalignments along each major axis. In Figure 4-3, a set of such candidate locations are shown for one patient, with the blue arrows indicating the normal vector calculated using the methods described above. The displayed vectors are those with a local WET gradient threshold of 15 mm and where the direction of the gradient vector is within 10° of one of the major axes of the patient (i.e. RL, AP or SI). Next, for each of these candidate locations, multiple, MC calculated RP were simulated through a set of deliberately misaligned CT data sets (‘error-
scenarios’). These scenarios were modeled by displacing the beam from the original location, assuming a worst case scenario error up to \( \pm 3 \times 3 \) \( \text{mm} \) and using a grid spacing of 0.5 \( \text{mm} \) around each RP location and resulting in more than 160 error scenario for each RP and beam direction. From these, a combination of three RP were selected that exhibited the largest changes in RIDD (indicated by the white circles in Figure 4-3).

In this work, a new metric, \( V(\bar{r}_i) \) - the range degradation index, is introduced as an indicator to quantify the resulting range variation of a proton pencil beam as a function of patient positioning error scenarios. The range degradation index is computed as the sum of the variances of both average proton range and proton range dilution for all considered error scenarios with respect to the reference values calculated on the nominal planning CT as follows:

\[
V(\bar{r}_i) = \max \left\{ \sum_{j=1}^{N} \left( \frac{\bar{r}_j - \bar{r}_i}{\bar{r}_i} \right)^2 + \left( \frac{\Delta r_j - \Delta r_i}{\Delta r_i} \right)^2 \right\}
\]

(4.1)

where \( \bar{r}_j \) and \( \Delta r_j \) are the average range and the range dilution, respectively, \( j \) and \( i \) are the corresponding RIDD of the resulting error and reference scenarios, respectively, and \( N \) is the size of the database. All MC calculated RIDD’s resulting from all error-scenarios of each RP were then stored to generate the patient, error-scenario and RP dependent RIDD database.

4.1.4 Simulation of daily RP positioning measurements

In order to simulate daily RP based positioning measurements, MC simulations of RPs were performed using 200 MeV pencil beams at the selected RP positions (three RPs) for each clinically acquired repeat CT for all patients. By comparing these simulated ‘daily’ RIDD’s with those in the pre-calculated database, the translational errors predicted by the RP approach were determined using least-squares matching of the ‘measured’ RP with those in the database, and the corresponding shifts determined from the error-scenario CT providing the best fit. These were then compared to the actual translational corrections determined from the orthogonal 2D X-ray positioning images on the day of treatment for the selected repeat CT.
Figure 4-3: Set of RP candidates (blue arrows) superimposed on lateral (a) and AP (b) proton DRR of a patient respectively. The white circles are the most sensitive locations that satisfy the pass criteria.

4.1.5 Determining rotational offsets – a phantom study

In the second part of the study, the potential of RP’s for determining rotational misalignment errors has been investigated. For this, a bespoke anthropomorphic phantom has been used, which is a modified version of the diagnostic head phantom model 711HN manufactured by CIRS (Albertini, 2011). This has been mounted on an in-house developed motion stage (Figure 4-4 (a)) that can implement high precision movements ($\delta_{sys} = \pm 0.09^\circ$) in all 3 rotational directions (roll, pitch, yaw). With this setup, a nominal (planning) CT scan of the phantom was first performed on a Siemens SOMATOM Sensation Open CT scanner (CT-on-rails). In order to simulate rotational misalignments, the phantom was then rotated to three quasi-randomly chosen positions (Table 4-2) and additional CT’s acquired for each of these. CT parameters for all acquisitions were 120 kV, 400 mAs and 500 mm FOV, together with a 2 mm slice separation/thickness.

For the selection of RP candidate positions in this second study however, a different approach had to be taken. As such, a set of MC calculated 177 MeV RP ‘radiographs’ (a 5 x 5 mm$^2$ grid of lateral RP covering the whole extent of the planning CT, resulting in more than 2000 RP’s) were calculated for all instances of the planning CT with rotational permutations of up to $\pm 2^\circ$ about the x, y and z axes in 0.5$^\circ$ increments, resulting in more than 700 RIDD per RP position. Finally, by combining range and range dilution changes, the 5 most ‘sensitive’ RP locations were determined, and the set of RIDD resulting from all rotational error scenarios for each of these used to construct the RIDD database. Finally, ‘measured’ RP’s in the selected locations were simulated through each of the randomly rotated CT acquisitions, and the best-fit entries in the database found to deduce the applied rotational errors.
4.2 Results

4.2.1 Determining translational offsets – a patient study

Figure 4-5 display the RP positions for patient 1. The RP’s have been localized on the patient skull as well as on the interface between skull and brain and comprise two RP in the lateral beam direction and one in the AP beam direction. A comparison between MC simulated RIDD of the database and the daily CT simulations of the same patient are shown in Figure 4-6. Plots (a, c, e) and (b, d, f) correspond to the results of the lateral, anterior-superior and inferior-superior, respectively of patient 1 and 3, whilst the cyan curve presents the RIDD of the anatomy base line. The black dashed curves are the daily measured RP. The best match is indicated with circles. The least square comparison indicates a match between the daily RP and the RP with -1.0 mm and 0 mm offset from anatomical base line for x and z direction respectively for patient 1. The visual comparison of the RIDD confirms this result despite the slight devation of the magnitude of the BC. This deviation can be explained by the sensitivity of the former to the residual error.
between references of the planning and the newly acquired CTs and also to the inequality of the CTs resolution. In addition it has to be taken into account that potential additional rotational misalignments of the patients have been ignored in this part of the work. Table 4-1 report the results of translational offsets from the RP method compared to the clinical offsets derived from the daily orthogonal X-ray radiograph. The differences between the clinically derived misalignments and the RP method are given along each axis, but also in terms of the vector length between the patient translations detected by each method. The RP 3D vector precision relative to the gold standard ranged from 0mm to 1.5 mm. Interestingly, this precision has been achieved even though the CT slice thickness is >1.95 mm and the RP pencil beams have a (best case) width of ~7 mm (FWHM) in air, not allowing for (MCS) in the patient.
Figure 4-6: RIDDC of RP propagated for two patients case 1 (left) and case 4 (right) panels as a function of translation positioning error in LR (a and b), AP (c and d) and SI (e and f) directions. The dotted curve corresponds to the RIDDC of the RP simulations in the new acquired CT. The cyan curve is RIDDC of the anatomy base line. The RIDDC with the black circle markers presents the best matched depth dose.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Scout method [mm]</th>
<th>RP method [mm]</th>
<th>Prediction accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>P1 (1)</td>
<td>-0.5 -1 -0.5</td>
<td>-1 -0.5 0</td>
<td>0.5 -0.5 -0.5</td>
</tr>
<tr>
<td>P1 (2)</td>
<td>0.5 0 -1</td>
<td>1.5 -0.5 -1.0</td>
<td>-1.0 0.5 0</td>
</tr>
<tr>
<td>P2 (1)</td>
<td>-0.5 1.0 1.0</td>
<td>0 0 1.0</td>
<td>-0.5 1.0 0</td>
</tr>
<tr>
<td>P2 (2)</td>
<td>0.5 0.5 1.0</td>
<td>0 0.5 0.5</td>
<td>0.5 0 0.5</td>
</tr>
<tr>
<td>P3 (1)</td>
<td>0.0 1.0 2.0</td>
<td>-0.5 0.5 1.5</td>
<td>0.5 0.5 0.5</td>
</tr>
<tr>
<td>P3 (2)</td>
<td>-0.5 1.0 1.0</td>
<td>0 0 0</td>
<td>-0.5 1.0 1.0</td>
</tr>
<tr>
<td>P4 (1)</td>
<td>0.0 0.5 1.5</td>
<td>-0.5 0.5 0</td>
<td>0.5 0 1.5</td>
</tr>
</tbody>
</table>

Table 4-1: Evaluation of the retrospective study with patient CT data to detect actual patient translational misalignments. All values are given in x, y and z coordinates. The prediction accuracy corresponds to the deviation between scout and RP method.

4.2.2 Determining rotational offsets – a phantom study

Figure 4-7 (a) illustrates the RP locations defined for the phantom study. The five lateral RP’s are situated in the skull base of the head phantom. Figure 4-7 (b)-(d) demonstrate the principle of the RIDD matching for random rotation errors. One of the five daily RP is compared with a subset of curves from the database. The agreement between the former and the latter (red and blue dashed lines) confirm our approach of deducing errors from
several instances. Table 4-2 summarizes the data obtained with the five RP points. The comparison between the predicted rotations and the actual rotations applied to the phantom are reported for the four studied cases. The results show that eleven from twelve single rotational errors of the phantom can be detected with a resolution of about $\delta_{\text{error}}=0.5^\circ$. Only in one case is the difference between the predicted and the measured rotation error about one degree. This can be explained by the distance between the RP position and the rotation center about x- and y-axis (larger than 322.5 mm). Thus the systematic error of the jig leads to about 1.2 mm deviation of RP position.

Table 4-2: Evaluation of the retrospective study with patient CT data to detect actual patient translational misalignments. The prediction accuracy corresponds to the deviation between scout and RP method.

<table>
<thead>
<tr>
<th>Rotational error [°]</th>
<th>Range probe method [°]</th>
<th>Prediction accuracy [°]</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0, 0.0, 0.0</td>
<td>0.0, 0.0, 0.0</td>
<td>0.0, 0.0, 0.0</td>
</tr>
<tr>
<td>0.0, 0.0, +1.84</td>
<td>0.0, 0.0, +2.00</td>
<td>0.0, 0.0, 0.16</td>
</tr>
<tr>
<td>+1.44, -1.77, 0.00</td>
<td>+1.00, -2.00, 0.00</td>
<td>0.44, -0.23, 0.0</td>
</tr>
<tr>
<td>-1.35, -2.09, -1.35</td>
<td>-2.00, -1.00, -1.00</td>
<td>-0.65, -1.09, -0.35</td>
</tr>
</tbody>
</table>
Figure 4-7: (a) locations of fingerprint RP for the rotation study are superimposed on the proton radiograph of the phantom. (b, c, and d) show RIDD of RP as a function of rotation positioning error for one, two and three axes respectively. The rotation of magnitude $x^\circ$, $y^\circ$ and $z^\circ$ applied a posteriori to the CT image matrix in the pitch, yaw, roll directions. The black solid curve is RIDD of the anatomy base line. The red dashed curve corresponds to the curves from RP simulations in the new acquired CT. The blue dashed curve presents the best matched RIDD.
4.3 Discussion

In this work, we follow-up on a suggestion in the work of (Mumot et al., 2010) that, in addition to it’s potential for validating proton range in-vivo, the range probe concept could also be used to deduce rotational or translational patient positioning uncertainties. The reported technique uses the concept of a small number of RP ‘fingerprints’ (3-5) resulting from the degradation of the BC passing through different density heterogeneities, together with a pre-calculated database of possible results calculated on systematically shifted and/or rotated instances of the planning CT. In two different studies, this approach has been shown to be able to detect randomly defined rotational errors at the level of 0.5 degree (for 11 out of 12 cases) and to within 1.5 mm (3D vectors distance) for translational offsets, when compared to patient positioning data acquired using planar, 2D imaging for real patients treated at our institute. As the proposed method can achieve clinically relevant rotational and translational positioning accuracies from measurements from only one or two beam directions, and using only a small number of probes, it would be a quick and dose-efficient method of checking patient misalignments. For instance, although not reported here, the doses within each range probe in the patient are at the level of a few mGy, a dose which is applied to only a very small volume of normal tissue. In addition, it could be combined with additional RPs for probing potential anatomical changes such as changes in cavity filling, and would also automatically allow for in-vivo range measurements. Thus, much information could also be obtained on the accuracy of range calculations by comparing the measured and predicted RP’s over a population of patients, also allowing for an estimate of the CT calibration accuracy.

However, the applicability of the positioning approach proposed here may be limited in its current form when being applied to non-rigid anatomical regions. Nevertheless, one application of the approach proposed here could be as a double check of patient positioning after daily 3D imaging (e.g. CT/CBCT) and for adaptive therapy. For instance, if it could be calculated quickly enough, then a daily specific RP database could be calculated based on the daily 3D image (thus also taking into account anatomical deformations and changes) and the RP method used to quickly confirm patient positioning just before treatment. Such an approach could be particularly interesting for centres that plan to use in-room CT for 3D positioning rather than CBCT (see e.g. (Pedroni et al., 2004)), as the imaging plane in this case will typically be a few meters away from the treatment isocentre, and thus a motion of the patient between imaging and treatment may occur. However for this, a much faster method of generating the RP database would be required than used here. As such, we have developed an analytical method of simulating RIDD after passing through CT’s in order to avoid the need for MC calculations. The results have shown that this technique enables generation of a large number of RIDD in a short time, even if more investigations are
required and a more accurate dose algorithm including scattering is preferable (see appendix 4.4).

In the work presented here, either rotations or translations have been deduced, but not both. In practice, the method would have to be enhanced to deal with combinations of both types of positioning error. In principle, this would mean generating a much larger database of pre-calculated RP results to which the measured RP’s would be compared, a probably intractable problem given that from this work, this would require more than 20 million scenarios. However, there are potential alternative solutions. For instance, RP’s could be combined with planar imaging (e.g. using the BEV X-ray system installed on our gantry, see e.g. (Pedroni 2010)), such that the 2D planar X-ray image is used to determine translational errors orthogonal to the beam direction, and RP’s to deduce the residual rotations. Alternatively, it may be possible to perform a two stage process where a set of optimally positioned RP’s are used to first determine translational errors, followed by a second set (not necessarily the same) for the rotations, applied after the translational errors have been corrected. Both approaches need to be investigated further. Nevertheless, the fact that in our simulations, translational offsets could be quite accurately determined from real patient data by the RP method, despite there being likely residual rotational misalignments between the repeat and planning CT’s, indicates that this approach could be viable.

Finally, although this work is partially experimental based (e.g. by basing the analysis on randomly rotated CT acquisitions and actual patient positioning data), all results of the effectiveness of RP’s are based on Monte Carlo simulations rather than actual RP measurements. As such, the approach needs to be more thoroughly tested under full experimental conditions, with RP’s actually being measured using (e.g.) a MLIC type detector as discussed above. This could first be performed using the same phantom and positioning jig as used for the rotational tests in this work, but also, after the necessary ethical approval has been acquired, on a set of patients, where RP positioning could be directly compared to X-ray or CBCT/in-room CT based positioning. A first experimental validation of this approach is reported in chapter 7.
4.4 Appendix – An analytical model of proton range probes

The potential of detecting the correct position error depends on both the accuracy on how the RIDD is measured exiting the patient and on the scope of the database. This latter requires the pre-calculation of a large number of RIDD simulating multiple error scenarios and can be very time consuming. A much faster method of generating the RP database, suitable to clinical application, is therefore required. As such, we have developed an analytical approach to the calculation of proton radiographs, which can be computed from CT data set and generate RIDD to avoid the need for MC calculations.

4.4.1 Analytical model for depth dose curve

Bortfeld (Bortfeld, 1997) suggested an analytical representation model of the proton BC. His model incorporates the important physical processes and was adapted for proton energies in the range 10 - 200 MeV. This formalism has been used and adapted to approximate PSI data (see Figure 3-2 (c)) ranging up to 230 MeV. Here we will explain the basic steps for building such a mode. We refer to (Bortfeld, 1997) for more details:

The dose model is described as the sum of the fluence stopping power and the reduction of the primaries due to non-elastic interactions with the medium (see section 1.1.1 and 1.1.4):

\[
D(z, \gamma) \approx -\frac{1}{q} \frac{d\Psi(z)}{dz} = -\frac{1}{q} \left( \Phi(z) \frac{dE(z)}{dz} + \gamma E(z) \frac{d\Phi(z)}{dz} \right)
\]

(4.2)

where \(\Psi(z)\), \(\Phi(z)\) and \(E(z)\) are energy fluence, the fluence and the residual energy, respectively as function of the depth \(z\). \(q\) is the mass density of the medium and \(\gamma\) is the fraction of the energy deposed by primary reduction (Bortfeld, 1997). The first part of the equation has been derived using equation (1.6). The dose as function of the residual range \(R_0 - z\) is expressed:

\[
D(z) = \begin{cases} 
(R_0 - z)^{-1} + (\beta + \gamma \beta p) (R_0 - z)^{1/p} & \text{for } z < R_0 \\
\frac{1}{p \rho \alpha \gamma} (1 + \beta R_0) & \text{for } z > R_0
\end{cases}
\]

(4.3)

where the value \(\beta \approx 0.010 \text{ cm}^{-1}\) has been found to produce the best match to our experimental data as slope of the primary loss (Lee et al., 1993). Figure 4-8 depicts a plot of this equation for two proton beams of 120 MeV and 190 MeV. The dose is normalized by \(C/10^9 e\) to convert from MeV/g to Gy, where \(e = 1.602.10^{-19} C\). The solid curves shows a depth dose without range straggling. Hence the very sharp fall-off when the protons reach the end of the range. The dashed curves shows the portion of the dose contribution due to non elastic interactions with nuclei which deacrease linearly as a function of the residual range \((R_0 - z)\) (Janni, 1982).
Figure 4-8: (blue solid) Depth dose curve of 160 MeV energy proton beam in water. The BC is computed using equation (4.2) and without considering the statistical range staggering. (Red dashed) the dose contribution attribute to the portion of those protons who have experience nuclear interactions.

To consider for the statistical range straggeling and primary energy spectra, the range variance is expressed:

$$\sigma^2 = \alpha' \frac{p^3 \alpha^2 / p}{3p - 2} R_0^{3-2/p} + \sigma_E^2 \alpha^2 p^2 E_0^{2p-2}$$

(4.4)

The value of the material parameter $\alpha' = 0.065 \text{ MeV}^2 / \text{cm}$ was found to produce the best fit.

$$\sigma^2 = \alpha' \frac{p^3 \alpha^2 / p}{3p - 2} R_0^{3-2/p} + \sigma_E^2 \alpha^2 p^2 E_0^{2p-2}$$

(4.5)

According to (Bortfeld, 1997)

$$D(z) = \begin{cases} 
D_1(z) & \text{for } z < R_0 - 10\sigma \\
D_2(z) & \text{for } R_0 - 10\sigma \leq z \leq R_0 - 5\sigma \\
0 & \text{for } z > R_0 - 5\sigma 
\end{cases}$$

(4.6)

where

$$D_1(z) = \frac{\epsilon \phi_0}{R_0 q \bar{\alpha} \bar{\rho}} (R_0 - z)^{1/p}$$

(4.7)

and

$$D_2(z) = \phi_0 \frac{e^{-\zeta^2/4\sigma^2}}{\sqrt{2\pi} \theta \bar{\alpha} \bar{\rho}} \left[ \frac{1}{p} \right] \left\{ \frac{1}{\sigma} D_{1/1}(\zeta) + \left( \frac{\beta}{p} + \gamma \beta + \frac{\xi}{R_0} \right) D_{1/1}(-\zeta) \right\}$$

(4.8)
where $D_x(z)$ is the integral resulting dose in the depth $z$, $\epsilon$ is the fraction of the primary fluence contributing to low energy fluence at the end of the range, $\sigma$ is the Gaussian range spectrum which contains the range straggling components of the mono-energetic beam and the range distribution resulting from the energy distribution spectrum. $\zeta(z) = \frac{R_0 - z}{\sigma(z)}$ is the residual range of protons normalised by the corresponding Gaussian range spectrum and $\mathcal{D}_\gamma(x)$ is the parabolic cylinder function. Finally, $\Gamma(x)$ is gamma function:

$$\Gamma(x) = \int_{0}^{\infty} e^{-t} t^{x-1} dt \quad (4.9)$$

The parameters were optimized based on comparing the model with the experimentally measured BCs. Both the proton range and the proximal- and the distal 80% depth have been compared.

### 4.4.2 Analytical proton radiograph

For analytically calculating RIDD, a modified version of the above model has been developed. In this, the physical RP (with Gaussian profile in air) is broken down into a sub-set of mini RP (beamlets), at the resolution of the CT data in which the RP has being modelled. Note however, that the proton beam broadening due to MCS was not taken in account. The residual proton range can then be estimated by relocating the analytical BC of a given nominal energy from its nominal baseline by a distance equal to the integral of the crossed RSP along the beam trajectory and then convolved with the beam profile.

$$WET = R_0 - \frac{\sum_j c_j \sum_{i=1}^{n} RSP_i^j}{\sum c_j} \quad (4.10)$$

where $c_j$ is the convolution factor of the beam profile of the $j$ beamlet and $n$ describes the number of crossed voxels. Starting from the CT data set of patient, the corresponding DRR was computed. A grid of 2 x 2 mm$^2$ spacing RP was computed assuming proton beam energy of 200 MeV and a beam of 3 mm sigma. To investigate the potential of this technique we have selected three cases from the translation studies (patient 1). The candidate RP locations with the most power prediction for translations along each major axis (L-R, A-P, S-I) was selected as discussed in (section 4.1.3). The daily RP based positioning measurements were then performed by generating the analytical data base of RIDD for the selected locations using the planning CT. Afterwards the analytical calculations were performed for each of the three selected, patient specific RP’s through each of the clinically acquired repeat CT’s.
Figure 4-9: (a) Collection of analytically calculated BC with an energy scope between 69 MeV and 234 MeV with 6.6 MeV energy steps. (b) Selection of measured (solid) and analytically calculated (dashed) integral depth dose of proton beam in water. The BCs are normed to the corresponding maximum dose. (c) Proton range obtained from the analytical model BC (80% distal fall-off) as a function of the proton range of the 57 measured data. (d) the deviation between the proton range as a function of the energy of the proton beam.

### 4.4.3 Results of the analytical model

The adapted analytical model was found to match very well with the measured data for all the available experimental beam energies. Figure 4-9 (c) shows the proton range obtained from the analytical model plotted versus the proton range of the corresponding pencil beam measurement. It can be clearly seen that the model matches very well to the measurement resulting in a linear correlation with maximal discrepancies of ±0.3 mm (Figure 4-9 (d)). However, the dose in the plateau region was found to be overestimated for energies higher than 120 MeV in comparison to the plateau regions of measured data. $\phi(E)\Delta E$ primary energy spectrum difference could be responsible for that deviation. We have added this value linearly to the range straggling for monoenergetic beams, but an accurate
incorporation into the model is more complex (Bortfeld, 1997). Nevertheless, the discrepancy remains very small (e.g. lower than 5%). In addition, the dose at the plateau region is assumed to be deposited within the irradiated object when performing PR and will not be taken into account when calculating residual RIDD in the detector.

Figure 4-10: (a & b) Digital mean proton range – and dilution radiograph calculated based on CT patient data and using 200 MeV analytical approximation for BC. Both radiographs are computed in the lateral direction. (C & d) MC based RP proton radiographs and range dilution of the same patient. The MC simulations were performed using 200 MeV and a grid spacing of 4 mm.

Using the above described model, both mean range and range dilution radiographs have been computed. The digitally calculated mean range radiographs agree well with the ones modeled using MC, with patient features being well preserved. The analytical dilution radiograph however, seems to slightly overestimate the range mixing especially at skull-brain interfaces. This is due to the fact that the protons at the interface to air are more energetic and the method doesn’t consider MCS effects in the continuous slowing down approximation. In addition, image blurring is caused by the convolution of the beam rays with the beam profile which was assumed to be Gaussian.
Figure 4-11: Set of RP candidates (blue arrows) superimposed on lateral (a) and AP (b) proton DRR of a patient respectively. The white circles are the most sensitive locations that satisfy the pass criteria.

Figure 4-11 displays the RPs locations of the patient which have been found to maximize the variation of the mean range and range dilution using the analytical approach. Similarly to the MC studies, RPs have been localized on the patient skull as well as on the interface between skull and brain, and comprise two RP in the lateral beam direction and one in the AP beam direction. A comparison between the planning CT data base and the daily CT calculated RIDDs are shown in Figure 4-12. Panels (a) and (b) correspond to the results of the anterior-posterior and the inferior-superior respectively, whilst the read dashed curve presents the RIDD of the anatomy base line. The fall off of the RIDD matches very well with the one from the data base despite the deviation of the proton fluence of the sub-BCs. The blue dashed curves are the daily measured RP. The results of the least square comparison are tabulated in Table 4-1 and compared also with the previous MC results. The prediction error of Case 2 was within 0.5 mm. On the other hand the other two cases were predicted with an error of 1.5 mm. Nevertheless this technique enables to compute patient proton transmissions images and to estimate the RIDD in a fraction of second and it could potentially be used as an alternative to the time consuming but more accurate MC simulations.
Figure 4-12: RIDD of RP propagated for patient case 1 as a function of translation positioning error in AP (a) and SI (b) directions respectively. The dashed red curve is RIDD of the anatomy base line. The dashed blue curve presents the best matched depth dose.

<table>
<thead>
<tr>
<th></th>
<th>X-ray</th>
<th>MC RP</th>
<th>Analytical RP</th>
</tr>
</thead>
<tbody>
<tr>
<td>P1</td>
<td>-0.5</td>
<td>-1.0</td>
<td>-2.0</td>
</tr>
<tr>
<td>P2</td>
<td>-1.5</td>
<td>0</td>
<td>-2.0</td>
</tr>
<tr>
<td>P3</td>
<td>0.5</td>
<td>-1.0</td>
<td>-2.0</td>
</tr>
</tbody>
</table>

Table 4-3: Evaluation of the retrospective study with patient CT data to detect actual patient translational misalignments using analytical model for BC. The results are displayed for X-ray, MC method and the analytical PR in x-, y- and z-directions respectively.
5. Lung imaging and tumour tracking using RPPR²

5.1 Introduction

The primary challenge in particle therapy today is the accurate delivery of the prescribed dose to the target. Induced uncertainties arising from the patient’s physiology such as intra-fraction tumour motions due to patient respiration or anatomical changes may compromise the advantages of this therapy modality (see Figure 5-1) due to the well-defined proton range in tissue and to the characteristic dose peak (Bortfeld et al., 2004). In order to improve therapeutic outcomes in patients with moving tumours, such as those located within lung, liver or abdomen regions, a precise spatial and temporal knowledge of tumour position during the treatment is therefore crucial. To mitigate this problem, several techniques for image-guided radiotherapy (IGRT) have been developed and some are under investigation for advanced motion compensation for moving tumours (Keall et al., 2004), (Rietzel et al., 2004) and (Riboldi et al., 2012).

X-ray fluoroscopy has been applied for direct tumour tracking (Shirato et al., 2000) and (Cui et al., 2007) or of implanted fiducial markers (Tang et al., 2007). The former approach in principle allows for real-time, and accurate, target localization. However it suffers from poor soft tissue contrast, especially in the medio-lateral direction and for small tumours. Fluoroscopy based on implanted fiducials near the tumour (e.g. gold markers) increase the visibility of regions encompassing the tumour, however are invasive and possible migration of the implanted markers can affect the accuracy of the target localization (Nelson et al., 2007). Furthermore, X-ray fluoroscopy results in additional dose to the patient since the dose is typically delivered over many treatment fractions (Jiang, 2006).

Alternatively, external anatomical surrogates can be used to indirectly track the tumour. Such techniques can be radiation free and rely on a regression model to relate internal tumour motion to the motion of the external sensor, typically placed on the patient surface. The online measurement of the coordinates of this latter are then used to predict the tumour location (Murphy, 2004) and (Poels et al., 2015). On the other hand, investigations have shown that the relationship between tumour motion and abdominal surface motion depends strongly on individual patients, and can be affected by inter-fractional anatomical changes (Hoisak et al., 2006) (Tsunashima et al., 2004). Finally, beam gating (Mageras et al., 2001), (Giraud et al., 2006) or breath-hold treatments (Hanley et al., 1999), (Wong et al., 1999) and (Gikas and Yorke, 2004) have also been implemented, with the breathing signal

² This work was presented at the PTCOG 55 Conference in 2016
resulting from external markers or spirometry being used to control the beam delivery. In this case, the radiation is delivered within only a fraction of the respiration cycle. Both techniques can significantly reduce the magnitude of motion of the target, and surrounding normal anatomy.

In comparison to imaging with X-rays, proton radiography has the potential to provide improved soft tissue contrast and therefore density resolution (Schulte et al., 2005) (Depauw and Seco, 2011) whilst also reducing imaging dose (Schneider et al., 2004) (Bashkirov et al., 2016). In addition, proton imaging has the potential for imaging (Testa et al., 2013), (Depauw et al., 2014) using exactly the same geometrical set-up as in the treatment (Beams Eye View (BEV) imaging). If tumour tracking with the beam could be fully exploited with sensitive and fast proton imaging, interplay effects between treatment beam dynamic delivery and respiratory related target motion could possibly be eliminated.

![Figure 5-1: Anatomical density changes caused through respiratory motion](image)

Several MC based studies have demonstrated the capability of tracking mobile tumours using PR. Depauw et al. (2014) have shown a better tumour edge demarcation of lung cancer using energetic protons and heavy ions. The authors have suggested angular and energetic cuts of the events and energy loss reconstruction based on MLP (Williams, 2004) in order to decrease the effect of MCS. The cuts allow to exclude those events undergoing large angle scattering and high energy loss due to nuclear interactions. A dosimetric benefit, especially for pediatric patients, has been also demonstrated in the same study. Spadea et al. (Spadea et al., 2014) have suggested an image processing method to increase the target contrast for PR. The method was adopted from (Yang et al., 2012), who proposed to use the pre-knowledge of tumour location from a planning CT data set to enhance the contrast of soft tissue in CBCT. In both studies, the authors have concentrated on particle coincidence tracking and have assumed that primary fluence spectra, and both position and direction of each particle, can be recorded before and behind patient (Depauw and Seco, 2011).
In section 2.3.5 we have reviewed the most recent works in integration based systems for proton radiography (PTI) and we have focused our attention on the technique based on range telescope detectors. Although first results of such technique are encouraging (Rinaldi et al., 2014) and (Farace et al., 2016), wide area MLICs are not yet commercially available (Rinaldi et al., 2013), and this PTI modality is also limited by the long time acquisition for large FOV images (Farace et al., 2016), making it currently unsuitable for tumour tracking. However, the major drawback is the poor spatial resolution in comparison to conventional X-ray radiography. The spatial resolution of PTI is intrinsically given by MCS (Schneider and Pedroni, 1994), (Sadrozinski et al., 2016) and (Plautz et al., 2014). The reconstructed range maps from such systems suffer strongly from range mixing and depend on the originating beam quality and on grid spacing (Krah et al., 2015). Nevertheless, the dosimetric advantages, higher geometrical accuracy (true BEV) and potential to verify CT-RSP calibration (Schneider et al., 2004), (Doolan et al., 2015) of PTI justifies further investigation, and may be able to compensate somewhat for its limited spatial resolution.

In the conventional X-ray angiography, Digital Subtraction Radiography (DSR) (Kruger et al., 1978), (Ovitt et al., 1979) and (Okamoto et al., 2000) is employed to increase the visibility of small structures. Reference radiographs (the mask) are generated prior to adding contrast agent. New radiographs are then generated with the same background, with the pre-contrast masks then being subtracted from the new radiographs, thus substantially increasing the contrast of the images. Applying the same idea to proton radiography, in a MC study (Spadea et al., 2014), the authors have manually manipulated X-ray DRR’s of the planning CT PR, such that the Gross Target Volume (GTV) is deleted. These aligned DRR’s are then subtracted from PR of the same patient. The promising results of their study have shown up to 400% increases in contrast enhancement in comparison to nominal PR. Inspired by these two approaches, in this chapter we propose a similar approach to increase the visibility of tumours if imaged using scanning beam PR. In other words, we have adopted a DSR technique to perform digital subtracted proton radiographs (DS-PR), based on prior knowledge of the patient’s CT data set (Spadea et al., 2014).

In a second part of this work, we take an alternative approach, and investigate whether there is nevertheless useful data in pure RPPR images (as opposed to DS-PR) that can be used as surrogate information for predicting tumour location on-line. As such, we analyze whether a smaller number of well selected sub-regions of RPPR, which could be imaged quickly and with low dose by scanning RP over these selected sub-regions of the patient, could predict tumour location over a complete respiratory cycle. In other words, can internal anatomical structures, resolvable in RPPR images, act as surrogates for tumour motion? For this, we have developed a correlation model between the motions of visible structures in the RPPR (Internal Anatomical Surrogates (IAS)) and the tumour location. It is our hypothesis that the trajectory of a tumour correlates deterministically with respiration induced organ motion over the respiratory cycle of the patient. Such predictor
regions are assumed to be monitored in BEV geometry. In order to speed up the tracking approach, and avoid unnecessary dose to the patient, the task of this work then can be described as locating a few IAS, such that their displacement (in range) have maximal predictive power as a function of tumour motion.

5.2 Methods and materials

5.2.1 Digitally subtracted Range Probe radiography (DS-PR)

Figure 5-2: Demonstration of the range probe setup for lung patients. The RP traverses the coronal plane of the patient. The residual energy is deposed in a plane parallel detector placed adjacent to the patient. The range telescope compromise many plates as range shifter and separated with air.

The concept of the DS-PR approach can be summarized as follows. Using CT data of the patient, the organs enclosing the tumour (e.g. the lung) are first delineated. In contrast to the approach of (Spadea et al., 2014), we have chosen to mask the whole organ instead of masking only the GTV, with the lung HU being set to that of air in the CT. We have taken this approach, as this prevents the tumour being partially shadowed by background anatomy in the case of geometric misalignments of the tumour between the CT and treatment beam or due to tumour motion (Zhang et al., 2013). The segmented and thus modulated CT is then used to generate 2D, range maps (calculated in the beam direction) which could then be subtracted from the actually acquired RPPR (acquired from the same beam direction). However, as we cannot yet acquire real RPPR’s on patients, in this study, clinical RPPR have been simulated using VMCPPro MC tools (Fippel and Soukup, 2004) and (Soukup et al., 2005). For these, pencil beam RP’s were simulated with a uniform pacing of 4 x 4 mm² orthogonal to the field direction, with the field size being extended to ensure the coverage of the ROI and the whole patient’s thorax (see Figure 5-3 (a) and (b)). All pencil beams were modeled as mono-energetic beams with energies of 240-250 MeV and with a lateral Gaussian profile in air of 3 mm sigma. Such a beam size is compatible with beams of such energy on Gantry 2 at PSI. The same phase space files as used to
simulate the RPPR\textsubscript{mask} has then been used to simulate a daily (treatment) RPPR calculated from different phases of a 4D-CT (RPPR\textsubscript{online}). Analogue to the DSR approach, each RPPR\textsubscript{mask} of each breathing phase (BPh) has then been subtracted from the corresponding RPPR\textsubscript{online} resulting in a DS-PR (see Figure 5-3). The two images don’t require alignment in this case, as both RPPR have been acquired with the same geometrical conditions. The target has been then delineated automatically on all images using a region growing algorithm, with the location of the seed being set at the position that corresponds to the center of GTV. The maximum intensity distance was set to the smallest WET value of the projection of GTV after conversion to RSP (Schneider \textit{et al.}, 1996).

Figure 5-3: Steps required for DS-PR of a lung patient. (a) and (b) are proton radiographs PR\textsubscript{mask} PR\textsubscript{online} performed based on the modulated CT (mask) and the online CT. Both PR\textsubscript{mask} PR\textsubscript{online} have been simulated in the lateral direction and using identical spacing of 2 x 2 mm\textsuperscript{2} and FOV. The pencil beam has a 250 MeV and a beam cross section of 3 mm sigma. (c) Is the resulting subtraction of (a) and (b). All the PR are superimposed with the projected GTV location (red)

5.2.2 Tumour tracking using RPPR surrogate regions

As an alternative to DS-PR, the aim of this second part of this study is to localize internal markers in RPPR images which correlate with the tumour trajectory motion over a complete respiratory cycle. Since these locations will also experience displacement arising from patient’s breathing, the objective is to find these locations (e.g. as function of time and space \(RPM(\vec{x}, t)\)) that best correlate to the motion of the tumour.

4D RPPR’s have been simulated from 4D CT data set of 10 BPhs phases. Each 2D RPPR (\(PR(t)\)) consists of equally spaced grid of 2 x 2 mm\textsuperscript{2}, 250 MeV monoenergetic RP’s, each of 3 mm sigma. The projected tumour region has been localized in each \(PR(t)\) and the position of the tumour \(T(x, t)\) has been considered to be the centre of mass of the projected target. The deformation vector fields \(V(\vec{x}, t)\) over the respiratory cycle have been
computed using deformable image registration (Thirion, 1998). With the peak exhale phase being considered as the reference image $PR(t_{ref})$. The $V(\vec{x}, t)$ indicates the projected 2D displacement of range maps to reference $PR(t_{ref})$ over the time series $(t)$.

For this approach we assume there are a few WET locations markers $RPM(\vec{x}, t)$ from $PR(x, t)$, that correlate with the projected tumour region motion $T(x, t)$. The correlation then can be expressed as a polynomial model:

$$T(t) = P[RPM(\vec{x}, t)]$$  \hspace{1cm} (5.1)

where $P$ is a polynomial of arbitrary degree and $(\vec{x})$ describes the 2D displacement field of each RP in $RM(\vec{x}, t)$. The general correlation can be summarized as a linear regression model over the whole respiratory cycle (Hastie et al., 2009):

$$\bar{T}_t = \beta_{0,t} + \sum_{i}^{N} \sum_{m}^{P} \alpha_{i,m}x_{i,t}^{m} + \delta_t$$  \hspace{1cm} (5.2)

where $\bar{T}_t = [T_1(t), T_2(t), ..., T_R(t)]^T$ is the centroid position of the target at the respiratory phase $t = 1, 2, ..., R$, $x_{i,t}^{m} = [x_1^{m}(t), x_2^{m}(t), ..., x_N^{m}(t)]^T$ is the time dependent displacement field of the IAS$_i$, $i = 1, 2, ..., N$ and $m \in \{1, 2, ..., P\}$ is the associated binary degree of the canonical form of the polynomial function. $\alpha_{i,m}$ and $\beta_{0,t}$ are scalars and $\delta_t$ denotes the noise of the model at BPh $t$ which can be associated to the lateral accuracy of the $RM(\vec{x}, t)$ due to intra-fractionation anatomical variation due to motion. The residual sum of the square of the errors of the regression is given as follows:

$$\sum_{t}^{R}(\epsilon_t)^2 = \sum_{t}^{R}(\bar{T}_t - \beta_{0,t} - \sum_{i}^{N} \sum_{m}^{P} \alpha_{i,m}x_{i,t}^{m} + \delta_t)^2$$  \hspace{1cm} (5.3)

To simplify the problem, we have assumed a noise free system ($\delta_t \approx 0$), since the $RM(t)$ are assumed to be directly measured prior to treatment delivery. In addition we have considered for our approach only RPs that yield high WET variations over the respiratory cycle, thus the ratio of the noise to the detected WET change should be negligible. For the mathematical representation, $\beta_0$ can be merged to the array $x_{i,m}^{m}(t)$ by increasing the variable number to $N + 1$. The residual sum of squared errors can then be expressed in a norm form:

$$\sum_{t}^{R}(\epsilon_t)^2 = \|\bar{T} - XA\|_2^2$$  \hspace{1cm} (5.4)

In order to construct the correlation function, the available data over the whole respiratory cycle was split to a training set $R^T$ and the rest to evaluation data set $R^E$ respectively, where $R = R^T + R^E$. For the training part, vector $\bar{T}_t$ contains the dynamic 2D coordinates of the position of the target with $\bar{T}_t = [\bar{t}_{1,t}, \bar{t}_{2,t}]$ and the size $2R^T \times 1$. $X$ are the global optimization variables assigned to the displacement field for all the RPs and over the BPhs
for training, which has a size of \((N + 1) \times m \times 2R^T\). In order to reduce the complexity of the solution, we have used a lasso regularization to enforce sparsity of the solution (Hastie et al., 2009). This reduces the number of selected RPM to only a few RPs.

\[
\hat{\alpha} = \arg \min (\bar{T} - XA)^T (\bar{T} - XA) + \lambda ||A||_1
\]  

(5.5)

Where \(\hat{\alpha}\) is a least square estimate, \(\lambda\) is the positive regularization parameter and \(||A||_1 = \sum_j \sum_i |a_{i,j}|\) is the \(L1\) norm. For our correlation, we have considered two different models. For the first model, we have considered a polynomial correlation between \(IAS(\bar{x}, t)\) and the tumour location \(\bar{T}_t\), while the model is assumed to be valid over the whole respiratory cycle. In this part of the work, we have evaluated the performance of the presented approach by parametrizing the required degree of the polynomial correlation to predict the tumour position. First we assumed the correlation to be linear \((m = 1)\) then have considered it to be quadratic \((m = 2)\). As an extension, we have also considered the hysteresis motion of the tumour region due to the elasticity properties of the lung tissues and to the respiratory volume to pressure relationship (AAPM Report 91, 2006). In other words, the motion trajectory of the lung sub-volume is not identical during the inspiration and during expiration. In order to increase the prediction power of the algorithm, we have therefore assumed two polynomial correlations, where one is adapted to track the tumour while the patient is in inspiration and a second model for the expiration phase. As such, we have split the training data set into two parts, and according to this, we have built the two polynomial correlations, one for inspiration and the second one for the expiration.

5.3 Validation

5.3.1 Patient data

To validate the approaches proposed in this work under clinical conditions, 4D CT data sets for four lung cancer cases have been considered. Each data set consists of a series of volumetric CT scans composed of 10 different breathing phases (0, 10, ..., 90\%) covering the entire respiratory cycle. The CT scans were acquired with 2 mm slice thickness and with a pixel size ranging from 0.977 \times 0.977 mm\(^2\) to 1.42 \times 1.42 mm\(^2\). For each case, the GTV was delineated on each phase, and these were considered as references for the comparison to DS-PR images.

5.3.2 Quantitative evaluation

A quantitative evaluation of the obtained image using the DS-PR approach was performed based on a binary classification test and quantification of the contrast to noise ratio (CNR). For the former we have calculated sensitivity, specificity, precision and accuracy (Olson
LU
and Dursun, 2008), by comparing the resulting range map with the GTV as gold standard. In order that both samplings match however, the range map was interpolated to the resolution of the reference 4DCT using a bivariate cubic spline approach. The CNR was then computed using (Rampado et al., 2006):

\[
CNR = \frac{\bar{R}_t - \bar{R}_h}{\sqrt{\sigma_t^2 - \sigma_h^2}}
\]

where \(\bar{R}_t\) and \(\bar{R}_h\) are the average image value in the ROI of the tumour and surrounding healthy tissue respectively. \(\sigma_t\) and \(\sigma_h\) are the corresponding standard deviation. This metric quantifies the density difference between the tumour and surrounding region, which is considered as image noise. The FOV was chosen such that the whole amplitude of tumour motion was covered. Concerning the prediction accuracy of the proposed correlation model for tumour tracking from surrogate RPPR regions, we have used ‘leave-one-out’ and ‘leave-two-out’ cross-validation approaches. For each patient, 10 CT data sets are available corresponding to the 10 BPhs of the patient. In each repeated test therefore, either 9 (leave-one-out) or 8 (leave-two-out) phases have been used to form a training set, and the model is then tested on the one or two phases which are left. The test was repeated 10 times for both cross-validation tests. For the ‘leave-two-out’ tests, the two phases chosen for the test were always two chronologically successive BPhs.

5.4 Results

5.4.1 Digitally subtracted proton radiography (DS-PR)

Figure 5-4 Left (a & d) and middle (b & e) depict a side by side comparison of reconstructed X-ray DRR reconstructed from the CT dataset (converted to a WEPL map using the HU-SP calibration) and a simulated 250 MeV RPPR of a single BPh of patient number one. The trachea, ribs and tumour can all be observed. However the poor intrinsic resolution and the grid spacing size have a substantial effect on the spatial resolution in comparison to the pure WEPL map. The right panels (c and f) show the reconstructed DS-PR images of the same patient. It can be seen that the DS-PR improves contrast substantially and the projected tumour region can be easily identified, even given the relatively small size of the tumour. As such, the density resolution has been substantially improved despite the grid spacing and range spectrum deterioration resulting from MCS, and this enhanced contrast allows to demarcate the projected tumour region.

The contrast resolution for RPPR and DS-PR has been quantified and compared for each patient over the whole respiratory cycle and for each technique. The results are summarized in Figure 5-5 (a). The average CNR over the 40 CTs has been found to be 1.82 ± 0.17 (1σ) for DS-PR, 0.73 ± 0.28 for RPPR and 1.20 ± 0.42 for the DRR’s. Each
column of the figure 5.5 contains the individual results of each case. The proposed DS-PR technique has improved the quality of the range map images by at least a factor two over all cases and also shows superiority in comparison to the simulated X-ray radiography.

![Image](image-url)

Figure 5-4: Radiographs of lung patient reconstructed from three different methods of a single breathing cycle. Upper and lower panels corresponds to lateral and AP BEV of the same patient. (a) and (d) panels correspond to X-ray DRR, (b) and (e) the WET from RPPR and (c) and (f) the DS-PR methods, respectively. The WET were simulated using 250 MeV proton pencil beams with a spacing 2x2 mm².

Figure 5-5 (b) depicts the results of the binary classification test. The sensitivity and specificity for DS-PR and RPPR respectively are 0.67 ± 0.07, 0.97 ± 0.03, and 0.53 ± 0.04, whereas the precision and accuracy are 0.93 ± 0.04, 0.85 ± 0.04 and 0.98 ± 0.04, 0.82 ± 0.04. These results, and the significant increase of the CNR, affirm the efficacy of this tool for detecting tumour regions. However, the slight reduction of the precision metric in comparison to the other techniques, indicates that DS-PR somewhat overestimates the projected tumour region, mostly due to the resampling that has been performed to compare the finite sampling of RPPR and the sampling of the ground truth (CT data).
5.4.2 Tumour tracking using RPPR surrogates

The performance of selected features of RPPR images as motion surrogates of tumour motion has also been investigated. Figure 5-6 summarizes the results of the leave-one-out tests of the patient’s study over the respiratory cycle. For each single BPh, the nine residual phases have been used as training data. The deviation of each test was estimated as the Euclidean distance between the predicted target and the reference coordinates taken from the 4D-CT. Figure 5-6 (a) shows the ‘optimal’ RP positions ($RM(\bar{x}, t = 10\%)$, which have been found using the correlation approach, in this case to localize the $2^{nd}$ BPh (10%). Figure 5-6 (b) shows the 2D comparison to the actual/theoretical positions of the projected tumour location predicted using the RP positions from Figure 5-6 (a). The three locations have been found to predict the target location with a 2D accuracy of 0.46 mm using nine phases as training data.
Figure 5-6: (a) Locations of RP markers found using polynomial correlation model superimposed on proton radiograph of patient1. The arrows show the displacement field corresponding to each location. The tumour is delineated red. (b) The results of cross-validation test corresponding to the 10th BPh. The dashed blue line is the tumour trace over BPhs1-9. Blue circles are the target-performance comparison, where red is the predicted location. (c) Correlation coefficient map of the patient anatomy shown in (a) and superimposed with internal markers of all breathing phases have been found to predict the tumour location. (d) shows the leave-1-out-cross-validation using 9 breathing phases as training for the whole respiratory cycle.

Over all patients, and for different predicted phases, our study has shown that the target can be localized on average with a 2D accuracy of $1.11 \pm 0.76$ and $1.12 \pm 0.43$ (mean ± 1σ) for patient one and patient two, respectively, based on an average of 5.9 and 3.3 RP per phase for patient one and two respectively. The accuracy of prediction for all cases was below 2 mm for all BPhs, except for one case (case one, BPh = 70%, corresponding to breathing phase of maximum exhale), which could be predicted only with an accuracy of 2.49 mm. A reason for this could be the low correlation between different lung structures, due to their elasticity properties and to the respiratory volume to pressure relationship (AAPM Report 91, 2006). In addition, the prediction accuracy in patient one fluctuates
more than patient two. This is due to inherent differences in density for the RPPR of the two patients. The RPPR of patient two shows a higher density resolution than patient one, since patient one has been monitored in medio-lateral direction, which is characterized by greater thickness (i.e. higher scattering power), in comparison to the anterior-posterior direction (patient two). Nevertheless, the results demonstrate the higher sensitivity of this technique to localize tumours. The correlation between the projected tumour motion and the proton radiograph over the whole respiratory cycle is shown in Figure 5-6 (c). The correlation map was compared to all $RM(\vec{x}, t)$ which have been found, using the approach described above, to correlate with the tumour location. It can be clearly seen, that most $RM(\vec{x})$ are located inside regions which correspond to the largest correlation coefficients, indicating that the selection criteria is robust. Figure 5-7 shows the results for the ‘leave-two-out’ tests, where the predicted target positions were always two chronologically successive BPhs. In this case, the prediction has been computed using two different polynomial degrees (i.e. linear and quadratic). Figure 5-7 (b) depicts the comparison of the actual and predicted locations for BPhs 8 and 9 for case one. It can be seen that the resulting deviation is lower than one millimeter and from 5-7 (a), it can be seen that increasing the degree of polynomial correlation decreases the mean variation of the prediction error, even if the magnitude of the smallest deviations are increased.

Figure 5-7: Prediction accuracy of the Leave-2-out -cross-validation tests. (a) Depicts a side by side comparison between the linear (lin) and quadratic (quad) correlation of the same training data sets. (b) Presents the target-performance comparison of Leave-2-out -cross-validation (predicting phase 8 and 9).

5.5 Discussion

In proton therapy, the geometrical uncertainty resulting from patient set-ups and inter- und intra-fractional uncertainties arising from patient respiratory affect the distal proton range and deteriorate the delivered dose (Bortfeld et al., 2004) and (Paganetti, 2012). The most recent reviews concerning the technological requirements for clinical, time-resolved pencil
beam scanning, have summarized that the limitation of this modality is due mainly to limitations in tumour targeting with high geometrical accuracy and the subsequent requirements for advanced imaging solutions (Knopf et al., 2016) and (Chang et al., 2017).

The potential of proton imaging for moving tumours and its dosimetric benefits, especially for pediatric patients, has been demonstrated using individual event tracking proton radiography by (Depauw et al., 2014) and (Spadea et al., 2014). However, scanned proton pencil beams, together with an integrated range signal collected in a range telescope, have also been proposed for imaging in rigid anatomies (e.g. in the head) (Mumot et al., 2010), (Rinaldi et al., 2014) and (Farace et al., 2016). In this chapter we have demonstrated the potential of such proton imaging systems (RPRR) as a tool for patient set-up and tumour tracking also in time resolved proton radiotherapy.

We have investigated two different techniques. First, a full imaging approach, attempting to suppress radiographic image features in order to increase tumour visibility especially in mediolateral projections, has been investigated (DS-PR). This method was inspired by X-ray digital subtracted radiography and the work of (Spadea et al., 2014), but here has been expanded to the RPPR technique. This makes use of a priori patient knowledge information and is based on large FOV radiographic images. The resulting improvement in contrast leads directly to improved tumour visibility in all considered patients, and over the whole respiratory cycle. As such, the CNR has increased by at least 70%, with a maximum enhancement of more than 330% for P1 and P2, respectively. The additional binary classification investigation, based on the GTV ground truth position, has demonstrated the prediction accuracy of the technique and shows that subtraction doesn’t cause any loss of anatomical features of the target. Even if the evaluation of the image quality of PR has shown encouraging results, the density resolution reached by DS-PR is higher than that using the simple RPRR approach. Furthermore, increasing the spatial resolution of such PR would require decreasing the 2D grid spacing between single RP, and thus will increase the number of delivered beams, and deteriorate the temporal resolution of the monitoring. Currently therefore, it is not possible to create RPPRs containing complete anatomical information (e.g. lung) of a patient under dynamic breathing. Nevertheless, DS-PR could be useful for the treatment of lung patients treated using breath-hold to detect intra-fractional shifts of the target position between breath holds. However this would require a range telescope with a large active area (e.g. see (Rinaldi et al., 2013)) and also a fast delivery system (e.g. (Pedroni et al., 2011)) to acquire the radiographic images in a reasonable time.

In the second part of the study therefore we have investigated the potential of a new, time-resolved tumour tracking technique based on the identification of internal anatomical structures, visible in RPPR type images, which can be correlated to motion of the tumour. For this, we have developed a numerical technique to select RP positions which provide covariates to improve the prediction accuracy for tumour location. The region selection is
based on polynomial correlations that relate these selected IAS to target motion trajectory. The technique requires only a subset of RP delivered from a single beam direction in order to localize the tumour, potentially making the approach fast and dose-efficient. Furthermore, the RP technique could provide additional information which could contribute to improvements in the quality of treatment, such as changes in anatomy and WET.

The results of the time-resolved RP tracking have shown that tumour location can be predicted with high accuracy using only a few single RP positions (4 - 6), and that by using 9 BPhs as training data, a 2D average deviation in predicted tumour position of lower than 1.2 mm can be achieved. However, although only a few RP positions are selected for the model, to measure their time resolved displacement, additional RP, surrounding the selected RP would also need to be measured. The feasibility of this approach in clinical practice still needs to be investigated however, in particular whether a set of RP scanned around a few, spatially distributed locations, could be acquired fast enough to truly act as a tracking signal. On the other hand, such an approach could be used on a periodic basis through a treatment to check the validity of other motion modelling approaches that may be in place. For instance, if an external motion surrogate is used as the primary patient monitor for tracking or gating, a model correlating the external to internal motion needs to be derived. The RP based correlation model described here could perhaps then be used as a method of checking the validity of such models during a treatment, for example between delivered fields. Based on the first result presented here, such an application of RPPR based tumour tracking deserves to be investigated in more detail.
5.6 Appendix - RPPR for liver imaging

The DS-PR technique described in this chapter has also been applied to a liver cancer patient, in order to investigate whether the contrast enhancement provided by the technique could help to resolve a liver tumour. Preliminary results for this, and an investigation whether other characteristics of proton interaction could be used for identifying liver tumours, will be briefly described in this appendix.

Figure 5-8: Radiographs of liver patient reconstructed from lateral direction. The red line is the tumour contour. (a) Panels correspond to X-ray DRR, (b) the WET from RPPR and (c) the DS-PR methods, respectively. The WET were simulated using 250 MeV proton pencil beams with a spacing 4 x 4 mm².

5.6.1 RPPR and DS-PR for liver tumours

Figure 5-8 depicts the results of RPPR and DS-PR for a liver case patient. Due to MCS and range mixing, the RPPR provides only poor contrast, and neither the liver nor tumour (highlighted by the red contour Figure 5-8 (b)), are visible. The application of the DS-RP approach (Figure 5-8 (c)), can suppress the surrounding anatomical features such that the liver can be visualized, however, the tumour was still not detectable in this case. However, it should be noted that the RSP of the liver and the target have been found to be $\overline{RSP}_{Liver} = 1.070$ and $\overline{RSP}_{Tumour} = 1.073$, as determined from the originating CT data. This 0.3% difference would result in WET difference of only 0.5 mm over the whole target, which is smaller than the depth resolution of the detector used in this study, and also smaller than the contribution of range straggling for the applied proton energy (Janni, 1982). Thus, without looking into alternative techniques, it appears that neither RPPR nor DS-PR would be able to resolve such liver tumours.
5.6.2 Imaging based on proton scattering

Plautz T. et al. (2014) have suggested to make use of the scattering-energy dependence to measure energy-loss. The authors have shown that scattering radiographs of thin objects have the potential to provide higher density resolution than energy-loss radiographs. However, this technique requires very precise and fast detectors that record both, the position and the angular entrance of single protons. Alternatively, Taylor et al., (2016) have used a large area, silicon micro-strip tracker to measure the rate of change of the mean-square scattering angle of protons exiting objects and have normalized it to the scattering power of water. The WET was estimated by using a scattering to WET calibration based on MC. In chapter 4, we have demonstrated that the quality of PR images created using RPPR can be improved when additional information of the resulting proton spectra of the measured single RP are considered (see Figure 4-2). As such, a similar approach to DS-PR has been investigated based on scattering. Instead of reconstructing range maps, we have calculated maps of beam broadening. The resulting beam deflection was approximated for each proton spot based on the simulated spatial beam profile:

\[
\tilde{\vartheta}_{x,y} = \sqrt{(\vartheta_{x,\text{out}} - \vartheta_{x,\text{in}})^2 + (\vartheta_{y,\text{out}} - \vartheta_{y,\text{in}})^2}
\] (5.7)

where \(\vartheta_x\) and \(\vartheta_y\) are the direction cosines of the assumed Gaussian spot beam profile at the entrance (\(\vartheta_{\text{in}}\)) and at the exit (\(\vartheta_{\text{out}}\)) in the plane x-y perpendicular to the mean direction. The resulting scattering maps (i.e. on entrance (in) and exit (out) of the patient were subtracted from each other. The results of this are shown in Figure 5-9. The radiograph was smoothed using a Gaussian filter with a sigma equal to the size of image pixel. The resulting scatter radiograph is a metric showing the scatter caused by the material difference between the segmented and the RPPR. These encouraging results demonstrate the potential of this imaging modality to increase the quality of proton transmission radiographs (Plautz et al., 2014) and (Taylor et al., 2016). In addition, such an approach to proton radiography wouldn’t require a range telescope to measure the RIDD but rather only a system to detect the beam profile.
Figure 5-9: Radiographs reconstructed using DS-PR and based on beam profile broadening. (a) The angles are calculated by subtracting the exiting beam size from the inside beam size. (b) The radiograph (a) was smoothed with a Gaussian filter.
6. In-vivo proton range reconstruction after anatomy changes

6.1 Introduction

As already discussed in chapters 1 and 2, the intrinsic energy loss of protons requires accurate knowledge of the water equivalent path length of the traversed anatomy. Typically, and in contrast to CT calibration range uncertainties and patient set-up errors, inter-fractional anatomical changes are not considered in robustness optimization of IMPT. Indeed, such geometrical changes (e.g. patient weight change, tumour shrinking etc.) could be substantially larger than the safety margin (Albertini, 2011) and (Bentefour et al., 2012). In clinical practice therefore, repeated volumetric X-ray imaging, such as CBCT or CT-on-rails need to be applied to quantify such changes and to adapt the treatment planning. Proton Radiography (RP) as an alternative to X-ray imaging offers dosimetric advantages and provides energy loss information without any misalignment between monitoring and treatment. On the other hand, only integrated information over the whole beam path is provided. Proton CT on the other hand has the potential to measure 3D maps of stopping power (Schulte et al., 2004). However, this concept requires sophisticated equipment and fast read-out electronics (Sadrozinska et al., 2013) and (Bashkirov et al., 2016). In this chapter therefore, we investigate the feasibility of extending the RPPR concept introduced in previous chapters to proton tomography, and further investigate the potential for detecting and predicting range changes due to anatomical changes from just a few proton radiograph projections (limited projection tomography).

6.2 Methods

6.2.1 Full projection, range probe tomography

In this section, we will first describe the concept and mathematical background to proton radiography based on multiple RPPR projections.

The 2D tomographic image to be reconstructed \( f(x, y) \) is assumed to contain a grid of \( N \) equally spaced pixels (Figure 6-1), where \( f_j \) denote the pixel \( j = 1, 2, \ldots, N \). The measured integral WEPL on beam exit is equal to the sum of the intersectional fraction \( w_{ij} \) of single pixels within the RP ray \( p_i \) \( i = 1, 2, \ldots, M \)., where \( M \) is the number of RPs over all the FOV.

\[ 3 \] This work was presented at the annual AAPM conference in 2016
and projections. The fraction is determined by the area between the ray \( p_i \) and the boundaries of the cell \( f_j \). The iterative solution requires solving the large linear system of the form

\[
\sum_{j} w_{ij} f_j = p_i \quad i = 1,2, \ldots M
\]  

A reconstructed tomographic image with \( N \) cells can be considered as an image of \( N \) degrees of freedom, which corresponds to only a single point in \( N \)-dimensional space and each linear equation represents a hyperplane in this space. A unique solution is given by the intersection point of all those hyperplanes (Kaczmarz, 1937). The computation starts with an initial guess \( f_j^{(0)} \) for \( j = 1,2 \ldots N \) which is projected on the first hyperplane. The resulting intersection point will correspond to the new solution \( f_j^{(1)} \) which will be again further projected on the equation of second hyperplane and go on to reach \( f_j^{(M)} \) and then projected back to the first equation of the hyperplane. A convergence is guaranteed only if a unique solution exists (Tanabe, 1971). Mathematically speaking, a solution \( \tilde{f}^{(i)} \) is obtained by projecting \( \tilde{f}^{(i-1)} \) on the hyperplane described by the \( (i) \) equation.

\[
\tilde{f}^{(i)} = \tilde{f}^{(i)} - \frac{(\tilde{f}^{(i-1)}, \overline{w}_i - p_i)}{\overline{w}_i, \overline{w}_i} \overline{w}_i
\]  

where \( \overline{w}_i \) is the weighting vector for all the \( N \) elements.

Assuming a matrix \( A \in \mathbb{R}^{M \times N} \), then \( N \) is the number of unknowns and \( M \) is the number of RPs multiplied with the number of projections. For each ray element RP, there is a sub region in the image \( f(x,y) \) which intersects with the pencil beam \( g_{rp}(x,y) = RP \cap f(x,y) \) (Figure 6-1, blue area), which is invariant from the image. However it depends only on the beam path.

\[
g_{rp}(x,y) = \begin{cases} 
0 \text{ pixel } (x,y) \text{outside intersection area} \\
1 \text{ pixel } (x,y) \text{inside intersection area}
\end{cases}
\]  

If we consider the weight of the beam path:

\[
a^{rp} = w^{rp} g_{rp}(x,y)
\]  

where \( a^{rp} \) and \( M \) denote the vectors of \( A^T \) as ray density contributions for a given RP and projection. It has to be noted that \( a^{rp} \) is quite sparse and only the cells from the image domain that intersect geometrically with the ray RP have a value different from zero. \( w^{rp} \) is a non-negative matrix containing the weighting of the unknown. The equation (6.2) above can be expressed (Gordon and Herman, 1974):
\[ x^{i+1} = x^i + \frac{\text{wet}_{rp} - a_{rp}^T x^i}{a_{rp}} \quad i = 0; 1; 2; \ldots I \]  

where \( \text{wet}_{rp} \) is the measured integral WET of the RP and \( I \) is the iteration.

Figure 6-1: Sketch of the algebraic reconstruction tomography of an unknown object. The image space is divided in equally spaced cells with the surface \( \delta^2 \). The orange area corresponds to the contribution of the cell \( w_{ij} \) and the beam \( 1 \) (blue area). Illustration was new interpreted from the (Kak and Slaney., 1988)

To avoid aliasing due to insufficient number of projections, the number of planar projections required to achieve tomographic imaging has to be determined as a function of the spatial resolution of the detector, given by the grid size \( \Delta d \) and the size of the region of interest. Assuming a given number of projections \( M_{proj} \) uniformly distributed over 180° this is given by.

\[ \Delta \varphi = \frac{\pi}{M_{proj}} \]  

According to Nyquist theorem (Nyquist, 1928), the highest spatial frequency obtained from the grid spacing is:

\[ \omega = \frac{1}{2 \Delta d} \]  

and the distance between sampling points in two consecutive projections is:

\[ \Delta \varphi \omega = \frac{\pi}{M_{proj}} \cdot \frac{1}{2 \Delta d} \]  

The distance between neighbors sampling points in the frequency domain of a single projection is then the reciprocal \( N_{RP} \) of the number of single RPs in one projection:

98
Finally, by setting the equality of the azimuthal- and the radial-resolution (Kak and Slaney, 1988) we obtain

\[
\frac{2\omega}{N_{RP}} = \frac{1}{\Delta d \cdot N_{RP}}
\]

(6.9)

\[
\frac{2\omega}{N_{RP}} = \Delta \phi \cdot \omega \leftrightarrow \frac{1}{\Delta d \cdot N_{RP}} = \frac{\pi}{M_{proj}} \cdot \frac{1}{2\Delta d} \leftrightarrow \frac{M_{proj}}{N_{RP}} \approx \frac{\pi}{2}
\]

(6.10)

Figure 6-2: An Illustration of the Kaczmarz’s iterative technique for solving problem with two hyperplanes. The iteration starts with a first guess which is projected on the first equation of the hyperplane and then onto the second iteratively until the unique solution is reached. Illustration new interpreted from the (Kak and Slaney, 1988)

6.2.1.1 Example RP tomographs

To make a first assessment of full-projection RP-CT as a tool for reconstructing proton stopping power maps, a CT data set of a patient has been used as input into RP-CT simulations. As for the required proton energies for these RP reconstructions, the simulations have been performed using 200 MeV protons, as this would be sufficient to penetrate completely through the head from all angular directions, and that a measurable residual Bragg curve is still deposited in the detector. The patient was assumed to be placed at the isocenter and the (water like) plane-parallel detector placed directly behind the patient. The detector is assumed to have a density resolution of 2 mm. The RP field was extended laterally to 270 mm allowing to cover the whole head from all directions. For each scan, we have applied two different grid spacings. In the relative homogeneous anatomic areas, we have used a grid distance of 5 mm (coarse) or 3 mm (fine resolution) between the spots, whereas in the more complex regions, we have applied spacings of 5 or
2 mm. For the 5 mm raster, we have used a nominal beam width of 7 mm FWHM and a angular resolution of 2°, while for the finer raster scanning, (e.g. 3- and 2 mm) we have assumed RP with cross sections of 4 mm FWHM and an angular resolution of 1°, respectively. The projections were equally distributed between 0° and 180°. A single slice scan then consisted of between 5040 to 25200 monoenergetic proton RP, depending on the grid spacing. The angular distributed RPPR were then reconstructed and have been further processed to build the corresponding sinogram. For comparison purposes, ‘ground truth’ proton tomographs (GT tomographs), based on the same reconstruction technique, have also been calculated, but based on proton DRR WEPL maps generated through the same patient CT, and with the same angular resolution.

Figure 6-3 shows the reconstructed 3D-WEPL of the example patient using the nominal beam set-up of 7 mm FWHM, a grid of 5 x 5 mm and an angular resolution of 2°. For comparison, the GT proton CT’s are also shown (Figure 6-3 (a) and (b)). This visual comparison shows that RP-CT has correctly reconstructed the patient geometry, with anatomical details such as the cavities being visible and correctly located. It’s even possible to distinguish between the thermoplastic mask used to fix the patient and human tissue. On the other hand, the RP based tomographs are blurred due to the lower spatial resolution of such a RP approach. Furthermore, the deviation maps (Figure 6-3 (e) and (f)) show quite high discrepancies between the reconstructed and the GT WEPL, especially at the bone-soft tissue and soft tissue-air interfaces, all of which provoke range mixing. Figure 6-3 (g) and (h) shows the reconstructed 3D-WEPL using a refined grid size of 3- and 2 mm with the narrow beam, and projections angles of 1°. It’s clear that scanning using smaller raster spots increases the spatial resolution of the reconstruction of the 3D-WEPL. Furthermore, the use of narrower beams results in a reduced range mixing and thus better demarcation of the different anatomical regions.
Figure 6-3: Comparison between proton DRR (a) and (b) and 3D-WEPL maps reconstructed using RP-CT. (c) and (d) are the corresponding reconstructed RM’s from 5 mm grid spacing, 2° angular resolution and beam width of 7 mm. (e) and (f) are the corresponding difference from the ground truth. (g) and (h) are reconstructed from spacing grid of 3 mm and 2 mm, respectively. For both reconstructions, angular resolution of 1° and beam size of 4 mm FWHM was applied. (i) and (j) are the corresponding difference from the ground truth.

6.2.2 Sparse projection range probe tomography

In the previous section, we presented the mathematical background to RP based proton tomography, and showed an example, simulated proton CT reconstructed using this method based on a full set of projections. Similarly to other chapters in this thesis however, in this section, we will investigate to what extent anatomical changes can be detected, and their magnitude estimated, by using only limited number of RP. In this case however, RP reduction will be achieved by investigating the potential of detecting range changes in the patient with a very limited number of RPPR projections. Indeed, in the following, we will investigate the possibilities of reconstructing WET changes due to anatomical changes based on the information of only two radiographic projections when used in combination with prior-knowledge of the patient’s anatomy from a reference RP proton CT. Although not investigated further here, the methods described here could of course be used for larger numbers of projections as well, with increasing accuracy.

The developed process consists of four steps:

- The acquisition or simulation of angularly spaced RPPR, and a full projection proton CT, based on the planning CT of the patient (RPPR_{plan} and pCT_{plan})

- The acquisition of two, orthogonal RPPR on the day of treatment (RPPR_{on-line}).
- The detection of density changes between the orthogonal \( \text{RPPR}_{\text{on-line}} \) and their comparison to the corresponding \( \text{RPPR}_{\text{plan}} \) from the day of planning.

- The Iterative reconstruction of a \( \text{pCT}_{\text{on-line}} \) based on prior knowledge of the \( \text{pCT}_{\text{plan}} \) and the detected changes between \( \text{RPPR}_{\text{plan}} \) and \( \text{RPPR}_{\text{on-line}} \).

Note, although a new pCT is reconstructed in this method \( \text{pCT}_{\text{on-line}} \), the aim is *not* to attempt to reconstruct a true representation of the 3D distribution of stopping powers in the patient, but rather to use this reconstruction as a predictor of *range changes* that may have occurred between the planning and treatment day. As such, it is the *integrated energy loss* (range) along lines to a reference point that is important rather than the individual SP values at any voxel. It is these integrated ranges that will be analyzed later to assess the usefulness of the technique.

### 6.2.2.1 Simulation of \( \text{pCT}_{\text{plan}} \)

In the current implementation, it is assumed that a MC simulated RP based pCT is first reconstructed based on the planning (X-ray) CT of the patient. In RP based proton radiography, we assume that the mean residual range information measured for each delivered RP can reconstruct the RSP in the beam path. This latter is assumed to be a straight line between the source and the detector. The axial acquisition geometry of the protonCT is described by the FOV, the grid spacing \( \Delta d \) and projection angles \( (\theta) \) between \( 0^\circ \) and \( 180^\circ \). To satisfy the Nyquist theorem (see section 6.2.1), in this work \( \Delta \theta \) has been chosen to be \( 2^\circ \) and projections have been equally distributed between \( 0^\circ \) and \( 180^\circ \). For each proton pencil beam, a RP-ID number is recorded \( p_i \ i = 1,2,\ldots,M \), where \( M \) is the number of the RP’s over all the projections. The \( \text{pCT}_{\text{plan}} \) has then been reconstructed using the already developed algorithm (see above). Figure 6-4 (a) shows a reconstructed \( \text{pCT}_{\text{plan}} \) for a test patient, overlaid on a pCT calculated on a repeat CT of the same patient (\( \text{pCT}_{\text{GT}} \)). Anatomical changes in the neck area are clear (identified as the green regions) indicating a shrinkage of tissue in this area between the planning and treatment day. Note however, that the \( \text{pCT}_{\text{GT}} \) displayed in Figure 6-4 (a) has been calculated only for reference purposes and to indicate the ‘ground truth’ of anatomical changes that have occurred. These will be used to assess the accuracy of the limited projection method later on.

### 6.2.2.2 Detection and localization of daily density changes

On the day of treatment, the anatomical changes resulting in range variations will be detected through the acquisition of only two, orthogonal \( \text{RPPR} \) (\( \text{RPPR}_{\text{on-line}} \)), from which range changes along these directions can be identified by calculating the difference in WET between these and the corresponding \( \text{RPPR} \) used from constructing the simulated pCT (\( \text{RPPR}_{\text{plan}} \)). Each RP for which a pre-determined WET difference has been detected is
then masked and potential locations of the sources of range change tracked back to the pCT plan. Intensity-based segmentation was performed and only the body region, which is enclosed inside the fixation mask, has been considered as ROI, while the background (e.g. air) has been assumed to be known. To avoid noise, a WET threshold was predefined (e.g. $\Delta r = 2$ mm) and only RP which measures difference greater have been considered. The sub-regions, where the RP projections are connected, were determined using forward projection and were considered as the location of the change. In order to provide faster convergence of the iterative method, we assume low-coherence between selected RPPR projections.

The results of this step, based on two RPPR$_{on-line}$ simulated from the anterior ($0^\circ$) and lateral ($90^\circ$) aspects, is shown in Figure 6-4 (d). Finally in this step, and assuming that only the masked regions have changed between the planning and treatment days, these changes can be forward projected over all projections, to transform them into the image reconstruction space (sinogram) (Figure 6-4 (c)). In this, the grey regions are considered the known projection values (given from the pCT$_{plan}$ projections) whereas the yellow regions are the unknown projections values resulting from the anatomical changes. The following iterative reconstruction process then attempts to solve for these unknowns using the prior knowledge information from pCT$_{plan}$ and under the condition that the orthogonal RPPR resulting from the reconstructed pCT (pCT$_{on-line}$) match with the measured RPPR (RPPR$_{on-line}$).
6.2.2.3 Reconstruction of correct projections

A linear set of equations was built corresponding to the two measured projections. The RP’s were considered as rods made up of equally spaced materials described by its WEPL and mass density, which have to be reconstructed as follows (Figure 6-6).

\[
\sum_{j} w_{ij} \text{wepl}(\rho_j)_j = WET_i \tag{6.11}
\]

where \( w_{ij} \) is the beam trajectory weighting, \( i \) and \( j \) are the indices of the proton beam and the reconstructed value, respectively. A threshold approach was performed and regions of the patient CT are assigned into one of four predefined mediums determined by their mass density range (Table 6-1) (Meier, 2015). In order to simplify the problem, for the reconstruction, only voxels corresponding to soft and low density tissue were considered as variable and unknown. Bone and synthetic materials (e.g. cortical bone, thermoplastic, vacuum pillow etc.) were assumed to be density invariant between the treatment fractions. Each voxel of the CT data was converted to mass density using an appropriate calibration curve (Figure 6-5). Due to the merging of on-line and prior knowledge, there is no unique solution for the system of equations with some measured RP being potentially biased by the range deviations resulting from MCS, range mixing or residual patient positioning errors between the actual and reference patient positions. As already discussed above, the solution will oscillate towards the actual hyperplane intersections (Kak and Slaney, 1988) which would not overlap with the hyperplane intersections of the reference data. To increase the robustness of the reconstruction therefore, constrained features have been
introduced. As such, the starting guess has been selected to be the pCT\textsubscript{plan}. In addition, a stopping criteria has been defined to limit the bounds of the reconstructed WEPL values in each iteration. The limiting bound was described as \([WEPL_{\text{min}}\text{,} WEPL_{\text{max}}]\) for each unknown. The RSP was adjusted according to data listed by (ICRU, Report 44, 1989) and (Schneider \textit{et al.}, 1996). The resulting reconstructed pCT\textsubscript{on-line} is shown in Figure 6-7.

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{figure6-5.png}
\caption{The scanner specific calibration curve associating CT number to mass density and based on surrogate tissue (ATOM\textregistered max).}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{figure6-6.png}
\caption{The localization of WET changes between pre and post-treatment (from gantry coordinate system) of two projections (gantry \(-90^\circ\) and \(0^\circ\)) matched to the coordinate system of treatment room. Each range probe (black point) is characterized by gantry coordinate system (origin) projected into CT data (yellow box). The range probe beam path is assumed to be a stack of materials (blue rods). The cross section of the two projected changes corresponds to the region where the WET has experienced a variation.}
\end{figure}
### Table 6-1: Mass density threshold used to determine material and based on tissue surrogate samples (ATOM®max).

<table>
<thead>
<tr>
<th>Material</th>
<th>Mass density [g/cm³]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low density (e.g. air, cavity…)</td>
<td>0 - 0.26</td>
</tr>
<tr>
<td>Soft tissue</td>
<td>0.26 - 1.16</td>
</tr>
<tr>
<td>Bone</td>
<td>&gt; 1.16</td>
</tr>
<tr>
<td>Synthetic material</td>
<td>-</td>
</tr>
</tbody>
</table>

Figure 6-7: Limited projection reconstructed treatment day pCT (pCTon-line) for the patient shown in figure 6-4. (b) the calculation of polar, integrated WER for quantitative assessment of the accuracy of predicted range changes. Just three examples of the 180 polar directions are shown, and for just one slice.

#### 6.2.2.4 Polar reconstruction of in-vivo proton range (WER)

To assess the predicted range changes resulting from the above described reconstruction process, polar WER maps have been calculated, as shown in Figure 6-7 (b). Angle dependent WER was calculated considering full rotation in 2 degree steps with each WER ray representing the (in-vivo) proton range from patient surface to a reference point in the patient, in this case the centre of the patient CT.

#### 6.2.2.5 Evaluation with patient data

Data from four head and neck patients and for which at least one repeat X-ray CT (CTon-line), acquired immediately prior to treatment, was available have been selected for the study. The CT scans were acquired with 2 mm slice thickness and pixel sizes ranging from 1.42 x 1.42 mm² (case 1,2, and 3) to 1.95x1.95 mm² (case 4,5 and 6). All CTon-line were
registered to the corresponding CT_{plan} in order to have the same origin and the same anatomical baseline. Proton radiographs (RPPR_{on-line}) from two angular projections (lateral and AP) were generated from MC simulations using a grid spacing of 2 x 2 mm\(^2\) or 4 x 4 mm\(^2\) (for patient 4) using proton pencil beams of 230 MeV and with 7.1 mm FWHM in air. To investigate the sensitivity of the approach for detecting density changes, the polar WET maps were compared to the ground truth (GT), calculated as differences from proton DRRs computed from CT_{plan} and the corresponding CT_{on-line}.

6.3 Results

Figure 6-7 shows the results for one transaxial slice of case three. The patient has suffered from shrinkage of the neck regions and also from a local variation of density due to residual set-up errors (Figure 6-8 (a & b)) and the resultant polar WET maps for this patient, and for the same slice, are depicted in Figure 6-8 (c & d). The optimized reconstruction renders the density structures and the anatomy baseline fairly well, as well as the range changes due to anatomic changes in comparison to the GT changes, with the magnitude of changes overlapping well between the two reconstructions (e & f). The spike-like artefacts (around BEV -44° (c) and around -94° (d)) are results from imperfect reconstruction and overestimate the GT value and are caused mainly large density discontinuities between the reference and on-line density maps and the threshold residual noise. The former factor originates from anatomy shifts of high heterogeneity regions (e.g. trachea, elements of fixation), whilst the latter factor has been adjusted in this work to be \(\Delta r = 2\) mm. The results could be improved by reducing this. On the other hand, increasing of the WET sensitivity would also decrease the signal to noise ratio, since some measured RP can be corrupted by uncertainties caused by patient set-up. A greater threshold would suppress the inherent uncertainties and influence from patient set-up; however it would also lead to a lower sensitivity and miss significant WET changes.

A qualitative evaluation for the prediction of range changes for all cases has been performed using acceptance values of 2 mm and 3 mm WET differences (Figure 6-9). For each patient, differences in WER changes between the data sets (see legends in the figure) have been calculated for all polar directions (180) and over all CT slices of the patients over which the RPPR projections were simulated, and the spread of these differences displayed in the form of a box plot. The proposed approach has been found to be quite sensitive to detect density changes of 3 mm in the cases 1, 2 and 3 (with about an 80% success rate), but has not been so successful for cases 4, 5 and 6. This can be explained with by the lower spatial resolution of the CT data for these patients (1.95 x 195 mm\(^2\)) and by the fact that in these cases, the RP radiography was simulated using a larger grid spacing (4 x 4 mm\(^2\)) than that used in cases 1, 2, and 3.
IN-VIVO PROTON RANGE RECONSTRUCTION AFTER ANATOMY CHANGES

(a) 

(b) 

(c) 

(d) 

(e) 

(f)
Figure 6-8: (a) shows the WET difference (in mm) of axial axis indicating anatomic changes between reference and pre-treatment CT data sets. (b) Shows the potential region, where density's change has taken place based on reference CT data and using two orthogonal projections of RPPR. (c) The polar WET difference between the patient surface and the iso-center. (Blue) is the ground truth, which corresponds to the difference between reference CT data and pre-treatment. (Orange) is the reconstructed data using the proposed approach. (Yellow) is the quantitative WET difference, which is measured using single projection RPPR (lateral). (d) is the polar WER of reference, pre-treatment and reconstructed anatomy of axial slice presented in (a).

Figure 6-9: Accuracy of the reconstructed WER in comparison to the ground truth. The Accuracy was calculated using a 2 mm (a) and 3 mm (b) WET difference criteria.
6.4 Discussion

Figure 6-10: (Upper panel) Two projections of WET difference maps detected in the pre-treatment rCT and superimposed on pRPPR. (Lower panel) The localized WET changes between pre and post-treatment matched to the coordinate system of the planning CT.

In this chapter, a method of reconstructing in-vivo proton range changes from multiple directions, but using only two RPPR projections has been presented. The technique is based on pre-knowledge of proton CT acquired based on reference CT data and allows to approximate the 3D range changes before treatment. Even if the number of the pre-treatment proton radiography fields required for the reconstruction is very small in comparison to real proton CT (Sadrozinski et al., 2016), we have assumed that the angular direction of this is set by the user. A more sophisticated method would be to automatically select the projection directions to sample based on pre-stage reconstruction and probabilistic assessment of anatomical changes, from which the most efficient projections could be calculated. An example for this is shown in Figure 6-10 (case 1). In this case, we have assumed that the density change occurs only in the nasal cavities and the change of the density is therefore enclosed within the bony structures. This assumption has allowed us to constrain the reconstruction even more and just to these regions. It can be seen, that the use of further information increases the robustness of the approach. In addition, it should be noted that all the results shown in this chapter are the result of just two RPPR
projections. Adding a few additional, angularly spaced projections would also increase the predictive power of the technique.

A limitation of this technique is the fact that the WET ‘rods’ resulting from the measured RPPR are assumed to be a stack of materials, the density of which are described by the WEPL. This approach however doesn’t consider statistical energy loss and the resultant scattering from the arrangement of the materials in the rod. As such, reconstructions in more complex geometries could result in large discrepancies to the ground truth. Furthermore, the technique was found to be very sensitive to residual patient positioning error. Therefore, this approach may need to be combined with a patient positioning step, either through using planar X-rays, or (potentially) through the use of single RP, as described in chapter 4. However, as RPPR$_{on-line}$ are anyway acquired as part of the process described here, these could also first be registered with the RPPR$_{plan}$ in order to correct for positioning misalignments (see chapter 3), before performing the reconstructions.

Although the limited project approach may not be accurate enough to directly use for replanning, a possible application could be as a tool to verify whether anatomical changes are sufficiently large, and potentially in the beam path of the treatment fields, to warrant re-imaging and re-planning of the patient. This could be performed by setting a threshold deviation of in-vivo proton range as an indicator for action level (Figure 6-11).

![Figure 6-11: Workflow of adaptive proton therapy using Range Probe (RP) technique to determine water-equivalent path length (WEPL) changes](image)

Figure 6-11: Workflow of adaptive proton therapy using Range Probe (RP) technique to determine water-equivalent path length (WEPL) changes
7. Patient positioning verification for proton therapy using Proton range probes: Experimental validation in phantom geometries

7.1 Introduction

In this thesis, all investigations of range probes and range probe radiography have been performed using MC simulations. In this final chapter therefore, we experimentally validate the use of such RP’s for both range validation and as a tool for online positioning using an in-house built MLIC as a detector. As such, the density resolution of the approach has been studied using tissue samples, and an anthropomorphic phantom used to experimentally study the predictive power of the RP based patient positioning approach described in chapter 4. In addition a new metric “The Bragg curve degradation index” has been introduced as a method to quantify the RIDDC resulting from a RP. The new metric enables to evaluate the similarity between the daily measured RIDDC and the simulated RIDDC of databank error scenario. The evaluation allows to take un consideration the intrinsic uncertainty of the technique. In this chapter we have also measured the in-vivo dose of the resulting from the approach.

7.2 Materials and methods

7.2.1 MLIC

To measure the residual proton range of the RPs, the MLIC developed at PSI has been used (Lin et al., 2009). This has an active area of $100 \times 100$ mm$^2$ and consists of 128 plane parallel ionization chambers (IC), which are read-out by two TERA06 Chips, hosted on a single TERA board (developed by University and INFN Torino and Terapia con Radiazioni Adroniche). Each IC has a water-equivalent path length (WEPL) of 2.27 mm. The charge profile collected by the IC stack is then transformed into a discrete WEPL-equivalent Residual Integral Depth Dose Curve (RIDDC) by substituting the IC locations with their effective WEPL. The stopping power ratio of the plates is considered to be energy independent, since only a small fraction of the incident energy, is deposited in the thin IC plates after passing through the irradiated object, (Newhauser and Zhang, 2015). To

---

4 All measurements in this chapter were actually performed previously in the frame of a master thesis (Hammi., 2012). However, the data has been newly analysed and assessed as part of this PhD work.
commission the MLIC for RP measurements, the RIDDC measured with the MLIC ($R_{\text{IDDC,meas}}$), has been compared with a reference RIDDC ($R_{\text{IDDC,ref}}$) which was measured using a water phantom (WP) and a wide-area parallel plane IC (8 cm diameter). The reference set-up allowed for depth resolutions of 1 mm in a water phantom. When the MLIC is charged by a proton beam, however, part of the charge is buffered in the plates and lowers the potential of the electrodes leading to an under-response of the ICs (Rinaldi I. et al., 2013). As such, there is a dependence of the peak-to-plateau ratio as a function of applied dose rate and exposure time (see e.g. Figure 7-8 (a)). If one waited long enough (a few seconds up to ~1 minute) this attenuated charge would be released through the amplifiers and the $R_{\text{IDDC,meas}}$ would be identical to the $R_{\text{IDDC,ref}}$. However, such a measurement time is too long for efficient RP measurements. Thus, an appropriate correction has been developed, such that the response of the MLIC fits the clinical data. The optimal corrected $R_{\text{IDDC,meas}}$ was found to be based on an offset value ($\Delta$) ($R_{\text{IDDC,\Delta}}$) and is a function of the continuous residual proton range in the detector (equation (7.1)):

$$R_{\text{IDDC,\Delta}}(z_i) = \frac{R_{\text{IDDC,meas}}(z_i) + \left(\frac{R_0 - z_i}{R_0}\right) \ast \Delta}{\max(R_{\text{IDDC,meas}}(z_i) + \left(\frac{R_0 - z_i}{R_0}\right) \ast \Delta)}$$

(7.1)

where $R_0$ is the nominal proton range of the beam energy. The index $i$ corresponds to the collocation of the $i$-th IC of the MLIC. The correction consists in calculating the offset $\Delta$ that minimizes the resulting square difference $\epsilon$ between measured and reference dataset (equation 7.2). The coefficient $R_0 - z_i$ was found to provide a better fitting as it compromises the effect of dose profile increasing due to slowing down of the protons as function of the depth.

$$\epsilon = \arg \min_{\Delta} \sum_{i=1}^{n} (R_{\text{IDDC,\Delta}}(z_i) - R_{\text{IDDC,ref}}(z_i))^2$$

(7.2)

This cost function has been minimized using downhill simplex (Nelder J.A. and Mead R., 1965). The optimal $\Delta$ was used according to equation 7.1 to correct the Bragg curve (BC). At the moment the offset correction is used only for RIDDC resulting from homogeneous material measurement or for those RIDDC with range degradation but with large plateau depth ratio in comparison to the peak broadening. 7.17.2

7.2.2 Range measurements through tissue substitute samples

For the RP patient misalignment measurements, the anthropomorphic head phantom described by Albertini et al. (2011) has been used. The phantom is a modified version of the diagnostic head phantom model 711HN manufactured by (CIRS, USA) which mimics an average male human head (18 x 22.3 x 27 cm$^3$) and is made of tissue-like materials (ATOM®max). As a first step, the WEPL of samples of the different materials used in the
phantom (as provided by the manufacturer) have been measured (Table 7-1). The samples were cylindrical in form (diameter = 35 ± 0.1 mm; length = 25 ± 0.1 mm). The measurements were performed at a gantry angle of 0° with pencil beam incident on the flat face of the cylinder. A 160 MeV beam was used with a Gaussian lateral profile of 3.2 mm sigma. MC simulations of the same set-ups were also performed used a CT for the input geometry. The CT was acquired according to the standard acquisition protocol for planning CTs at PSI and the HU converted using the clinically used stoichiometric calibration curve (Schneider et al., 1996). A good agreement between measured and CT-calculated RSP of the same probes has been evaluated in a detailed study and was 1.5% and 2% for soft and bony materials, respectively (Albertini, 2011).

7.2.3 Anthropomorphic phantom measurements

7.2.3.1 Misalignment measurement

The RP position verification approach is based on changes in the RIDDC profile, as a result of patient misalignments (Hammi et al., 2017) which is due to the variation in the density in the beam path impacting on the residual energy fluence of the primary protons and the subsequent multiple Coulomb scattering (MCS) (Lynch and Dahl, 1991), (Schneider et al., 1998). As such, a measurement of selected RPs is required on the treatment day that can then be compared to a pre-calculated database of RIDDC. This contains MC-simulated RIDDC ($RI\text{DDC}_{MC}$) at the same locations and for misaligned instances of the planning CT (error scenarios). A key element of the proposed approach is to localize those RP locations that would result in large and unique changes in RIDDC profile as a function of patient misalignments relative to the reference case “RP fingerprints”. In a previous work, we have introduced the range probe degradation index as indicator to localize those RPs case (Hammi et al., 2017). To experimentally validate this approach, the phantom has been mounted on an in-house developed motorized stage (see Figure 7-3 (a) and (b)) that can implement high precision rotations ($\delta_{sys}=\pm 0.09°$) in all three rotational directions (pitch, yaw and roll) corresponding to the x, y and z axis of the coordinate system of the CT data set. The set-up has been mounted on the patient couch and a CT acquired with 140 kV/400 mAs, and a 2 mm slice thickness. From that, a set of deliberately misaligned CTs (error-scenarios) have been generated, assuming either translational ($T$) or rotational ($\theta$) errors. Translational errors were simulated with magnitudes of ±1 mm and ±3 mm in the S-I ($T_z$) and A-P ($T_y$) directions, whilst rotational errors were modeled within intervals of $[-4°, 4°]$ in 2° steps in the pitch $\theta_x$ or roll $\theta_z$ directions. Over all error scenarios, RPs of energy 177 MeV and a beam width of 3.2 mm sigma have been simulated in the lateral direction and through two positions (see Figure 7-1 (a)), which were found to be sensitive to the error scenarios induced in the CT. Using the same jig and table mounting, the phantom was then mounted on the gantry in
treatment position. The translational errors were performed by moving the patient couch, while rotations were performed with the motion stage. In each instance (including reference position) the RP of 177 MeV were applied laterally.

![Image](a) ![Image](b)

Figure 7-1: (a) RP (red circle) selected for the misalignment study. RP1 and RP2 are located in the back of the ear regions and between frontal bone and brain. (b) Resulting WEPL (mm) difference between nominal and translation error (1 mm) in the A-P direction.

To deduce the potential misalignment, those error scenarios ($R_{IDDC_{MC}}$) have to be compared with the $R_{IDDC_{meas}}$ to find the best match. Previously we have suggested comparing the sum of squares of the depth dose profile (Hammi et al., 2017). The technique is robust and easy to implement on the other hand it doesn’t consider the degree of the broadening. Furthermore the approach requires applying identical beam energy for the simulation and the measurement. In this work a new metric, the Bragg curve degradation index ($BCD_i$) is introduced that parametrizes an arbitrary RIDDC resulting from proton pencil beams with a known initial energy.

7.2.3.1.1 Bragg curve degradation index

The range $R$ of monoenergetic proton beam is defined as the distal 80% ($R_{80}$) of the Bragg peak (BP) (Gottschalk B., 2012), which coincides with the proton mean projected range. In addition, at this value the distal fall off is independent of the initial spectral energy distribution of the beam. The RIDDC however is risen by superposition of the differently shifted BC, what can’t be assessed by the conventional $R_{80}$, since the primaries have impinged laterally different densities and the BC may have a ripple shape.

The $BCD_i$ will enable to quantify the complex weighted superposition and the broadening of the resulting range spectra, what will help to study the similarity between different RIDDC independently from the acquisition modality. We have defined three parameters: range dilution ($\Delta r$), weighted mean WEPL ($\bar{r}$) and degradation area $\Sigma (R_0 - z)$. Hammi et al (2017) have defined $\Delta r$ as the difference in range between the most proximal and the deepest pristine BC proton range spectra, while $\bar{r}$ was defined as the fluence weighted range spectra (see Figure 7-2). The two parameters were found to be energy invariant. The
3rd parameter is defined as the integrated dose profile over the depth (area under curve). The latter parameter has been included as it provides an additional metric (i.e. together with \( \bar{r} \) and \( \Delta r \)) that indicates the complete mix of residual primary energies in the RIDDC rather than just the minimum and maximum energies (e.g. range dilution \( \Delta r \)). The residual range spectrum of the primaries was obtained by de-convolving RIDDC using a pristine BC of the nominal RP energy as base. The residual ranges which have been found outside 3\( \sigma \) range interval around the mean weighted range and have fluence below 2\% have been cut-off from the spectrum as they are assumed to be secondary events with large scattering angles resulting from nuclear interactions.

Figure 7-2: Example of the resulting range dilution of RP measured (diamond) through heterogeneous interface of anthropomorphic phantom and using a 177 MeV proton pencil beam and a MLIC detector. The weighted range spectra (dashed lines) result after de-convolving RIDDC. The corresponding fit of the sum of range spectra (blue solid line). The range spectra principle is described in detail in Hammi et al., 20017

7.2.3.1.2 Matching space

Each RIDDC will be presented with its metrics in a so called 2D / 3D “matching space”. The abscissa and the ordinate correspond to \( \Delta r \) and \( \bar{r} \) respectively (see Figure 7-6). Thus, the characteristics of the resulting \( \text{RIDDC}_{\text{meas}} \) can be described as a point in a 2D or 3D matching space and compared to the pre-calculated database of error scenarios, \( \text{RIDDC}_{\text{MC}} \). The error scenario \( \text{RIDDC}_{\text{MC}} \) with the closest 2D/3D Euclidian distance to the \( \text{RIDDC}_{\text{meas}} \) in the matching space (equation (3)) is then selected to be the predicted error scenario of the phantom. In the practice however, \( \text{RIDDCs} \) are affected by intrinsic uncertainties in both measurement and simulation. The accuracy of the \( \text{RIDDC} \) evaluation in the MLIC is given by the half of the thickness separation of the IC (1.13 mm WEPL) (Bashkirov et al., 2016). While the inherent range uncertainty of the \( \text{RIDDC}_{\text{MC}} \) is determined mostly by the HU-RSP calibration, what corresponds to 1.1\% of range (see section 7.3.1). These uncertainties have been taken into account when those parametrized \( \text{RIDDC}_{\text{meas}} \) were compared to error
scenarios, which then render these points as circles (2D) or spheres (3D) in the matching space (see e.g. Figure 7-6 and Figure 7-7). The magnitude of this latter reflects the precision and the efficacy of the approach. Ideally the \( RIDDC \) of an optimal RP location would result in large space separations in the matching space between the circles/spheres of the error scenarios. The separation between the metrics would increase the probability to deduce the accurate error scenario. However RP locations, those result in error scenarios which overlap with each other. Would imply similarity between the \( RIDDC \) of alternative (and wrong) error scenarios and is an indicator of low sensitivity of this RP to those error scenario.

![Figure 7-3](image)

**Figure 7-3:** (a-b) Set-up used for RP misalignment experiment. (a) View of the mechanical design of the motorized fixture to steer the anthropomorphic head phantom. Figure courtesy of (Albertini, 2011). (b) The anthropomorphic phantom is mounted on the rotation jig and placed between MLIC (right side) and delivery unit (left side). (c-d) Set-up used for detailed in-phantom dose measurements at Gantry 1. The TLDs are placed on the Gafchromic films on both surfaces and in the middle of the anthropomorphic phantom.

### 7.2.3.2 In-vivo dose measurements

In order investigate the expect in-vivo dose when a clinical RP is delivered, a detailed in-phantom dose measurement has been carried out using Thermoluminescent Dosimeters (TLD). This would allow to determine the in-vivo local dose scaled to the maximum deposited dose at the RIDDC of a RP with known fluence, since this latter can be measured outside the patient.
The LiF:Mg,Ti (TLD-100) (Harshaw Chemical Company) is the standard detector used to carry out in-vivo dose measurement on patient at PSI. The TLD are cylinder of 6 mm length and 1 mm diameter and have a density similar to soft tissue. The detectors were divided into three groups: Entrance, middle and exit. Three TLDs were placed on the left and the right temples of the phantom, while five detectors were pasted between the lateral components (middle) of the phantom, which is sliced along the lateral plane (see Figure 7-3). The placement of the single TLDs were adjusted vertically. The packets have been aligned in a straight line corresponding to the beam path. The packets were arranged to fit within the axial beam profile. The placement of the packets was based on a template that was based on the patching of the Gafchromic films. This latter was used in order to demarcate visible locations on the phantom (e.g. three locations), where the TLDs was placed. The TLD position was verified using the laser positioning system (see Figure 7-3 (c) – (d)). The phantom was immobilized on the patient couch, the gantry rotated to -90.0° and a single lateral RP of 177 MeV was applied with a dose of 500 mGy at the BP. The selected delivered dose is many times larger than it would be used in the clinical practice. However it was scaled up to enhance the sensitivity of the TLD response in comparison to the fluctuation of the background signal. The TLDs were calibrated according to standard calibration performed at PSI. The deviation was 2% for the two groups at the entrance and in the middle of the phantom, while a 3% deviation was found for the TLDs group that has been placed at the exit of the RP. The TLDs readouts were carried out using a Teledyne Brown Engineering System 310 TLD reader and the corresponding standard anneal heating cycle used at PSI. To remove the background signal resulting from the fading at low temperature, the TLDs are pre-heated at 100°C just before the read-out. The TLDs have been read out within 8 s and at a temperature of 300°C, what corresponds to the 5th peak of the glow curve of a TLD-100.

7.2.4 MLIC dose sensitivity tests

In order to minimize dose to the patient, it is important to quantify the lowest proton fluence that can be applied in a single RP (under clinical conditions) in order to measure a useful and precise signal in the MLIC (Rinaldi et al., 2013). As such, we have also investigated the precision of MLIC response for RPs delivered with varying proton fluence and in clinical condition. A set of RPs of 177 MeV energy were delivered with a physical doses between 10 – 40 mGy (as estimated at the peak of the BC), in intervals of 5 mGy. For each measured current profile the corresponding offset $\Delta$ was computed according to section 7.2.1. The obtained $\Delta$ values were used to correct the corresponding raw data according to equation 7.1 (see Figure 7-8 (b) and (c)). The proton range $R_{80}$ of reconstructed $RIDDC_{\Delta}$ were then compared to reference BC resulting from WP measurements and a 177 MeV pencil beam.
7.3 Results

7.3.1 Range measurements through tissue substitute samples

The results of the WEPL values of the probes are shown in Table 7-1. Except of the measurement of the low density tissue (e.g. sinus cavities), the mean deviations were 0.41% ±0.62% and -0.29% ±0.09% (mean ± sd) for MLIC and MC respectively. The largest measured deviation was detected in the high density material and is1.02% and 0.35%, respectively. The comparison between MLIC and MC shows that RP can predict RSP with accuracy of 0.70%. The uncertainty remains below the theoretical limit of range straggling (Janni, 1982). A higher deviation of 5.67% was found in low density tissue (sinus cavity). This deviation is due to the large effective depth resolution of the MLIC (e.g. 2.27 mm) in comparison to the thickness of the probe (4.77 mm WEPL). Concerning the simulations, this is mainly due to the intrinsic uncertainty related to the HU-RSP conversions, which is large for low density tissues (Yang et al., 2012). The 95% confidence interval (95 CI) of the deviations are given by [-0.35, +0.11] and [-0.01, +0.17] for measurements and simulations respectively (see Figure 7-4 (b)). Both distributions overlap with a mean difference lower than 0.2 mm WEPL, with the MLIC measurements having a larger variation in deviations than the MC, which can be explained by the differences of the depth resolution of the two range telescopes.

<table>
<thead>
<tr>
<th>Sample; [g/cm³]</th>
<th>WEPLWP</th>
<th>WEPLMLIC</th>
<th>WEPLMC</th>
<th>Δ (MLIC-MC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sinus cavities (0.21)</td>
<td>4.77</td>
<td>5.20</td>
<td>4.90</td>
<td>0.3</td>
</tr>
<tr>
<td>Soft tissue (1.05)</td>
<td>25.90</td>
<td>26.0</td>
<td>25.80</td>
<td>0.2</td>
</tr>
<tr>
<td>Spinal cord (1.07)</td>
<td>26.15</td>
<td>26.40</td>
<td>26.10</td>
<td>0.3</td>
</tr>
<tr>
<td>Brain (1.07)</td>
<td>26.49</td>
<td>26.70</td>
<td>26.40</td>
<td>0.3</td>
</tr>
<tr>
<td>Trabecular bone (1.16)</td>
<td>29.40</td>
<td>29.70</td>
<td>29.30</td>
<td>0.4</td>
</tr>
<tr>
<td>(TS1): Bone &amp; Brain</td>
<td>55.90</td>
<td>55.70</td>
<td>55.70</td>
<td>0</td>
</tr>
<tr>
<td>(TS2): Bone &amp; Brain &amp; Spinal cord</td>
<td>82.05</td>
<td>81.80</td>
<td>81.90</td>
<td>-0.1</td>
</tr>
</tbody>
</table>

Table 7-1: Various tissue substitutes chosen for the RP measurement and the error resulting from the comparison between MC-calculated WEPLMC and measured WEPLMLIC with results of water phantom (WEPLWP).
IN-VIVO PROTON RANGE RECONSTRUCTION AFTER ANATOMY CHANGES

Figure 7-4: (a) Comparison between RIDDC\textsubscript{meas} (dashed) and RIDDC\textsubscript{MC} (solid) resulting from a 160 MeV RP passing through tissue substitute material. The legend depicts the tissues used for the measurements. TS1 and TS2 reference to tissue substitute combination (DTB 109 & BT 358-1) and (DTB 109 & BT 358-1 & VSC 31) respectively. The magnified box depicts the Bragg peak area in the red box. (b) Plot depicts the deviations resulting between MLIC and WP measurement (blue square) and MC and WP (red diamond). The lines and the area are the mean values and the 95% confidence intervals.

7.3.2 Anthropomorphic phantom measurements

7.3.2.1 Misalignment measurements

The \( RIDD\textsubscript{mlic} \) (solid lines) and \( RIDD\textsubscript{MC} \) (dashed lines) obtained from the two selected RP locations (see Figure 7-1 (a)) to detect error scenarios (\( T_y \) (a), \( T_z \) (b), \( \theta_z \) (c) and \( \theta_x \) (d)) are depicted in Figure 7-5. The RIDDs were normalized to their maximum values. The effect of density changes in the beam path, due to patient positioning errors, is clear. The degradation of \( RIDD\textsubscript{MC} \) agree well with the \( RIDD\textsubscript{mlic} \), especially at the distal fall-off region. On the other hand, a slight deviation is observed in some error scenarios. The reason for the variations in the range spectra is the combined effect of multiple Coulomb scattering and the uncertainties of the traversed density heterogeneity lateral to the beam, since the residual energy \( E_0 - E \) determines exactly the stopping power. This uncertainty is due mostly to the HU-RSP conversion and to the residual repositioning uncertainties from the mounting of the jig on the couch between the pCT and day of measurement. Also farther source of errors related to the stochastic noises in the CT data acquisition have been reported (Paganetti H., 2012). Another source of error is the fluctuation of the charge read-out of the detector, which is quantified to be up to 10%. Unfortunately, due to an electronic problem with the MLIC, measurements for the nominal RIDD at RP2 could not be performed and are missing in Figure 7-5 (d).
Figure 7-5: Comparison between RIDD<sub>meas</sub> (dashed) and RIDD<sub>MC</sub> (solid). The RPs were performed using a single proton pencil beam of 177 MeV energy and spot size of 3.2 mm sigma. Panels (a) and (b) display translation errors $T_y$ (A-P) and $T_z$ (S-I) respectively in millimeter. Each color corresponds to an error scenario. Panels (c) and (d) display the results of the rotation errors about $\theta_z$ (roll) and about $\theta_x$ (pitch) respectively in degrees (see legend). The black curve (0 mm or 0°) corresponds to RIDD measured at the anatomy base line, when no error occurs. The results of RIDDC in (a), (b) and (c) are measured at RP1 location, while results of plot (d) are obtained at location RP2.

Figure 7-6 depicts the results in the 2D matching space. The selected two locations for RP have shown a 100% correct predictions of the error scenarios $T_y$, $\theta_z$ and $\theta_x$ (Figure 7-6 (a), (c) and (d)). RP1 however has predicted only 2 of 5 for the $T_z$ error scenarios (Figure 7-6 (b)). This significantly reduced sensitivity to longitudinal translations is due to the fact that the arrangement of the heterogeneity interfaces in this location is parallel to this translation direction (see Figure 7-1). We can resume, that RP1 is highly sensitive for vertical translation $T_y$ and rotational error $\theta_z$, but not suitable to detect translation errors along the SI direction. The empty space between single scenarios (circle of the same color) indicates the prediction power of the selected fingerprint, when incorporating range uncertainties (e.g. HU-RSP, detector resolution etc.). While the intersection area between
the circles indicate similarity between the involved error scenarios, what would correspond to uncertainties that may confuse the matching process, and could lead to the prediction of a wrong error scenario.

![Figure 7-6: 2D Matching technique for comparison between parametrized RIDD\textsubscript{meas} (blue) and the pre-simulated database of error scenarios RIDD\textsubscript{MC} (red). The sign text inside the circle depicts the magnitude of positioning error. Each RIDD is parametrized by a single point of two coordinate, namely range dilution (x-axis) and weighted mean range (y-axis). Each point is extended by a value (radius), which corresponds to the intrinsic range uncertainty of the modality. The black arrows connect the measured RIDD to the best match from the database, which corresponds to the shortest distance. Panels (a) and (b) correspond to $T_y$ and $T_z$, respectively. Panels (c) and (d) correspond to $\theta_z$ and $\theta_x$ errors respectively. The intersection area between circles is assumed as the uncertainty that reduce the power of the prediction.

The integrated intersection area over the scenarios quantifies inversely the sensitivity of single RP to detect error scenarios in the database. The prediction power of the selected RP and the corresponding error scenarios, considering the intrinsic limitations of the detector is depicted in Table 7-2. This latter was found to be higher for the measurement than the MC for $T_y$, $\theta_x$ and $\theta_z$, what can be observed in Figure 7-6. Only at the matching space $T_z$
error, the $RIDDC_{meas}$ show a weak $\Delta r$ changes between the measured RPs. A way to increase the prediction power is to increase the depth resolution of the range telescope and also to use more combinations of RP.

The matching results after a 3rd parameter was added to the matching technique are shown in Figure 7-7. This 3rd dimension reflected the degradation area of the RIDDCC. It can be seen that expanding the criteria reduces the similarity of possible error scenarios in the database (intersection volume of the spheres) without changing any parameters of the measurements.

<table>
<thead>
<tr>
<th></th>
<th>$T_y$</th>
<th>$T_z$</th>
<th>$\theta_z$</th>
<th>$\theta_x$</th>
</tr>
</thead>
<tbody>
<tr>
<td>MC</td>
<td>0.960</td>
<td>0.854</td>
<td>0.982</td>
<td>1</td>
</tr>
<tr>
<td>MLIC</td>
<td>1</td>
<td>0.7372</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 7-2: Quantification of the power prediction of the selected RPs. The prediction power is the area of the circles subtracted from the integral of overlapping area between databases (Figure 7-6), when incorporating range uncertainty of the method.
Figure 7-7: Three dimensional Matching space of RP using three criteria: range dilution, weighted mean range and degradation area of the RIDDC. The $RIDDC_{meas}$ (opaque) and $RIDDC_{MC}$ (transparent) are compared in 3D domain. Each color corresponds to an error scenario (see legend). Panels (a) and (b) correspond to $T_y$ and $T_z$ error, respectively. Panels (c) and (d) correspond to $\theta_x$ and $\theta_x$ errors respectively. The intersection area between circles is assumed as uncertainty of the prediction. The blue dashed lines connect each daily $RIDDC_{meas}$ with the best fit in the error scenarios.

7.3.2.2 In-vivo dose measurements

The in-vivo TLD measurement has been carried out at three different locations in the phantom. In each group of TLD, the highest measured dose is selected as the true local dose for the location. TLD responses were 172 mGy ± 3.4 mGy at the first phantom surface of the phantom, 145 mGy ± 2.9 mGy at the lateral middle plane and 141 mGy ± 4.2 mGy at the exit temple of the phantom, what correspond to 34.4%, 29% and 28.2% of the set dose of the RP. The measured local doses agreed well to the expected dose at sub-peak region of an arbitrary proton beam resulting BC (i.e. peak-to-plateau ratio was 27% of depth dose curve for 177 MeV). The dose at the surface entrance was 5% higher TLD dose than expected. The deviation can be explained by the contribution of the liberated secondary electrons at the air-surface intersection where the proton beam has incident. The TLD response at the deeper location was lower than dose at surface entrance. This reduction of the proton fluence on the central-axis of the pencil beam is due to the lateral proton disequilibrium caused by the accumulated MCS and to the small size of the detector in comparison to the beam cross section.
With this experiment we have quantified the in-vivo dose \( t \) when a clinical RP is delivered with a known fluence and dose at the maximum of the BC. However, this experiment was performed using a rather high dose as in the clinical practice. Table 7-3 shows the expected dose scatted down when a clinical RP is delivered with a physical dose of 1 mGy at the peak.

<table>
<thead>
<tr>
<th>Location on the patient</th>
<th>Dose [mGy]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entrance</td>
<td>0.344 ± 2%</td>
</tr>
<tr>
<td>Middle</td>
<td>0.290 ± 2%</td>
</tr>
<tr>
<td>Exit</td>
<td>0.282 ± 3%</td>
</tr>
</tbody>
</table>

Table 7-3: The expected in-vivo dose on three location of the head patient, when a RP of 177 MeV is delivered with 1 mGy dose at the peak.

### 7.3.3 MLIC dose sensitivity tests

The results of the dose rate sensitivity of the detector are shown in Figure 7-8. Without any correction for the non-linear response of the MLIC (see Figure 7-8 (a)), there is a clear difference in the peak-to-plateau ratio when the delivered dose rate vary. A visual comparison between the plateau regions of the \( RIDD\_\text{meas} \) shows that the signal fluctuation between adjacent ICs seems to be similar and less dependent from the applied primaries fluence. On the other hand, the magnitude of this fluctuation decreases with decreasing the residual proton range, and becoming small in the BP region. This is due to the signal to noise ratio of the read-out, which is given by the inherent energy deposition of the protons. The highest fluctuation was observed at the first IC at the entrance of the MLIC. This background signal is due mainly to the absence of shielding in comparison to deeper located ICs. The low charge detected at the channel no. 48 of the RP with the applied dose of 15 mGy (the terracotta RIDD at depth ~110 mm WEPL) is an artefactual error. The fall-off regions of the \( RIDD\_\text{meas} \) agree well with reference measurement. The absolute error was found to be constant for all applied RPs and is -0.76 mm (-0.35%).

The corrected \( RIDD\_\Delta \) are shown in Figure 7-8 (b). Figure 7-8 (c) depicts the values of the \( \Delta \) offset as a function of the applied dose at the PR. The \( \Delta \) values were found to increase linearly with increasing the fluence, at least in this dose range. The correction step seems to be quasi dose-invariant as it does affects only slightly the \( R\_80 \) (\( \sigma=0.01 \) mm). The \( RIDD\_\Delta \) agree well with the WP with a \( ^{95}\text{CI} \) below 0.03 %, what corresponds to an error below 0.1 mm WEPL (Figure 7-8 (d)). The \( RIDD\_\Delta \) experience however, a shift of about 0.9 mm (\( R\_80 \)) in comparison to the corresponding raw data. This is due to the high gradient of the distal BC, which is given mainly by the inherent range straggling and is 5 mm WEPL at 80%-20% for the applied energy (e.g. 177 MeV).
Figure 7-8: Integral depth-dose of a measured 177 MeV proton pencil beam with several doses compared to water phantom measurement without (a) and with correcting for non-linear response of the detector (c). (b) The offset values are plotted versus the dose delivered. (d) Plot depicts the deviations resulting between MLIC and WP measurement, when applying several doses. The blue and red diamonds correspond to raw data and after correction. The lines and the area are the mean values and the 95% confidence intervals.
7.4 Discussion

In this work, we have experimentally investigated the concept of proton range probes (RP) for patient positioning, which requires only the delivery of individual pencil beams and an in-house developed MLIC. Firstly the accuracy of range verification has been investigated using electron density simples. In addition the potential to deduce translational and rotational patient positioning uncertainties has been studied using an anthropomorphic phantom from a single beam incident direction.

The results of the tissue-like study have shown that RP can predict RSP with a mean accuracy up to 0.7%. A higher deviation of 5.67% was found in low density tissue (sinus cavity). Moreover, results of the RP performed on the heterogeneous regions of the anthropomorphic phantom (Figure 7-1 (a)), have shown good agreement between simulations and the MLIC measurements. The proton range has been predicted with an accuracy of 1.0% + 0.54%. This owing mostly to the range degradation caused by the tissue heterogeneities lateral to the pencil beam. In addition it has to be taken into account that this value contains already the I-value uncertainty. Nevertheless this uncertainty remains below the intrinsic uncertainty of such detector, which mostly dominated by the range straggling and depth resolution of the MLIC.

In this work the $B\overline{C}D_i$ and the matching space have been introduced to quantify and compare depth dose curve suffering degradation due to traversed lateral density heterogeneities. A RIDDC can be presented as 3D variables what enable to compare individual RIDDCs. This is more robust and precise than the usually compared 80% fall-off position, since this latter is valid only for monoenergetic proton beam or spread-out Bragg peak without widening of the distal fall-off, while $B\overline{C}D_i$ consider the residual proton energy fluence. The matching process provides a distance metric. Given RIDDCs resulting from multiple potential error scenarios, the two with the shortest distance are the most likely to be similar to each other. In this work the distance was incorporated as Euclidean distance. A more elegant way would be to introduce coefficients to tune the weight of the 3 variables.

$$d_{ij} = \sqrt{c_1(r_i - r_j)^2 + c_2(\Delta r_i - \Delta r_j)^2 + c_3\left(\Sigma(R_0 - z_{i,n}) - \Sigma(R_0 - z_{j,n})\right)}$$

where $d_{ij}$ is the metric distance resulting from two RIDDC $i$ and $j$. $c_\times$ is the weighting coefficient and $\Sigma$ and $n$ are the integral and the indexing along the z-direction.

From the analysis of the misalignment measurements, we can conclude that the degradation index proposed here, can be used as an indicator to assess the sensitivity of RP location towards positioning errors and such to define the patient specific finger print RP. The anthropomorphic experiment and the matching technique have shown that 1 mm translations and small rotational errors can be discriminated using only a single, well
defined RP. However in this we have assumed only a limited number of potential error scenarios in addition either rotations or translations have been deduced, but not both. Further studies are required to investigate more complex error scenarios cases, since in the practice a large database of error scenarios would have to be built with smaller error steps in addition the method would have to be enhanced to consider also combinations of different DoF of positioning error. Nevertheless in the measurement performed here, we have considered a fingerprint RP based on only two pencil beams and from only 1 single beam direction. In principle, in order to increase the robustness of the power prediction of the RPs for more complicate error scenarios, the number of RPs has to be increased. Furthermore the mutual results of multiple RPs have to be considered simultaneous, which will enhance the predictive power of the approach. This would require more refine data processing algorithm, what will be the subject of further developments.

The accuracy of this method depends on the accuracy of the RIDDC measurement in the range telescope. In addition, various potential geometrical errors, such as daily anatomical changes and HU-RSP conversion uncertainty, may also impact the accuracy of detecting positioning errors with this approach, especially as this method makes use of only a small number of pencil beams. Such uncertainties could be responsible for multiple matches of the $\text{RIDDC}_{\text{meas}}$ with different errors scenarios, which would bias the matching technique. For this reason we do consider the uncertainties in the HU-RSP conversion in the parametrization (Unkelbach et al., 2009) (e.g. weighted WEPL and range dilution) in addition we currently consider the approach only in rigid anatomies, and avoid anatomical cavities or soft tissues than may vary over the course of therapy. A potential way to compensate for the uncertainty resulting from this latter, could be to combine the RP with an additional grid of RPs (e.g. (Rinaldi et al., 2014) and (Farace et al., 2016)) to perform small field of view proton radiography for detecting potential anatomical changes. Furthermore, the technique can be also used auxiliary to kV X-ray imaging to verify residual and intra-fractional positioning errors between delivered fields or it can be used at those proton center that are using in-room CT for patient positioning verification as the imaging is performed with different geometrical arrangement and is typically few meters away from the treatment iso-centre, what could results into patient motion in the way between the imaging and treatment.

The in-vivo local dose study confirms that when applying a RP with given fluence, only a fraction (~30%) of the applied maximal reached dose at the peak is absorbed within the patient, what can be explained by the inherent properties of the energy loss of protons. That makes the integral absorbed dose to be only a few per mille in comparison to large field of view pencil beam based transmission imaging (without considering the fluence), since the local deposed dose is only absorbed in a very restricted volume, corresponding to the lateral cross-section of the pencil beam. Although the dose rate applied for the positioning experiments is too high (100 cGy at the BC maximum), subsequent
measurements have shown that the RP can be delivered by using 0.5 mGy (in clinical condition), whilst still providing a $R_{DIDC_{meas}}$ with a reasonable signal-to-noise ratio at our MLIC.

In summary, the proposed RP positioning method is fast and suitable for clinical application, as it requires only a range detector which can be positioned at the opposite side of the patient couch. However, although we have validated in this work that the RP technique can detect translational or rotational patient misalignments experimentally, it needs to be more thoroughly tested with more complex 3D positioning errors, such that limitations of the technique in clinical practice can be determined.

7.5 Conclusion

The use of proton range probes for range verification and position verification in proton therapy has been experimentally investigated. Integral range validation with sub-millimeter resolution in simple phantoms has been demonstrated, whilst translational misalignments and rotational misalignments of an anthropomorphic phantom of 1 mm/2° have been resolved using two well selected RPs. These results now need to be confirmed in a more clinical setting in order to fully explore the potential of the proton range probe as a tool for range and positioning validation in proton therapy.
8. Conclusions and outlook

The intrinsic energy loss of protons allows for very conformal dose deliveries, leading to dose escalation, and the potential to improve local control while sparing surrounding tissues. On the other hand, due to the steep distal gradient of the dose-depth curve, uncertainty in the beam may provoke a shift in location of the distal dose fall-off, potentially causing under-dose in the target location or over-dosage of healthy tissues. In clinical practice, in-vivo proton range is calculated by calibrating X-ray CT to relative proton stopping power, which introduces an inherent source of range uncertainties already at the treatment planning stage. During treatment however, further sources of uncertainties, such as patient misalignments and anatomical variations along the beam path, can also occur. To compensate for these uncertainties, the target volume is typically expanded by applying safety margins, leading to increases in the volume of surrounding healthy tissue receiving high doses with the risk of reducing the therapeutic ratio. In this work, the concept of proton transmission imaging using proton pencil beam scanned “range probes” (RPPR) has been introduced and its potential for monitoring patient positioning, motion and anatomical range changes investigated.

8.1 Range probe radiography

To investigate the feasibility of RPPR, a toolkit has been developed which allows to perform MC based RPPR based on clinical data using the realistic beam parametrizations of both gantry 1 and gantry 2 at PSI. All range maps have been reconstructed from residual proton range and not from residual energy. The advantage of this approach is the fact that the mean range is determined by the primaries while residual energy also includes contributions from secondary particles. As such, a plane parallel range detector is sufficient to perform RP measurements. Both energy-range dependence of the pristine Bragg curve, and the effect of the range straggling on the peak to plateau ratio, have been determined. In addition, an optimization procedure has been developed to characterise residual range spectra of RP even when the Bragg curve has been degraded due to the RP passing through complex density heterogeneities in the patient. This approach allows us to determine the residual mean proton range and to extract additional information from degraded Residual Integrated Depth Dose (RIDD) curves measured in the detector. In chapter 3, both the accuracy and predictive power of this approach has been investigated, together with the sensitivity of the approach to the beam width of the applied RP and their energy.
8.2 Patient positioning using proton range probes

In chapter 4, the potential of a small number of RP to deduce patient positioning uncertainties has been presented. The method makes use of the hypothesis that 3D patient positioning can be directly deduced from the measurement of RIDDs of a small number of RPs, selected such that they have maximal prediction power for patient misalignments. The reported technique uses the concept of a small number of RIDD ‘fingerprints’ resulting from the degradation of the Bragg peak passing through different density heterogeneities, together with a pre-calculated database of possible results calculated on systematically shifted and/or rotated instances of the planning CT. A selection approach was developed to find the optimal locations of RP. The selection quantifies the degree of range mixing of a proton pencil beam as a function of patient positioning error scenarios. To validate the approach, a semi-experimental study was performed using a phantom which was deliberately moved to a randomly selected positioning error. As such we have shown that rotational errors could be resolved up to 1° using only 5 RP, all coming from a single beam direction. In addition, the results of a retrospective study on repeat CT’s and positioning data of real patients has shown that the technique, even when using only 3 RP positions, can also detect translational errors with an accuracy of 1.5 mm.

This RP positioning approach has subsequently been validated experimentally using an anthropomorphic phantom and precise positioning system (chapter 7). The measurements were performed using 177 MeV pencil beam RP with transversal beam widths of 3.0 mm (sigma) at the iso-center, and the residual proton range detected using an in-house developed multi-layer ionization chamber (MLIC). A method to detect the best fit has been proposed. For each single fingerprint, the resulting RIDD is expanded as an ellipsoid in a 3D error scenario domain with the axes corresponding to the magnitude of the uncertainty of the system. The quantification of the results has shown that even 1mm translational, and 2° rotational, misalignments can be resolved. The uncertainty resulting from converting HU-RSP has been evaluated with the mean error being found to be 1% and a maximal deviation was found to be below 2.1%. This result confirms well with the results of Schaffner and Pedroni (1998).

The experimental validation performed in this work has been conducted assuming only a small number of potential positioning error scenarios and the selected RP were evaluated independently from each other. More measurement are required in which additional errors scenarios are taken into account and the collective RPs have to be evaluated as a mutual indicator. This would also increase the robustness of the process of finding the best fit.

We have also introduced the principle of proton range dilution radiograph, which can be calculated based on the same measured data as energy loss radiography. Such radiographs provide information about the relative stopping power (RSP) differences between the
materials crossed by the proton beam and can provide higher, and different, contrast than simple energy loss images, since the latter depends on the thickness and the RSP of the materials, while the former depends additionally on scattering and complexity of the density heterogeneities passed through by the RP (Plautz et al., 2014).

Finally, the RIDD error data base used by the positioning approach was calculated using MC techniques. However, given the number of error scenarios that have to be modelled (many thousands), this is a very time consuming technique. As such, in the appendix to chapter 4, a method for analytically calculating RIDD for RP analysis has been proposed, which uses a superimposition of analytical model of Bragg curves (BC) (Bortfeld 1997). The model has been calibrated to experimental data of gantry2 over a range of energies. However, the model doesn’t account for the inherent scattering of protons, and considers only those protons which traverse the absorber in straight lines. We believe that more accurate results could be obtained if the effects of multiple Coulomb scattering (MCS) could be included in the model.

8.3 Proton radiography and RP’s for imaging and tracking lung motion

Inter-fractional organ motion, or longer timescale organ drifts, affect the well-defined distal proton range and deteriorate the delivered dose. An accurate treatment delivery therefore requires a high precision of imaging and motion tracking (Bortfeld et al., 2002), (Chui et al., 2003), (Onimaru et al., 2008). In chapter 5, we have demonstrated potential applications of RPPS for imaging in the lung region, and RP’s as a potential tool for the tracking of tumour motion surrogate regions. As such, an approach of digital subtraction proton radiography has been presented with the aim to improve the image quality of RPPR images in the lung region. The results have shown significant increase of contrast in comparison to analogue RPPR and also to X-ray digital reconstructed radiograph (DRR). In addition, automated tumour localization on all methods has demonstrated a high accuracy in comparison to ground truth images (GT). Nevertheless, the time to acquire such images, requiring as they do a 2D scan of individual RP over the area of interest, is currently too long for this technique to be used for motion tracking. In the second stage of the chapter therefore, an online motion tracking approach, based on small sub-regions of RPPR images, has been investigated and a tracking algorithm developed for detecting surrogate motions which correlate with tumour respiration motion. The model has been successfully validated using simulated DRR from the 4D-CT data sets.

Our MC simulations however were performed based on 4D-CT data sets representing a single, averaged breathing cycle, and didn’t account for irregularities of patient breathing and corresponding geometrical change. In addition the 3D data sets of each breathing phase were assumed to be completely stationary. Further investigations are therefore
required to account for the viability of the approaches in real clinical conditions, such as under conditions of irregular breathing. Such studies however could be performed by applying the RP surrogate tracking method to multiple 4D-CT data sets generated from 4D MRI (Boye et al., 2013). Indeed, so-called 4DCT(MRI) data sets could also be used as training sets for RPPR surrogate tracking, providing a wider variety of motions which could thus lead to more robust motion models.

8.4 Detecting anatomical range changes using proton radiography

Variation in a patient’s anatomy through the course of treatment (e.g. due to weight changes, cavity fillings, tumour shrinkage etc.) can result in substantial changes in in-vivo range, with potentially severe dosimetric consequences on tumour dose-coverage and sparing of organ at risk. In clinical practice, such changes are mitigated by re-planning the treatment according to the current geometrical condition (e.g. via a repeat CT). However, this is a time consuming procedure which, with all steps, can take one to two days to complete. As such, a tool to quantify geometrical changes on a daily basis, together with the resulting deviations of in-vivo range in the beam direction, could be beneficial. In chapter 6 therefore, we have presented a preliminary study into the potential of reconstructing radial water equivalent range (WER) changes using just two RPPR projections in combination with pre-knowledge of the patient from a reference CT. A quantitative evaluation of the reconstructed beam eye view (BEV) in-vivo ranges, have shown a good agreement with ground truth changes (assessed from differences between the planning and repeat X-ray CT’s) demonstrating that such reconstructions could provide useful information about range changes from any beam direction, potentially providing a tool to help the decision making of when a plan adaption is required. As such, a range verification workflow has been presented, based on RPPR measurements, to determine whether the treatment can be delivered or a new CT and re-planning are required.

8.5 Further research and outlook for clinical implementation

Proton radiography, in particular scanned RP radiography, is a promising tool for clinical proton therapy. It requires only a gantry compatible of pencil beam scanning and a large area, plane parallel detector (e.g. an MLIC) as a detector on the exit side of the patient. The approach doesn’t require changes in the treatment procedure, and the absorbed dose in the patient is small (a few mGy). Before clinical trials can be conducted however, further experiments are required and more simulations required under realistic clinical conditions. In particular, many of the applications studied here would likely be sensitive to major anatomical changes between the planning and treatment days, and the robustness of all techniques need to be assessed against such changes. Methods for dealing with these would
be to use deformable registration algorithms to match the geometry of the day with that of the reference (planning) images, with orthogonal X-ray or RPPR images providing the geometrical information to drive such deformations. Nevertheless, the feasibility and accuracy of such manipulations have to be investigated in detail.

The majority of this work was conducted using MC simulations, and assuming the availability of a large area, integrating range telescope. The measurements performed in this work were conducted using a MLIC detector developed at PSI (Lin et al., 2009) for daily QA measurements of proton range. The uncertainty of the determination of proton range using such a detector is determined by the accumulated range straggling along the proton beam path and the accuracy with which this can be measured in the ionization chambers (IC). For proton imaging, it has been suggested that a nominal depth resolution superior to 1.5% of the total range is required (Bashkirov et al., 2016), corresponding to a plate thickness of the MLIC of 5.3 mm WEPL for energy measurements at 240 MeV. This resolution however, although sufficient to measure the residual range of primary proton transmission, may not be sufficient to fully capture the shape of the residual RIDD, a characteristic which has been exploited in many of the applications reported in this work. We recommend therefore that a depth resolution of about 1 mm WEPL would be required. This would increase the accuracy of determining the mean residual proton range and the range dilution. Furthermore, it will reduce the potential of false positive errors in the matching approach.

However, current MLIC’s are already large and cumbersome, as they have been designed to measure depth-dose curves for energies of up to 200 MeV or more, making them many cm’s thick. In addition, the active area was conceived to measure only a few adjacent pencil beams close to the iso-centre position. As such, it is unsuitable as a detector for large FOV RPPR acquisitions. We therefore recommend developing a prototype MLIC detector suitable for clinical trials which can provide a large active area, such that imaging can be performed throughout the body, without moving the patient couch to align the scanning beam with the detector, an approach taken by (Farace et al., 2016) and that is as thin as possible. As such, we have performed a first analysis on the possibility of optimizing the required thickness of such a detector. The results are shown in figure 8-1.

If we assume that the energy of the RP’s could be adapted based on a-priori knowledge of the thickness of the patient through which it will be applied (a reasonable assumption given that fixation devices are used for all proton therapy patients, and positioning offsets will be typically no more than a few millimeters), Figure 8-1 shows that 90% of the resultant RP RIDD’s in the degraded Bragg peak region could be fully collected using a detector with a total water equivalent thickness of only about 6 cms.

We are currently working on the development of such a detector to test this hypothesis, and should this be successful, this could indicate that a ‘slim’ MLIC, capable of being mounted
permanently on a proton gantry, is a possibility. In addition, there would be an advantage to making such a detector as efficient as possible, in order to reduce the fluence (and therefore dose) of the RP’s necessary for accurate measurements of Bragg peak shape in the detector.

Figure 8-1: Histogram of the detector thickness needed to measure all possible residual integral depth dose curve for an average head and neck patient
References


Enghardt W., Parodi K., Crespo P., Fiedler F., Pawelke J. and Pönisch F. (2004 (2)). Dose quantification from in-beam positron emission tomography. Radiotherapy and Oncology, 73 (Supplement 2), 96-98.


potential value of target immobilization and reduced lung density in dose escalation. *Int J Radiat Oncol Biol Phys* 45, 603–611.


Janni J.F. (1982). Proton range energy tables, 1KeV - 10 GeV. *Atomic Data and Nuclear Data Tables* 27, 147.


