1

Introduction

In February 1994 a project named ‘The Dosimetry and Beam Diagnostics for Radiotherapy with Proton Beams’ was started at the Kernfysisch Versneller Instituut in Groningen. This project was part of the ‘Beleidsruimte 1993’ of the Stichting voor Fundamenteel Onderzoek der Materie (FOM), which is financially supported by the Nederlandse Organisatie voor Wetenschappelijk Onderzoek (NWO). The aim of this pilot project was to be a first step towards the realization of a proton therapy facility around the AGOR facility in Groningen. A beamline was constructed which is suitable for performing radiobiology experiments and which can be adapted for the treatment of patients. The purpose of the work described in this thesis was to develop dosimetry and quality control instrumentation especially suited for scanning beams. This introduction is intended to relate this work to conformal radiotherapy, proton therapy and quality control. This work has been performed in the environment of nuclear and atomic physics, but mainly relates to the field of medical physics. Therefore in addition to issues specific for protontherapy, also some general concepts of medical radiation physics will be presented in this chapter.

1.1 Proton therapy rationale

1.1.1 Role of radiation oncology

Next to cardiovascular diseases the most frequent cause of death in the Netherlands is cancer, 35 thousand people per year [30]. This number is expected to increase because of the rising life expectancy in the western world. When the present rates are extrapolated, about one out of three persons now living will eventually develop this disease, and one out of five deaths will be due to cancer [120]. According to the WHO a patient is cured from cancer when no sign of recurrence of the primary tumour or metastasis is detected for 5 years. The three major treatment modalities and their results can be seen in table 1.1.

With the current progression of diagnostic methods (CT, MRI, PET) it is expected that more patients will be eligible for loco-regional treatment (only surgery and/or ra-
Table 1.1: Cancer cures by treatment modality (from [126, 134])

<table>
<thead>
<tr>
<th>modality</th>
<th>% of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>cured: surgery alone</td>
<td>22 %</td>
</tr>
<tr>
<td>cured: radiotherapy as the prominent agent</td>
<td>18 %</td>
</tr>
<tr>
<td>cured: chemotherapy as the prominent agent</td>
<td>5 %</td>
</tr>
<tr>
<td>not cured: uncontrolled primary tumor</td>
<td>18 %</td>
</tr>
<tr>
<td>not cured: uncontrolled metastatic disease</td>
<td>37 %</td>
</tr>
</tbody>
</table>

diotherapy) because more cancers may be detected before metastases have developed. This has contributed during the last few years to a growing interest in achieving a better physical conformation of the dose to the tumor, because this will enable higher doses to the tumor and thus a larger probability of sterilizing the tumor. Improving the local control of the primary tumor will thus lead to higher cure rates [123]. Since improving the dose conformation also preserves the healthy organs better, it will improve the quality of life which has become an important issue of interest during the last years. This also holds for the patients which cannot be cured.

1.1.2 The biological effect of ionizing radiation

The most important parameter in radiotherapy is the absorbed dose, which is the deposited energy per unit mass. Its unit is Gy, which is defined as 1 Gy = 1 J/kg = 6.24·10^{12} MeV/kg. We first will describe the interaction of ionizing radiation with individual cells, and then proceed with the description of the response to ionizing radiation of tumors and healthy tissue. In the last part the dose accuracy is related to the clinically observed dose-response curves.

Mechanisms of cell killing

In radiobiology, classically two types of cell death can be distinguished, namely reproductive (mitotic) death and interphase death. The first type is related to dividing cells (e.g. in tumors and many types of healthy tissue), the second mainly to nondividing or slowly dividing cells (e.g. in nerve tissue). When very high doses (> 20 Gy single dose) are used also dividing cells can undergo interphase death. In radiotherapy the total dose will mostly be given in small (2-4 Gy) fractions. Therefore most tumor cells and cells from radiosensitive healthy tissues will experience reproductive cell death. The molecular target for reproductive cell death is DNA.

In first approximation we can assume that damage to the DNA-helix in two opposite strands at the same position will sterilize the cell. Ionizing radiation that passes through a cell will damage molecules in the cell either by direct ionization and/or excitation or most important indirectly by water radicals (OH-) produced by radiation which can travel ≈ 1 nm before reacting with the molecules.

An estimation of length dimensions in mammalian cells is given in table 1.2. These
1.1 Proton therapy rationale

<table>
<thead>
<tr>
<th>structure</th>
<th>length</th>
</tr>
</thead>
<tbody>
<tr>
<td>cell diameter</td>
<td>20 μm</td>
</tr>
<tr>
<td>cell nucleus diameter</td>
<td>6 μm</td>
</tr>
<tr>
<td>total length of human DNA</td>
<td>1.8 m</td>
</tr>
<tr>
<td>DNA helix diameter</td>
<td>2 nm</td>
</tr>
<tr>
<td>free radical diffusion length</td>
<td>1 nm</td>
</tr>
</tbody>
</table>

Table 1.2: Estimation of length scales of mammalian cells (from [4, 58])

Numbers imply that the biological target size is small (5-10 nm). Experimental evidence for this has been obtained from studies where the cell survival for a constant dose has been measured as a function of ionization density [14]. It has been found that most cells are killed when the ionization density is around 100 keV/μm. This coincides with an average distance of 2 nm between two ionization events, which is just the distance between the two DNA strands (assuming that the energy per ionization event is around ≈ 200 eV [14]). When the ionization density increases further, energy is lost to ionizations which do not contribute to cell killing anymore [58] and the cell killing probability per energy deposited decreases again. In figure 1.1 a schematic illustration of the interaction of an ionizing particle with DNA can be seen.

In this thesis we consider radiotherapy with high energy protons, which have a low ionization density. In section 2.1.2 it is shown that 200 MeV protons have a mean energy loss of 4.5 MeV/cm in water. This implies that in order to deliver 1 Gy to tissue (≈ water) ≈ 1.4·10^9 protons per cm^2 are needed. From table 1.2 we conclude that ≈ 0.5% of the cell volume is sensitive to radiation (the sensitive volume is assumed to be a cylinder determined by the length of the DNA-helix and the sum of the DNA-helix diameter and the diffusion length of the OH--radicals). This sensitive volume is expected to be distributed homogeneously in a spherical volume. A ratio of volumes of 0.5%, implies a ratio of areas of 3% (0.5%^2). Therefore it is expected that ≈ 130 protons are passing through the sensitive area of each cell for each Gy.

From cell survival experiments it is known that for an applied dose of 1 Gy (which is the order of magnitude of one fraction in fractionated radiotherapy) roughly half of the cells will die [58]. This means that the efficiency for cell killing is low. There are several reasons for this:

1. The statistical nature of the energy loss process which becomes important on a microscopic scale. In section 2.1.3 it will be shown that the probability for transfer of energy $T$ roughly varies with $1/T^2$ from the ionization energy up to a certain (kinematical) maximum $T_{\text{max}}$. This means that small energy losses are much more probable than high losses. Only when more than ≈ 200 eV is transferred the ionization is violent enough to create damage [14], either by creating a OH--radical or by directly hitting the DNA. By integrating equation (2.12) in section 2.1.3 it can be calculated that the energy loss by collisions in which more
than 200 eV is transferred only contributes to \( \approx 42\% \) of the total energy lost by the proton.

2. The requirement for creating permanent damage is that two opposite strands are damaged. When we assume that the energy transferred to atomic electrons again is deposited in packets of 200 eV, this means that for a single 200 MeV proton the average distance between two violent ionizations is \( \approx 1 \mu m \). It is clear that the probability of a single proton causing a double strand break (distance between strands: 2 nm) will be very low.

3. The OH\(^-\) radicals can be scavenged by chemical substances before hitting the DNA. Therefore they cannot create damage anymore to the DNA.

4. Even in case both strands of the DNA have been damaged, the cell might repair part of the damage. These repair processes can take several hours.

The time scales involved in the both the physical/chemical and biological processes of cell killing can be seen in table 1.3. From this it can be concluded that the time in which the dose is delivered does not play a large role, as long as it is small compared
Table 1.3: Time scales involved in the biological effect of ionizing radiation (from [58])

<table>
<thead>
<tr>
<th>Process</th>
<th>Timescale (s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>passing time incident ionizing particle</td>
<td>$10^{-15}$</td>
</tr>
<tr>
<td>lifetime of a secondary electron</td>
<td>$10^{-15}$</td>
</tr>
<tr>
<td>lifetime of an ion radical</td>
<td>$10^{-10}$</td>
</tr>
<tr>
<td>lifetime of a free radical</td>
<td>$10^{-5}$</td>
</tr>
<tr>
<td>chemical changes in bonds</td>
<td>$10^{-5}$</td>
</tr>
<tr>
<td>biological processes</td>
<td>$10^2-10^6$</td>
</tr>
</tbody>
</table>

to biological time scales. On the other hand, splitting of the dose into several fractions, which is called fractionation, does have a large effect, because cells are able to repair before new damage is created.

The dose-response relation

Since the probability of cell killing is small per cell, but at the same time the number of protons and cells is very large, it is possible to use Poisson statistics to model cell killing. An exponential relationship between the cell survival on the applied dose is therefore expected. The model which describes the experimental cell survival best is the linear-quadratic model [26, 58]:

$$S(D) = e^{-\alpha D - \beta D^2}$$  \hspace{1cm} (1.1)

where $S(D)$ is the survival fraction as a function of dose $D$ and $\alpha, \beta$ are tissue and beam particle dependent constants. Some examples of cell survival curves are shown in figure 1.2. At low doses the cell death resulting from permanent damage of the DNA-helix is the result of a single ionization event. The probability of interaction is in that way proportional to the exponent of the dose. At higher doses, damage of the opposite strands of the DNA-helix can be produced by ionizations originating from separate events. The probability of such a double hit is then proportional with the exponent of the quadratic of the dose. When this quadratic component dominates, the survival curve bends over and curves [58]. The ratio $\alpha/\beta$ for normal tissue varies between 1 (for kidneys) to 13 (for testis). In case of densely ionizing radiation, for example produced by neutrons or heavy ions, the shoulder in the cell survival term caused by the quadratic term is absent and only an exponential dependence of dose remains. This can be explained by the large probability of double strand breaks in case of densely ionizing radiation, which limits the repair possibility.

In first approximation it is possible to model the response of a given cell system or organ to fractionated irradiation by taking the product of the individual surviving fractions. Especially for large $\alpha/\beta$ (>10) tissue there is a big difference whether the dose is applied at once or split into a number of fractions with a time in between in the order of magnitude of the biological timescales, 3-5 hours. In that case for each fraction the survival curve will start again with the region where the linear part dominates. For
Figure 1.2: Shape of survival curve for mammalian cells exposed to radiation. The long dashed line shows the survival to densely ionizing radiation, the solid line shows the survival curve according to equation (1.1) for $\alpha/\beta = 8$ and the small dashed line represents the effect of fractionation.

a certain total dose, the total survival is larger than in the case where the dose is applied at once, in which case the quadratic term dominates. It is possible to define an effective dose $D_{eq}$ which corresponds to the same amount of cell killing as a single dose would give.

The next step is to calculate the probability that a certain tumor is completely killed for a given dose. A macroscopic detectable tumor has in the order of $10^8$ clonogenic cells (cells being able to replicate themselves). Because the number of surviving cells has to be quite small when one wants to completely sterilize a tumor, it is possible to use the Poisson distribution to calculate the probability of having zero surviving cells [26]:

$$P(D) = e^{-N(0)\prod_{i=1}^{n} S(D_i)}$$  \hspace{1cm} (1.2)

where $N(0)$ is the original number of clonogenic cells, $\prod_{i=1}^{n} S(D_i)$ the product of surviving fractions $S(D_i)$ of a single effective dose $D_i$ (assuming that the dose per fraction is constant) and $n$ the number of fractions. In figure 1.3 the probability as a function of dose is plotted for a model tumor ($\alpha/\beta = 8.9$, dose per fraction 2.5 Gy, effective dose 2.73 Gy). The dose-response for tumor tissue is defined as the probability that a tumor is sterilized: the Tumor Control Probability (TCP).

It is also possible to model the complication probability for normal, healthy tissue as a function of dose, for example using the Cox logistic model [33]. In figure 1.3 the results can be seen for both a small (say, 1 cm$^3$) and a large volume (say, 10 cm$^3$) of
normal tissue. The parameters at 50% response are: 55 and 60 Gy for the large and small volume respectively, steepness in both cases 10%/Gy. The dose-response for normal tissue is defined as the probability that complications occur: the Normal Tissue Complication Probability (NTCP). The combined plot of TCP and NTCP illustrates a number of issues in radiotherapy:

1. Tumor tissue is in general more sensitive to fractionated radiation than normal tissue, this is the reason why radiotherapy works at all. As has been pointed out before this is because tumor tissue grows faster than normal tissue, and therefore will spend a larger fraction of its time in the division phase [58]. Also the repairing processes are different for tumor tissue and normal tissue. The product of the TCP and (1-NTCP) curves for the different organs is called the probability of uncomplicated control, the position where the maximum occurs determines the most optimal dose for a certain tumor.

2. The dose-response curves both for normal tissue and tumors are very steep. The clinical observed maximum percentage change in response per percentage change in dose, the normalized dose gradient $\gamma$, varies from 0.4 %/Gy (Hodgkin’s disease) to 8 %/Gy (larynx) [26]. Although in general the clinical value of $\gamma$ is lower than the tumor model prediction (according to equation (1.2)), it is possible to make an estimate on the effects of dose errors using this model. Depending on the value of the normalized dose gradient Brahme concluded that standard deviations in the mean dose of 1.5% can already decrease the TCP with
5%. To investigate the effects of dose errors it is also possible to start from normal tissue complications. Mijnheer et al. [90] looked at clinical available data (which is limited to only small complication probabilities) and concluded that an increase in absorbed dose of, on average, 7% can result in unacceptable risks. Because severe complications are regarded worse than recurrent tumors, an ethical criterium for the maximum allowed uncertainty of the delivered dose can be derived: the absorbed dose in the specification point should be known within ±3.5 % (1 s.d.) [90].

3. For most tissues the complication probability for normal tissue decreases with smaller irradiated volumes: for the same deposited energy the effect decreases. This makes it possible to increase the dose in a tumor, and thus to increase the TCP, when one is able to limit the total irradiated volume of healthy tissue. The pathobiological basis of this volume effect is not yet fully understood, but generally it is assumed that the functional organization of an organ plays an important role [59]. Principally organs can have a parallel organization, in which its total function is distributed among a number of identical subunits, or a serial organization, in which its functioning is determined by the weakest spot in the chain, or a combination of the two. An example of a parallel operating organ is the liver, of which the performance after an irradiation is directly proportional to the number of functional subunits that have survived. The spinal cord however is serially organized: when a slice has received a certain threshold dose, the total functioning of the spinal cord will be stopped. It is expected that a parallel functioning organ will have a strong volume effect, because a high dose in small volume will not prevent the total organ from functioning. A serial organ is expected to have a threshold dose, above which the functioning will stop, independent from the volume. Surprisingly for the spinal cord also a dependence on the irradiated volume exists. This can be explained by cell migration between healthy and damaged tissue [129]. However much research has still to be done on these phenomena.
1.1.3 History of progress in radiation oncology

When evaluated historically, the progress of radiation oncology goes side-by-side with technologic advances in the dose delivery system. Already 2 years after the discovery of X-rays [111] the possible application of radiotherapy was proposed [48]. After the introduction of 250 kV orthovolt equipment, however, technologic progress remained limited for some time. The only significant improvement in radiation oncology was the introduction of fractionation. After World War II the so-called ‘megavolt’ era was entered, when nuclear reactors made the production of large $^{60}\text{Co}$ sources feasible. The 1.33 and 1.17 MeV $\gamma$-rays which originate from this source have a much larger penetration depth than the previously used X-rays, so that for the first time it was possible to treat deeper lying tumors. In table 1.4 the improvements are summarized.

The success obtained with this megavolt therapy triggered the development of dose delivery systems with even better characteristics. Thanks to the technology developed for radar in World War II it became possible to develop linear accelerators for radiotherapy. At the end of the 1960s these linacs started to replace the cobalt units in the hospitals, which culminated in the current number of 4000 installed linacs worldwide [114]. Present day radiotherapy linacs accelerate electrons up to 25 MeV. These electrons can be used directly, or which is more often the case, hit a target and produce bremsstrahlung. By using advanced beam collimating techniques combined with rotations of the treatment head around the target volume it is possible to obtain complicated dose distributions.

A logical extension of this progress in physical characteristics is the use of protons for radiotherapy. The much bigger rest mass of the proton compared to the electron makes them an ideal particle for radiotherapy: protons deviate much less from a straight line along their trajectory than electrons and, unlike X-rays, at the end of their path they slow down and stop. The resulting dose distribution was for the first time observed by

<table>
<thead>
<tr>
<th>Type of cancer</th>
<th>kV X-rays</th>
<th>$^{60}\text{Co} \gamma$'s</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hodgkin’s disease</td>
<td>30-35%</td>
<td>70-75%</td>
</tr>
<tr>
<td>Cancer of the cervix</td>
<td>35-45%</td>
<td>55-65%</td>
</tr>
<tr>
<td>Cancer of the prostate</td>
<td>5-15%</td>
<td>55-60%</td>
</tr>
<tr>
<td>Cancer of the nasopharynx</td>
<td>20-25%</td>
<td>45-50%</td>
</tr>
<tr>
<td>Cancer of the bladder</td>
<td>0-5%</td>
<td>25-35%</td>
</tr>
<tr>
<td>Cancer of the ovary</td>
<td>15-20%</td>
<td>50-60%</td>
</tr>
<tr>
<td>Retinoblastoma</td>
<td>30-40%</td>
<td>80-85%</td>
</tr>
<tr>
<td>Seminoma of the testis</td>
<td>65-70%</td>
<td>90-95%</td>
</tr>
<tr>
<td>Embryonal cancer of the testis</td>
<td>20-25%</td>
<td>55-70%</td>
</tr>
<tr>
<td>Cancer of the tonsil</td>
<td>25-30%</td>
<td>40-50%</td>
</tr>
</tbody>
</table>
Figure 1.4: Comparison physical dose distribution of 6 MV X-rays (dashed line), 175 MeV protons (dashed-dotted line) and energy modulated protons (solid line) in water. The 6 MV X-ray curve has been calculated using PHOTOCAT (AIC software 1993), the proton curves using PTTRAN [16].

William Bragg Sr. in 1904 using helium nuclei in air [25]. The dose distribution of 175 MeV protons and X-rays from a 6 MV linac (this is the bremsstrahlung produced by 6 MeV electrons) in water can be seen in figure 1.4.

Because most tumors have a larger size than the width of the Bragg peak, usually proton beams of different energies are combined to cover the tumor volume. In this way the ratio: peak dose/entrance dose decreases. But, as figure 1.4 shows, for deep lying tumors this dose distribution is still very favorable compared to X-rays. In clinical situations however a deep lying tumor is never treated with the beam entering from only one direction. In figure 1.5 a comparison can be seen for a treatment with two fields in opposite directions of a deep lying tumor with $\varnothing = 7$ cm. It is clear that in this case a large reduction of the dose in the irradiated healthy tissue is obtained.

**Proton therapy**

In 1946 Robert Wilson proposed for the first time to use protons for radiotherapy [138]. During the 1950s patients have been treated successfully at the Lawrence Berkeley Laboratory, California [125]. But after 50 years proton therapy still has not become widely available. An obvious reason is that the cost of a proton accelerator is larger than the cost of an electron accelerator. Due to the large magnetic rigidity of high energy protons, also bigger magnets are needed to deflect them, which is necessary to enable irradiation of the patient from different directions. Raju [107] gave some additional reasons:
1.1 Proton therapy rationale

Figure 1.5: Comparison of a two opposed fields irradiation of a deep lying tumor for X-rays and protons using the curves from figure 1.4.

- proton therapy was proposed at the same time when megavoltage X-ray therapy was considered, and physicians were already acquainted with X-rays.

- nuclear physics was so well funded in the 1950’s and 1960’s that accelerators were fully used for nuclear physics.

- poor experience with neutron therapy made physicians cautious in performing research with new particle types.

The present situation of proton therapy is in a sense a chicken-and-egg situation: more proton facilities are needed to do clinical trials. Clinical results are necessary in order to determine whether the building of new proton facilities is worthwhile. At this moment only for the ocular melanoma and skull base tumors there is clinical evidence that protons are superior. These are examples of tumors close to critical structures. For other indications the clinical superiority still has to be demonstrated. Amongst the most promising are [29]:

1. Tumors with a poor response to conventional radiotherapy, that are expected to respond better to higher doses. Examples: adenocarcinoma of the prostate or salivary glands.

2. Tumors for which it is important to reduce the total volume of irradiated tissue. Examples: paediatric tumors, tumors in the head and neck region.

3. Extended tumors with poor prognosis where protons can provide better palliation with less complications. Example: pancreatic tumors.
At the moment of writing this thesis there is a steep rise in clinical experience thanks to the realization of the world's first hospital based facility in Loma Linda, California, which is in operation since 1994. Another hospital based facility which is completed at this moment is the Northeast Proton Therapy Centre connected to the Massachusetts General Hospital in Boston. Together with the start-up of new accelerator laboratory based facilities such as the 200 MeV proton gantry at the Paul Scherrer Institute in Switzerland and a number of centers in Japan it is expected that the coming decade is going to be crucial for the future of proton therapy.

**Heavy ion therapy**

Parallel to the developments in proton therapy, the use of heavy ions such as carbon and neon for radiotherapy is considered [46]. Since the charge of these ions is much larger than protons, their ionization density is also much larger. Because of their large mass, they also deviate less from a straight line. They combine therefore a high Relative Biological Effectiveness (similar to neutrons) with a superior physical dose distribution (similar to protons). A comparison between the different particle types is shown in table 1.5.

As has been pointed out in section 1.1.2, a high RBE is not necessarily an advantage for radiotherapy, since the usefulness of radiotherapy depends largely on the difference in response between tumor tissue and healthy tissue. Much is still unknown about the side effects of high RBE radiation, for example with respect to the late effects. Another problem is that the fractionation schemes (see section 1.1.2) used in current radiotherapy cannot be applied for heavy ion therapy, since they depend very much on the biological effectiveness. For certain types of tumors which are difficult to sterilize using low RBE irradiation the use of heavy ions may be favorable.

**Dynamic beam delivery systems**

Also in X-ray radiotherapy the interest in achieving dose distributions which are better conformed to the tumor has increased during last years, which goes under the label of ‘conformal radiotherapy’. Because the depth dose distribution of X-rays cannot be varied, one has to combine several beam directions (in radiotherapy known as fields) in order to obtain conformation. To achieve a homogeneous distribution in the tumor, the fields need not to be homogenous itself. The calculation of the most optimal field shape has been considered to be an inverse problem and very similar to the reconstruction

### Table 1.5: Comparison of the different radiation modalities

<table>
<thead>
<tr>
<th>Particle Type</th>
<th>Physical Dose Distribution</th>
<th>Biological Effectiveness</th>
</tr>
</thead>
<tbody>
<tr>
<td>X-rays / Electrons</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Protons</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Neutrons</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>Heavy Ions</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>
of CT projections [137]. From this calculations complex - intensity modulated - field shapes result, which can be produced in a number of ways: the conventional method is to use absorbers with a variable thickness, but a more flexible and promising method is the use of dynamic collimators, which can be moved during the treatment. The complexity and safety requirements are of course much larger.

The use of dynamic beam delivery systems is very advantageous for proton therapy too. Because of the physics of proton interaction with matter, the use of dynamic systems cannot be avoided for producing proton intensity modulated dose distributions. The first example of such a dynamic beam delivery is build at PSI\(^1\) in Switzerland: the spot scanning technique. A schematic view of this technique can be seen in figure 1.6. In the spot-scan technique a pencil beam is positioned in one lateral dimension by a scanning magnet, in the other lateral dimension by moving the patient table and in the depth dimension by inserting a variable number of range shifter plates. When the desired position is reached, for a predetermined time the beam-block is taken away, and the prescribed dose in the spot is delivered. After this the beam will be positioned to the next spot and the process is repeated (the system is described in detail in chapter 5.

An additional advantage of this technique is that it allows a compact gantry (beam swinging machine). In radiotherapy it is desired to be able to irradiate the patient from all directions. Because protons with an energy of interest for therapy (\(\leq 250\) MeV) have a large magnetic rigidity, big magnets are necessary to bend them. Conventional techniques that are used to spread the proton beam from pencil beam size (\(\varnothing \approx 5\) mm as it leaves the accelerator) to the size needed to cover the tumor volume (up to \(\varnothing =30\) cm)

\(^{1}\)Paul Scherrer Institute in Villigen near Zürich
are based on scatterfoils. Since the scatter angle that can be obtained in this ways is limited, they require a large distance between the last bending magnet and the patient. For the Loma Linda gantry this has resulted in a gantry with a diameter of 12 m. Thanks to amongst others the spot scanning technique the PSI gantry has a diameter of only 4 m.

Another scanning method is investigated at the heavy ion facility in GSI: the raster scan technique [57]. In this technique the beam is continuously on, and the dose distribution is determined by the speed of scanning. Advantage of this method is the higher efficiency, which permits higher dose rates and thus shorter treatment times. A disadvantage is that it needs a very steady beam, and very fast (and thus power consuming) magnets.

Advantage of all the methods in this section is that they allow to apply very complicated - intensity modulated - dose distributions, which reduces the number of fields necessary. However because the systems are dynamic, they require a lot of additional verifications to ensure a safe treatment, which is the subject of the next section of this chapter.
1.2 Quality Control

As pointed out in section 1.1.2 the success of radiotherapy largely depends on how accurate one is able to deliver a prescribed dose to a patient. For a state-of-the-art radiation technique such as protontherapy this is even more important. In conventional radiotherapy the procedures that confirm that the equipment works, and continues to work, according to its specifications are described as Quality Assurance [99]. An important feature of such a program is the independent testing and verification against existing standards, which is described by the term Quality Control. The main subject of this thesis will be the QC of dynamically scanned proton beams. Since the most important difference with conventional systems relates to the beam delivery, we will focus on the dosimetric aspects of QC. This QC for scanning beams can be deduced from the QC of standard radiotherapy and from proton therapy with passively scattered beams. This chapter explains the relation between the different procedures, while the details of the procedures are described in the following chapters. In figure 1.7 a schematic overview of the dosimetric procedures is given. The symbols contained in this figure will be explained in the text and are also listed in appendix B.

1.2.1 Absolute dosimetry

The goal of absolute dosimetry is to ensure consistency between different protontherapy and other radiotherapy centers. To obtain reproducible results the dose has to be measured in a reference situation (large homogeneous field, specified source-surface distance, specified depth in a water phantom). In principle the most direct way to determine an absolute dose \( D_{w,Q} \) (the subscript \( Q \) denotes the user’s beam quality, \( Q_0 \) the reference beam quality and \( w \) water) is the use of a water calorimeter, in which the temperature rise as a function of dose is measured. However, in practice calorimetry is very difficult. Not only because the increase in temperature is very small (\( \approx 0.5 \) mK for 2 Gy) but also because the irradiated water and suspended contaminations undergo chemical reactions which can be endothermic or exothermic. This leads to what is called a thermal heat defect, i.e. a difference between the energy absorbed by the material from the radiation and the thermal energy released. Although the understanding of this effect has improved during the last years to the extent that calorimetry may be expected to be the reference dosimeter in the future [118], at this moment most proton therapy centers still make use of air filled ionization chambers for their reference dosimetry.

This reference ionization chamber has to be calibrated, which means that a calibration factor \( N_{w,Q} \) has to be determined which relates the measured signal \( M_Q \) of the ionization chamber to the absorbed dose \( D_{w,Q} \) in the user’s beam. Different methods can be applied:

1. using the already existing comprehensive system of dose calibration standards for X-rays and electrons. This system consists of a worldwide network of na-
**Figure 1.7:** The dosimetry chain from calibration to patient dose. $N_w$ is the absorbed dose to water chamber factor, $Q_0$ reference beam, $Q$ users beam, $M$ electrometer reading, $D_w$ absorbed dose, $C$ correction factors. More explanation is given in text.

1. correctional standard laboratories [62, 63, 96, 97] and it is based on the calibration with $^{60}\text{Co}$ $\gamma$-rays. Disadvantage: a conversion factor $k_Q$ has to be determined for the difference in response between a $^{60}\text{Co}$ beam and the user’s beam. This introduces uncertainties.

2. comparing the chamber reading in a proton therapy centre which already has a calibrated beam, for example using calorimetry. Also in this case a factor $k_Q$ is necessary to correct for differences in beam energy and energy spread [131].

3. using chemical methods such as Fricke dosimetry [44], which is based on the
change in light absorbance in a ferrous sulphate solution under influence of irradiation. Disadvantage of this method is the large dependence on ionization density.

4. using specially developed methods for proton beams such as faraday cup dosimetry. Disadvantage: a faraday cup only measures the proton flux so knowledge on the beam energy and energy spread is needed [54].

A big advantage of the first method is that it has a direct traceability to the national and international standards, which has lead the ECHED to recommend this method [135, 136]. Also in a forthcoming report from the ICRU on proton dosimetry it is the first choice.

The protocols in this method, however, generally tend to be quite complex which is due to the fact that for historic reasons they start from an ion chamber calibrated for one quantity, air kerma, which must be transferred to obtain another quantity, absorbed dose in water [62]. To overcome these complexities, primary standards laboratories are busy developing standards for absorbed dose in water for photon beams from $^{60}$Co [61]. Once one has obtained a $N_{w,Q}$ -factor, the $N_{w,Q'}$ -factor can be determined by multiplying it with a $k_Q$-factor [9, 86]:

$$k_Q = \frac{(s_{w,\text{air}})_Q (w_{\text{air}})_Q p_Q}{(s_{w,\text{air}})_0 (w_{\text{air}})_0 p_0} \quad (1.3)$$

where $(s_{w,\text{air}})$ is the stopping power ratio water to air (see section 2.1.2, tabulated in [67]) and $(w_{\text{air}})$ the mean energy to produce an ion pair in air both in the reference beam $Q_0$ and the user’s beam $Q$. $p_Q$ is the product of various smaller correction factors and will be discussed in more detail in section 2.2. In a recent dosimetry intercomparison between 13 proton therapy centers [132] it was found that calibration factors differed as much as 8% from the mean value. By using $^{60}$Co calibrated ionization chamber dosimetry, identical dose protocols and conversion factors and by specifying dose to the same material the difference between various calibration factors might be expected to shrink to ±1.5% (1 s.d.)

1.2.2 Relative dosimetry

The next step in the dosimetry chain is the determination of the shape of the dose distribution. With absolute dosimeters it is difficult to measure the dose as a function of position, since their position sensitivity is not large. More position sensitive dosimeters are often relative, i.e. their response is expected to be proportional to the dose in a small region. It is assumed that its response will be constant over a short period of time, so that the dose in a certain point can be related to the dose in a reference point. Ultimately one is interested in the dose distribution as it will appear in the patient, but to obtain

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reproducible and consistent results, first the dose distribution in a water phantom is measured. This can be done by moving a detector in 3 dimensions, and measuring the ratio detector signal/reference signal: \( M_Q(x, y, z)/M_Q(\text{ref}) \) as a function of position. In proton therapy the following detectors are generally being used:

- **Thimble ionization chamber.** In which a central electrode is surrounded by a graphite coated wall [86]. The sensitive volume varies between 0.01 - 0.6 cm\(^3\). Advantage of this type of chamber is that it is cylindrical symmetric with the axis perpendicular to the radiation field, so the sensitivity does not vary along a lateral profile. A disadvantage is that the small chambers (0.01 cm\(^3\)) need a large dose to achieve a sufficient signal to noise ratio while for larger volume chambers (0.6 cm\(^3\)) there is an uncertainty on the effective point of measurement.

- **Plane parallel ionization chamber.** This type of chamber consists of 2 parallel electrode foils, separated by a small (≈ 2 mm) air gap [86]. Advantage is that the effective point of measurement is very well known, disadvantage is that it can only measure the dose gradient in one direction.

- **Diode detector.** This consists of a p-type silicon junction [110]. Advantage is a small measurement volume (0.2-0.3 mm\(^3\)) with a large signal, disadvantage that the yield very much depends on the irradiation history and that the physical properties (density, excitation potential) of silicon differ much more from those of water than air.

- **Diamond detector.** This is a relatively new type of detector of which the operation is based on the same principle as a diode [130]. Advantages are a better stability because of less sensitivity to radiation damage and more water-like properties. A disadvantage is that only very few natural diamonds are suited for this purpose, so the production is limited and it’s use is not widespread.

With relative dosimeters we are able to check the stability of the beam delivery system on a day to day basis. A QC-program will include these checks on a regular basis, typical once per day. The initiation and control of a new irradiation technique (treatment plan) happens less frequently. Then one is also interested in the deviations from a certain dose calculation to the real dose distribution in the patient. Especially of interest are the regions where there are transitions of tissue type, e.g. near bones or lungs. For this we can use an anthropomorphic (=human alike) phantom, which has room to place dosimeters at specified positions. From such measurements we can assess the accuracy of the dose calculations and determine which correction factors \( C_{\text{phantom}} \) are needed to derive the dose distribution in the patient from the water measurement \( D_{w,Q} \). Because of the existence of standardized anthropomorphic phantoms (e.g. the Alderson Rando phantom), it is also possible to perform inter-institutional comparisons.
1.2.3 In vivo dosimetry

The actual dose distribution in the patient is also influenced by the accuracy of positioning \( C_{\text{patient}} \). Therefore it is desirable to be able to deduce the dose distribution with respect to anatomical structures in the patient during irradiation, which is called in vivo dosimetry. It is evident that this will not improve the positioning itself, but it allows an afterward QC verification if the dose delivery is within specifications. One of the advantages of the use of protons, namely that they completely stop in the patient, turns out to be a disadvantage here: unlike X-rays it is not possible to use portal imaging [22, 37, 72, 73] to measure the patients exit dose and thus make an estimate of the dose in the patient. However, other methods are being developed to obtain some information on the absorbed dose in the patient.

The fact that protons induce nuclear reactions during their interaction with matter instigated studies to see whether reaction products (such as \(^{13}\)C, \(^{14}\)O, \(^{15}\)O and \(^{13}\)N) can be detected for example with PET [56, 100]. But even if successful, because of the rapid decrease of the cross section with proton energy, it is not feasible to measure the positrons emitted from the reaction products with sufficient signal-to-noise ratio in the neighborhood of the Bragg peak. In case of heavy ion therapy, one could use radioactive \(^{11}\)C beams, which can be monitored on-line during the treatment [102].

Other methods which are employed for in vivo dosimetry are the placement of point detectors such as diodes [38] or TLD’s [79] on the patient skin, but also with this methods the uncertainties on the dose inside the patient remain large (\( \approx 10\% \)). A satisfactorily solution for the problem of in vivo dosimetry for proton therapy, has still not been found.

1.2.4 QC for dynamic dose delivery systems

The conventional way of performing QC has a limited use in dynamic dose delivery systems such as for instance shown in figure 1.6. If the shape of the dose distribution has to be measured, the complete scanning procedure has to be repeated for each point. This will take a very long time and the probability of missing an irregularity in the scanning beam will be large. Therefore it is helpful when the dose can be measured in many points simultaneously, preferably in 2 or 3 dimensions. Examples of presently considered methods are:

- **1 dimensional**: a linear array of diodes [51]. This is a brute force approach which contains many point detectors that are combined. The drawbacks are: the electronics is complicated, every channel has to be calibrated and it is difficult to obtain sufficient position resolution within a reasonable number of measurements.

- **2 dimensional**: film dosimetry [128]. The oldest method of detecting ionizing radiation [111] is still widely used. Advantages are a very good position resolution and a small volume which makes it possible to use multiple films in one
measurement, for example to measure a depth dose curve with a sandwiched stack of phantom material and film. Disadvantages are the difficult calibration which depends on how the film is developed and the time it takes to get results.

A modern successor of film is the electronic portal imaging device (EPID), which directly provide digitized information on the dose distribution. A number of a physical principles are employed, for example systems based on segmented liquid ionization chambers, systems based on scintillation detectors and systems based on amorphous silicium (a review can be found in [24]).

The method studied in this thesis is the scintillator screen + Charge Coupled Device camera. The use of scintillating screens for measuring dose distributions has already a long history in the form of fluoroscopic imagers. With the progress in light detection technology, such as the CCD camera (developed for astronomy), the sensitivity of this method has increased substantially.

- **3 dimensional**: MRI gel dosimetry [83, 98]. The Fricke-ferrous sulphate solution as mentioned in 1.2.1 exhibits in addition to the change in light absorbance also another phenomenon: the NMR water proton relaxation rate is proportional to the absorbed dose. When the ferrous sulphate solution is mixed with a tissue equivalent phantom gel, it is possible to reconstruct from the map of NMR relaxation rates a full three-dimensional dose distribution. A problem with this Fricke gels are the poor sensitivity and the poor resolution because of diffusion of the iron ions through the gel.

An improvement is the use of tissue equivalent gels infused with acrylic monomers (for example BANG: bis-acrylamide-nitrogen-gelatin) which polymerize to form microparticles trapped in the gel matrix under influence of irradiation. These gels have a much better stability and sensitivity. To overcome the need of having a NMR scanner available for the gel readout, also methods are being investigated to make use of the change in light scattering of the gel in order to reconstruct the dose [50]. Unsolved problems are the complex dependency of the signal on ionization density and the high sensitivity of the signal to phantom temperature.

The 1 dimensional brute force method can also be extended to 3 dimensions, for example as is the case in the magic cube [82] which is inspired by the high energy physics sampling calorimeters. It consists of tissue equivalent slices interleaved with segmented, large area ionization chambers. Special electronics has been designed to cope with the ≈ 9000 channels which are needed for a spatial resolution of 0.5 cm.
Table 1.6: Comparison of 3 volumetric dosimetry measurement methods (from [83, 102], chapter 4)

<table>
<thead>
<tr>
<th></th>
<th>MRI Gel dosimetry</th>
<th>PET system</th>
<th>CCD+screen</th>
</tr>
</thead>
<tbody>
<tr>
<td>position resolution</td>
<td>1-2 mm</td>
<td>4.7 mm</td>
<td>1.8 mm</td>
</tr>
<tr>
<td>dose reproducibility</td>
<td>5-8 %</td>
<td>?</td>
<td>3 %</td>
</tr>
<tr>
<td>dose range</td>
<td>1-12 Gy</td>
<td>&gt; 1-2 Gy</td>
<td>0-15 Gy</td>
</tr>
<tr>
<td>dose rate</td>
<td>not important</td>
<td>not important</td>
<td>not important</td>
</tr>
<tr>
<td>signal → dose</td>
<td>linear; in Bragg peak</td>
<td>complex</td>
<td>linear; in Bragg peak</td>
</tr>
<tr>
<td>time to obtain data</td>
<td>1 day</td>
<td>seconds-minute</td>
<td>1-3 seconds</td>
</tr>
<tr>
<td>portable</td>
<td>yes (phantom)</td>
<td>no</td>
<td>yes</td>
</tr>
<tr>
<td>3 dimensional</td>
<td>yes</td>
<td>yes</td>
<td>? yes ?</td>
</tr>
</tbody>
</table>

1.2.5 Motivation

In table 1.6 an overview is given of 3 systems which are able to perform 3 dimensional volumetric dose measurements: the MRI gel method, the PET system (which is only feasible for heavy ion beams, see section 1.2.3) and the CCD+screen system which is the system we have studied.

Although the polymer gel method is very promising, and probably will be an important tool in the future, we decided to concentrate on using an established technology which has not yet been used for protons: a scintillator screen which is read out by a CCD camera. Such a system had the advantage that relatively little time was needed for hardware development. We have performed detailed studies on its dosimetric properties at a number of proton therapy facilities. For a complete understanding of the experimental results, especially in comparison with calibrated ionization chambers, the use of Monte Carlo methods turned out to be essential. Because available Monte Carlo codes all have their limitations, either because they were not designed for this application or because they are too restricted, it was also necessary to make a detailed study on the use of these codes for proton dosimetry.
1.3 Outline of the thesis

In chapter 2 the theory of proton interaction with matter is presented. This interaction has been split into a part dealing with proton-electron and proton-nucleus collisions. Both the continuous energy loss and the statistical fluctuations in the energy loss process are treated. The second part of chapter 2 deals with cavity theory, which relates the dosimeter signal to the actual dose distribution.

In chapter 3 the use of Monte Carlo methods for proton dosimetry is studied. A code especially designed for this purpose, PTRAN, is compared with two general purpose codes, FLUKA and GEANT. The codes are compared with measurements which have been performed at a number of experimental facilities. Since the codes differ mainly in their treatment of nuclear interactions, the second part of chapter 3 contains a detailed study on the influence of nuclear interactions on the resulting dose distribution. The last part of chapter 3 presents results of calculations on the effect the dosimeter itself has on the outcome of dose measurements.

In chapter 4 the dosimetric properties of the CCD+screen system are investigated. The linearity of the signal with the dose, the signal-to-noise ratio, the spatial resolution and the influence of ionization density have been studied. To facilitate comparison with standard dosimetry devices, the measurements described in chapter 4 are obtained at passively scattered beam delivery systems: 80 MeV protons at the facility in Louvain-la-Neuve and 175 MeV protons at the The Svedberg Laboratory facility in Uppsala. The reproducibility and stability of the system have been examined by comparing the results that have been taken over a period of 1.5 year. The decrease of light signal in regions with a high ionization density (i.e. in the Bragg peak) is compared with the calculations presented in chapter 2 and 3.

In chapter 5 the application of the CCD+screen system in a scanning beam is presented. The measurements described in this chapter have been performed at the spot-scanning gantry of PSI, Switzerland, which is described in brief. The dosimetric properties are compared with the results of chapter 4. The capability of the CCD+screen system for detecting irregularities in the scanning pattern has been experimentally determined. In the last part of chapter 5 the verification of treatment plans using the CCD+screen system is discussed.