Construction and analysis of a proton radiography setup using Timepix based time projection chambers for tracking

by

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ABSTRACT

One possible method of treating and trying to destroy tumors is by using an external beam of protons. Protons have an advantage when compared to conventional radiation therapy, because they deliver a large part of their dose at a certain depth, which depends on their initial energy and the type of material traversed.

To fully make use of this property, and deliver a maximum dose in the tumor while trying to spare healthy tissue a good understanding of the topology of the tumor and the surrounding tissue is required. Converting X-ray CT-scans data to the proton stopping power results in an uncertainty in the protons’ range. To reduce this uncertainty it is better to directly use proton imaging, using protons of higher energy that pass through the body, obtaining information by measuring their trajectories and energy loss in the body.

This thesis describes the development, and testing of a setup to do this, and the analysis of the data obtained in this way. We use Timepix based gas detectors as trackers to reduce possible disturbance of the protons’ trajectories due to tracking, and a $\text{BaF}_2$ crystal scintillator for measuring the remaining energy. With the setup it is possible to discern different materials in the radiographs of selected samples; the largest obstacles for clinical use are a limited acquisition rate and spatial resolution.
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Chapter 1

Introduction

Since the early 20th century, radiation therapy has been used for the treatment of tumors in the human body. Ionizing radiation, emitted by radioactive materials or generated by accelerators, is used because it has the potential to kill cells. Since both healthy and cancerous cells are affected by ionizing radiation, it is desirable to deliver the radiation dose as much as possible to tumors, while minimizing radiation to surrounding healthy tissue.

Radiation therapy using accelerators is called external beam therapy. Conventionally, this is done by using high energy X-ray photons, generated in a vacuum tube from accelerated electrons hitting an anode. Depending on the kind of tumor and its location in the body, using protons or heavier ions instead of X-rays can be advantageous. This is because photons, when traveling through matter, either pass unperturbed or have a high momentum transfer interaction, making their averaged dose distribution look like an exponential falloff from entry to exit point. Protons on the other hand undergo a lot of small impact interactions, slowing them down and deposit most of their energy at the end of their range. The end point can be varied because it depends on the protons’ initial energy. This makes protons especially useful in maximizing dose at the specific depth of a tumor and thereby minimizing the radiation dose delivered in healthy tissue, especially behind the tumor. The physics of protons interacting with matter is described in chapter 2 of this thesis.

The range of a proton depends on its energy and the composition of the matter it traverses. To get the dose exactly where it needs to be it is therefore necessary to have accurate information about the proton stopping power of the tumor and the surrounding tissue. A lot of information can be obtained from X-ray CT-scans; these scans however can’t accurately be translated to proton stopping power information. The X-ray CT data yields an uncertainty of about 5% in the proton range. By using complimentary information from proton CT-scans it may be possible to lower this range uncertainty to about 1%. Because of the multiple scattering of protons, it is best to measure tracks and energy loss of single protons. In chapter 3 we discuss our setup used to do this, by using time projection chambers for tracking and a scintillator as a residual energy detector. We continue previous work done by [1] and [2].

Experimental data was obtained from both cosmic particles and a proton beam from the AGOR cyclotron at KVI in Groningen, the results of which are presented
in chapter 4. Finally, we compare our approach to similar experiments in chapter 5.

The idea to use protons for radiation therapy is not new, and was first proposed in 1961. Since then development has continued and there are now tens of proton therapy facilities around the world. In the Netherlands, there are no such facilities; but in 2013 four licenses were granted for the start of proton therapy centers. Currently two centers in Groningen and Delft have started construction and expect to start treating actual patients in 2017.
Chapter 2

Physics in Medicine

2.1 Radiation

Radiation can be used in medicine in two ways: for diagnostic purposes and in radiation therapy. As photons or particles travel through the human body, different tissues in the human body interact in a different way with it. This is utilized in diagnostics: by measuring residual intensity (in case of X-rays) or residual energy (in case of ions), it is possible to generate images of the contents of body parts.

For radiation therapy the disruptive power of the ionizing radiation is used. Higher intensity photon or particle beams are aimed at a tumor to try and kill the cells. Ionizing radiation can directly damage DNA, or indirectly by generating free radicals. Single DNA strand breaks are usually easily repaired by the cell, so the aim is to cause multiple strand breaks, which usually results in cell death [4].

2.1.1 X-rays

Lower energetic X-rays (20-150 keV) are often used for diagnostics. They are sent through a body part, and because different tissues have different attenuation coefficients, information about the internal structure of the body part can be obtained from the residual intensity. The absorbed dose is kept as low as possible, while trying to optimize the image quality.

Higher energetic (1-20 MeV) X-rays from an external beam are used for treatment of tumors. The higher energetic photons can ionize atoms by means of either the photoelectric or the compton effect, thereby damaging DNA either directly or indirectly through the creation of free radicals. Both healthy and cancerous cells are effected by radiation, so the challenge is to deliver a maximum dose in the tumor, while minimizing damage to healthy cells.

X-rays, when traveling through tissue, have a mean free path of several centimeters [5]. This means they will either pass freely through a body part, or have a point of interaction at a certain depth. This behaviour shapes the depth-dose distribution, with the dose decreasing exponentially as a function of depth. As an example, the depth-dose distribution for 15 MV X-rays in water is given in figure 2.1. X-rays have a low entrance dose in the first centimeter (a 'skin-sparing' effect), but the dose quickly peaks and decreases exponentially. This means that healthy
tissue, both in front of and behind the tumor, receives a significant unwanted dose of radiation. By using a beam from different angles it is still possible to maximize the dose in the volume occupied by the tumor.

2.1.2 Particles

For charged particles passing through matter the situation is quite different from the X-ray scenario. Instead of having a single point of interaction, the ions continuously interact with the electric field from electrons and nuclei, each interaction causing only a small loss of energy and perturbation of the ion trajectories as they continue to slow down. This process is called multiple Coulomb scattering. As the proton decelerates, the energy loss per unit length increases (see figure 2.2a); which causes the energy loss to peak sharply at the end of the protons range. For a single proton this peak, called the Bragg peak, is very sharp, but its position varies per proton due to the statistical nature of multiple Coulomb scattering. Thus, when averaging over several protons, the peak becomes wider, an effect that is called range straggling (figure 2.2b).

When comparing the depth dose distribution of protons (image 2.2b) to that of X-rays (image 2.1, the potential benefits of using protons becomes clear: there is a lower entrance dose, and almost no exit dose behind the Bragg peak.
(a) Energy loss ($\frac{dE}{dx}$) of protons in water.

(b) Average dose of 1500 protons of 100 MeV in water shows the Bragg peak including the effect of range straggling.

If a tumor has a larger size than the width of the Bragg peak, it is necessary to use protons with a range of energies, adding up the Bragg peaks so that the whole tumor volume receives the maximum dose. This results in a slightly higher entrance dose, though the exit dose is still very low. In figure 2.3a, the resulting so-called spread-out Bragg peak is shown by adding the depth-dose distributions of protons with energies ranging from 125 to 150 MeV, obtained from simulations in SRIM [6]. The lateral profile for 150 MeV protons is also given in figure 2.3b, which shows that multiple Coulomb scattering, besides energy loss, also causes a slight perturbation of the trajectory.

(a) Ionization distribution of 125-150 MeV protons in water. The sum results in the spread-out Bragg-peak (red line).

(b) Lateral ionization profile; 150 MeV protons in water.

Figure 2.3: Depth and lateral ionization distributions, from SRIM.
2.2 Imaging

From the previous section we know that protons, compared to X-rays have an advantage when it comes to sparing healthy tissue around a tumor. However, to fully utilize its potential, it is necessary to control the energies of the incoming protons so that the Bragg peak and the tumor location are aligned as best as possible. This requires information about the stopping power of the tissue along the proton trajectories. Any uncertainty will require a doctor to use a wider margin around the tumor to make sure the whole volume receives a sufficient amount of radiation.

About 3-5 percent of the uncertainty in the proton range comes from the conversion of X-ray CT to proton stopping power data [7]. This is because X-ray attenuation is mostly determined by electron density whereas proton stopping power also depends on elemental and molecular composition. Other sources of uncertainty come from changes in the body that happen between planning and treatment, and movement of the patient (breathing cycles, for example) during treatment, which require different methods to remedy.

A way to lower the uncertainty caused by the conversion of X-ray CT data to proton stopping power information is by using complementary information from proton CT scans. Protons, with such high energies that the Bragg peak lies behind the body, can be used to directly obtain information about proton stopping power of tissue in their traversed path. This requires tracking their incoming and outgoing trajectories and measuring the energy lost along their way. There is however a fundamental limit to the accuracy of this method. Since the protons have multiple small-angle interactions in the tissue, the traversed path within the body cannot be exactly known. At best the entrance and exit position and angle can be measured, from which an estimate of the traversed path can be made.

When comparing the imaging capabilities of protons to that of X-rays, a few things are of importance: protons have more sensitivity for small density fluctuations, and offer a higher contrast-to-noise ratio at a significant lower dose, but the spatial resolution is more limited due to the effects of multiple Coulomb scattering [18].
Chapter 3

Experimental setup

As explained in the previous chapter, to obtain proper proton stopping power data, it is necessary to determine the entry and exit vectors, and measure the energy loss of individual protons. An illustration of the detector setup is given in 3.1, and details of the individual parts are given in the other sections of this chapter.

![Detector setup, with example proton track](image)

Figure 3.1: Detector setup, with example proton track

The current system results in a 3 cm x 3 cm imaging plane, and a maximum acquisition rate of 50 Hz, which is still both too small and too slow for actual medical purposes.
3.1 Time projection chamber

Figure 3.2: Illustration of the principles of a time projection chamber. An incoming particle ionizes the gas and the electrons drift down due to the electric field between the cathode and the grid. When the electrons reach the grid, the high electric field causes an avalanche of electrons which can be detected by the pixel’s electronic circuit.

To obtain the data that is needed to reconstruct the tracks of the protons that have passed, we use two time projection chambers, one before and one after the phantom. Protons travelling through the TPC’s ionize the gas. By applying an electric field, the liberated electrons will drift towards the grid, after which they cause an avalanche of electrons in a narrow region with a high electric field. The generated avalanche can finally be detected by the pixels of a Timepix chip (see figure 3.2).

3.1.1 Drift chamber

The drift chamber consists of a piece of printed circuit board on the top (serving as a cathode) and bottom (guard); the bottom has a hole so it can fit over the two gridpix chips (figure 3.3b). Kapton foil (50 µm thickness) with 0.5 mm wide aluminium strips (30 µm thick), spaced every 1 mm is wrapped and glued around the PCB to create a closed, gas tight chamber. The cathode is held at -2000 V, and a resistor chain runs across the aluminium tracks down to the guard, which is held at around -440 V - it is calibrated so that the field between the guard and the grid is homogeneous because the spacing between the two is not exactly known. The kapton foil effectively serves as a field cage, keeping the field homogeneous and minimizing edge effects within the chamber. See figure 3.3a for a schematic and dimensions of the TPCs.

3.1.2 Timepix chip

The Timepix chip is a pixel chip made using 250 nm CMOS technology, developed by CERN [8]. With 256x256, 55 µm sized pixels, each pixel has its own pre-amplifier, adjustable discriminator and 14 bit counter. The small size and sensitivity of the
Figure 3.3: Time projection chamber
pixels and in depth knowledge and experience with them at Nikhef make them an
good choice for the detection of electron avalanches in our TPCs. The pixels can
operate in one of three modes:

- Counting mode: the counter is increased each time the signal goes above a set
  threshold level. This mode is useful in X-ray imaging.

- Time over threshold (ToT) mode: the counter is increased by every pulse of
  an external (100 MHz) clock, as long as the signal is above threshold. This
  can be used for the energy measurement of X-ray photons.

- Time of arrival (ToA) mode: the counter is increased each clock cycle after
  the signal goes over threshold, until the shutter closes. If the shutter is closed
  by a trigger, this means the drift time can be measured. Thus if the drift
  velocity is known, the z-position of the ionization location can be determined,
  which allows the reconstruction of tracks in 3 dimensions. This is the mode of
  operation used for our TPCs.

### 3.1.3 Gridpix

As explained before, the pixels are not sensitive to single electrons, so there is a need
to amplify the electrons. To make this possible, a grid, called Ingrid is placed on top
of the Timepix chip. The assembly is called GridPix [9]. The grid is a 1 µm thick
aluminium layer with holes etched at the same spacing as the pixels (55 µm), and
held in place 50 µm above the chip by spacers (image 3.4). By placing a voltage on
the grid, so that there is a high electric field (in the order of $10^4$ V cm$^{-1}$, depending
on the gas that is used and the required gain factor, see section 3.1.5) between the
grid and the Timepix chip, drifting electrons are forced through the holes in the grid and are then so much accelerated that they are able to ionize other atoms, creating an avalanche, that is then collected by the pixel anodes. To prevent sparks from damaging the Timepix chip, there is a Si$_3$N$_4$ protection layer applied on the pixels. The Timepix chip is wire-bonded to the readout board. Because the wirebonds are fragile and to prevent sparks, they are protected by applying glob top, an epoxy-based compound that hardens to provide mechanical support. The globtop also covers part of the chips, rendering these areas dead, as can be seen in figure 3.5: between the chips for both TPCs, and for pixels with $0 < y < 50$ for the chips in TPC 1. There are a few extra dead areas on the chips, probably caused by defects in the manufacturing process of the the Ingrid.

Each pixel has a 3 bit adjustable value to compensate for pixel-to-pixel threshold variations. Using Pixelman [19], a scan is done over all pixels and the values are optimized so that each pixels threshold is as close as possible to the mean threshold of all pixels. Ideally this should result in a flat heatmap for the whole chip, but as can be seen in figure 3.5, this process didn’t work optimally for the Timepix chips in TPC 2.

### 3.1.4 Construction

Unfortunately, during testing one of the chips in the existing detectors stopped working and a new one had to be constructed. Two Gridpix chips were already available, but a new field cage had to be made. The two pieces of printed circuit board were made-to-measure at the Nikhef workshop, after which assembly was done in a cleanroom.

First, the kapton foil was cut in the right size, and wrapped tightly around the bottom PCB plate with the hole for the chips. It was held in place using some adhesive tape on the inside, with the edges folded back to make it easier to remove later. Then, on the inside, the corners were soldered to the nearest conductive track on the kapton foil (figure 3.3b). The top PCB was then inserted and the corners soldered to to the tracks on top of the kapton foil through the hole in the bottom plate.

After glueing the kaptoin foil to PCB boards on both ends the assembly was left to dry in a makeshift clamp to keep the field chamber as straight as possible. Then the tape was removed and gas connectors glued in place. The field cage was then...
glued gas-tight directly on a Relaxd readout board with the Gridpix chips in place, completing the time projection chamber.

3.1.5 Gas

The two drift chambers are filled with a gas mixture of 80% Helium and 20% Isobutane (iC$_4$H$_{10}$). While this gas is not ideal when it comes to diffusion and amount of ionizations, it is known to be relatively safe with regard to sparks. Since the Gridpix chips of the used production were quite fragile, we decided to use this gas mixture for our tests. When considering the gas mixture there are a few things of importance [10]:

- **Amount of ionizations**: The amount of primary ionizations, caused by an incoming charged particle through the gas should not be too low, in which case there are low statistics which hinders the reconstruction of a track with sufficient accuracy. But when it is too high, there could be possible overlap caused by several drifting electrons ending up on the same pixel.

- **Gain**: The pixel electronics are not sensitive to single electrons. Therefore they need to be amplified. This is done in the amplification stage, between the grid and the collecting anodes on the pixels. In this field drifting electrons should be accelerated enough to ionize other gas atoms. Electrons are again accelerated and cause further ionizations. Thus an electron avalanche starts, and enough electrons should be created for the pixel electronics to be able to detect them. Gain is determined by the Townsend coefficient $\alpha(E)$, the average number of ionizations per unit of length. It depends on the used gas and is a function of the electric field. The gain over a distance $x$ for a single electron is given by

  $$G(x) = e^{\int_0^x \alpha(E(z))dz},$$

  or, for a constant electric field,

  $$G(x) = e^{\alpha x}.$$ (3.1)

  The minimum threshold for Timepix is about $3 \times 10^3$ electrons; to get a sufficient efficiency we aim for a gain of $2 \times 10^4$ [10], in the gap between the grid and the chip (50 µm). Using the simulation software GARFIELD [11], we can get for a given gas mixture an estimate of $\alpha(E)$ (figure 3.7). By using 3.2 and the results from GARFIELD, this means that for our He / iC$_4$H$_{10}$ mixture, a field of about $10^5$ V cm$^{-1}$ is required, which roughly corresponds to a voltage of -500 V on the grid. From experimenting, -400 V proved to be enough.

- **Quenching**: Pure noble gas atoms can be ionized or excited. When excited they typically return to the ground state by emitting a UV photon. This photon can ionize a gas atom, starting another avalanche. Thus a pure noble gas would be unstable, which is why a quencher gas is added to the mixture. Quencher gases are molecular gases that have rotational or vibrational absorption bands in the UV-range, so they suppress the effects of UV photons.
• Diffusion: Primary electrons created in the drift volume drift down to the anode along the electric field lines. As they drift they scatter on gas atoms, deviating them from their path. The magnitude of the diffusion is different along the field lines (longitudinal) and transverse, and depends on the gas composition and electric field. An estimate for diffusion is also obtained from a GARFIELD simulation and shown in figure 3.6b. In our case, we have $2000 - 400 = 1600$ V in the drift region of 3 cm, which corresponds to a transverse and longitudinal diffusion of respectively 200 and 160 $\mu$m $\sqrt{\text{cm}}^{-1}$.

• Drift speed: A higher electric field will mean a higher drift speed. It can also be obtained from GARFIELD (figure 3.6a). For the field in our drift volume this means a drift speed of about 1.9 cm $\mu$s$^{-1}$. The drift speed together with the Timepix clock speed of 100 MHz, determines the bin size with which the height of a hit is measured. With a 100 MHz clock the bins are sufficiently small compared to the inaccuracy caused by diffusion, however during one of the measurements the clock was mistakenly set to 10 MHz, (i.e. 2 mm bins), causing a high inaccuracy in the height measurement.
Figure 3.7: Townsend (solid) and attachment (dotted) coefficient vs electric field strength, from GARFIELD.
3.2 Residual energy detector

After traversing the sample under study (and the triggers and time projection chambers), we need to measure the residual energy of the protons, so that we obtain the amount of energy lost in the sample. This is done using a scintillating BaF$_2$ crystal. The BaF$_2$ crystal is large enough for it to be able to completely stop protons in our energy range (up to 150 MeV). The detector was already available from a previous experiment, and consists of the BaF$_2$ crystal, wrapped with teflon and a layer of UV reflecting aluminium foil (figure 3.8).

The light, created in the crystal by an incoming particle, travels through a quartz window to a photo multiplier tube (Hamamatsu R2059-01), where it liberates electrons that are amplified in the tube, effectively converting the light signal into an electric signal that can be sampled by an ADC (analog-to-digital converter).

A useful feature of BaF$_2$ is that it has both a fast ($\tau=0.6$ ns) and a slow ($\tau=600$ ns) light response [3]. The fast signal is thus useful as a trigger, whereas the slow signal is sampled by an ADC and after calibration used to determine the residual energy.

There are reports of a rate dependancy of the calorimeter setup [1] [2], which we didn’t confirm; however we were careful to keep the beam intensity as stable as possible during measurements.

The data acquisition setup is discussed in section 3.4.2, and the calibration and energy resolution in section 4.1.
3.3 Trigger and logic

Because we want to record individual proton events, a proper trigger logic is necessary, which controls the opening and closing of a the shutter of the Timepix chips, and to signal the HiSparc box so that it saves the pulse from the calorimeter PMT. The logic is implemented on logic NIM units. The setup is slightly different for high rates (in a proton beam, figure 3.9) and slow rates (when measuring cosmics for testing purposes, figure 3.10). This is because it is preferable to have the Timepix shutters always open, as opening the shutter after a trigger is possibly too late and might introduce some electronic noise. When measuring cosmics we get a rate of about 1/minute, and all the background radiation collected during this time would saturate a lot of pixels. So in this case the shutter is only opened after a trigger. When measuring in the proton beam (50 Hz rate), the background is not a problem, and the shutter can be kept always open.

The fast signal of the calorimeter and the signal from the small scintillator plate are both connected to a discriminator, that sends a logical 1 when the signal crosses a set threshold level. Their outputs are connected to the inputs of a coincidence unit, which outputs a logical 1 when both inputs are high at the same time, i.e. when a proton has passed through our setup. The output of the coincidence unit signals the start of a measurement; the ‘Veto timer’ is started so that no more coincidence events are counted when a measurement is still in progress and another timer, the
'Drift timer' is also started. The drift timer is set to 2 µs, which is slightly above the maximum drift time (3 cm / 2 cm µs⁻¹ = 1.5 µs). After this time all electrons have been collected on the Timepix chip and the shutter can be closed, so the 'Shutter timer' is started. Also, it signals the Hisparc box to save the pulse shape of the slow signal from the BaF₂ crystal.

When the shutter is closed, the Relaxd boards 'busy' out becomes high; at this point the data is sent over their ethernet connection to a PC. This process of reading out the chips and sending the data to the PC takes about 20 ms. This is the biggest limitation we currently have on the data acquisition rate. Reading out a Timepix chip takes the Relaxd board about 8 ms. In principle the Relaxd boards are able to read out 4 chips simultaneously, however it is limited to sequential read-out when only 2 chips are used, adding up to the largest dead time of 16 ms.

When this is done the busy signals go low again, when both are low the output of the logic fan becomes low, which causes a coincidence unit (which using a single input, effectively is falling edge detector) to reset the 'Veto timer', thereby opening the shutter again and releasing the veto, so the whole system is back in its original state, ready for the next event. An illustration of the logical states after a coincidence event is given in figure 3.11.

To make sure data acquisition starts at the same time for both Relaxd boards and the HiSparc box, we used a GPIO (general purpose input/output) pin of a Raspberry pi to control the veto: the veto is held high initially, and only when all three software threads are ready to take data is it released. This ensures that data taking is synchronized from the first event on.

The NIM units internally use -1 V for logical 1 and 0 V for logical 0. The
external devices (HiSparc box, Relaxd boards and Raspberry pi) use TTL levels however (respectively +5 V and 0 V for logical 1 and 0), so the NIM ⇔ TTL conversion units are needed to convert between logic levels.

Figure 3.11: Illustration of the logic states after a coincidence event.
3.4 Data acquisition

3.4.1 Relaxd

The Timepix chips are read-out using a Relaxd board. As explained before, they normally allow parallel readout of up to four Timepix chips, but are limited to sequential readout when two chips are used as in our case. Data transfer to a pc is done through a 1 Gbit/s ethernet connection. The maximum readout speed that can be obtained is thus about 20 ms, which limits the event rate to a maximum of 50 Hz.

3.4.2 HiSPARC

The calorimeter PMT is sampled by a HiSPARC II box. The box contains two ADCs, each sampling every 5 ns in anti-phase, effectively giving a 2.5 ns sample size, which is more than enough for the $\tau = 600$ ns slow response of the BaF$_2$ crystal. Each sample is 12 bits and the input range is 0-2.5 V, which is perfect for the amplitude of the signal (see figure 4.1).

The box has a few nice features: first, a pre- and post-trigger timing window can be set, so that the whole pulse can be saved. Secondly, it has a buffer size of 40000 samples, so that several events can be saved before it has to be read out.

The connection to the PC is through a USB interface, which proved to be problematic. Sometimes the PC suddenly takes several hundreds of milliseconds to poll the HiSPARC box for data, in which case the buffer can quickly fill up so that new events are discarded. To take care of this problem a busy out signal (high when the buffer is full) was added, controlling the veto on the coincidence unit.

3.4.3 Software

Data acquisition software is written in Python. The main process creates three child processes, two for each Relaxd board and one for the HiSPARC box. Each process polls for new data in a loop. Synchronization is important, if one of the detectors misses an event, there is no longer a correlation between subsequent events from the different detectors.

Loss of synchronicity happened a lot with the first test run at Agor, mostly caused by delays occurring in the data acquisition software, leading to skipped events. Events were timestamped however, although inaccurately as it was implemented in software causing high random delays - in the same order of size as the time between two events. This meant we could reconstruct most of the data sets (7.1).

As it turns out, most skipped events happened because of hard disk writing. The time it takes to write data to a hard drive is erratic and can take up to several hundreds of milliseconds. Because this disk writing happened in the same loop as data polling, one pass of the loop could take too much time, so that it was too late to poll for the next event and it would be skipped. To remedy this, we changed the software so that disk writing happens in a separate thread from the main thread. The main thread polls data and stores it in memory. the disk writing thread copies
this data to another memory location and then writes it to disk from this second location. This means that the main thread only has to wait for this memory-to-memory copy process, which is very fast, and is then free to continue polling for new data from the Relaxd board. The other thread takes care of writing the data to disk; any delays in this will thus not stall the main thread.

This fixed most of the synchronicity issues, however occasionally (about once every 10,000 events) it still occurred. The problem turned out to be the HiSPARC II box. Apparently, the polling of data through the USB interface can still take up too much time (although very rarely), allowing the buffer of the HiSPARC box to fill up, which then discards all new events. Luckily, through correspondence with the creators of the HiSPARC II box [20], we were able to implement a busy (buffer full) signal from the box. By controlling the veto with this signal, no new events are allowed as long as the buffer is not read out.

All data is written as compressed ROOT-files, and the data from the Relaxd boards is also first zero-suppressed. The Python code is fast enough for the maximum 50 Hz rate (the Relaxd loop takes about 2 ms), however, it probably needs to be re-written in a compiled language to speed it up if higher rates are desired.
Chapter 4

Analysis

In the previous chapter we have explained the online data acquisition, in this chapter we explain how the data is further analyzed offline. Several things have to be done:

- The pulse shapes from the calorimeter have to be converted to an energy value, using a calibration with protons of known energy.

- We have to look for events that contain a single proton track in both TPCs.

- For these events, from the set of hits, proton tracks have to be reconstructed. This also requires knowledge of the spatial resolution of the hits.

- We need to know the alignment of the individual TPCs, i.e. their position in a global reference frame.

- Finally, we have to combine the spatial and energy information to make energy and scattering radiographs.

We have two data sets, one obtained in April 2013 and one in May 2014, both using the AGOR cyclotron at KVI, Groningen. Several problems met during the 2013 run were fixed (see section 7.1) with the 2014 data. All analysis related plots in the following sections have been made using the 2014 data set.
4.1 Energy Calibration

4.1.1 BaF$_2$ response

The energy of the protons that have passed through both tracking detectors is retrieved from the signals of the BaF$_2$ crystal. Both the fast and the slow signals carry information. We have chosen to use the slow one to extract the energy information. The light created in the crystal by incoming protons is converted in the PMT to an electronic signal, which is sampled by a HiSPARC II unit as explained in the previous chapter. We have saved the whole pulse; the response to a 150 MeV and a 60 MeV proton are given in figure 4.1.

As a measure for the energy we can either use the height of the peak, or the total integral of the signal. From figure 4.2 it can be seen that this doesn’t matter much. The height of the peak is used for calibration, because it is less sensitive to pile-up, which happens if two signals overlap when two protons arrive really close to one another.

There are two possible pile-up cases: either there was a preceding signal or there is one that follows. The second scenario is more likely, because the timing window is larger after the the peak than before, and a preceding signal is likely to have already caused a trigger. If there is a second signal, it will add to the total integral. However it won’t add to the peak height if it happens close to or after the first peak.

4.1.2 Calibration

Energy calibration can be done by comparing the peak height of protons of known energy. At AGOR, the protons coming from the accelerator are 150 MeV. Lower energies are obtained by letting them pass through aluminium degraders, of varying thickness, which can be inserted or removed from the beam so that different energies can be provided on target. A histogram of peak heights for different energies is given...
in figure 4.3. The peak is wider for lower energies; as the protons go through more aluminium, the energy distribution spreads due to range straggling. The average of a gaussian fit for each peak is plotted against the proton energy in 4.4. Interpolation is done by using a third order polynomial fit through the points.

### 4.1.3 Energy resolution

The energy resolution at 150 MeV is easy to obtain directly from the calorimeter response. Although the detector response has a tail at low energies the bulk of measurements lie in a gaussian shaped peak, with $\sigma_E = 0.018$, or about 4% FWHM. This includes the initial spread in energies of the beam, but this is expected to be a small effect ($\sigma_{\text{beam}} \approx 10^{-3}$).

For the lower energies it is more difficult to obtain a resolution, since the spread in energy is increased as the protons go through aluminium degraders of increasing size. We can obtain still obtain a number for the resolution at these lower energies by assuming an energy distribution after the aluminum degraders similar to simulation in SRIM [6]. The actual energy resolution is then given by $\sigma_E^2 = \sigma_{\text{obs}}^2 - \sigma_{\text{SRIM}}^2$. The results are given in figure 4.5, showing that the resolution $\sigma_E$ is below 2% at 60 MeV.
Figure 4.3: Slow signal peak of runs with protons of different energy.

Figure 4.4: Energy calibration, conversion of peak height to energy in MeV.
<table>
<thead>
<tr>
<th>Energy [MeV]</th>
<th>$\sigma_{E}/E$</th>
</tr>
</thead>
<tbody>
<tr>
<td>60</td>
<td>0.005</td>
</tr>
<tr>
<td>80</td>
<td>0.01</td>
</tr>
<tr>
<td>100</td>
<td>0.015</td>
</tr>
<tr>
<td>120</td>
<td>0.02</td>
</tr>
<tr>
<td>140</td>
<td>0.025</td>
</tr>
</tbody>
</table>

Figure 4.5: Energy resolution vs. energy. This is the value of $\sigma$ for a gaussian fit in the peak, additionally the detector response shows a tail at low energies.
4.2 Track reconstruction

Tracking of the protons is done before and after the phantom with Gridpix based time projection chambers. The $x$ and $y$ positions of each liberated electron are indirectly determined from the pixel position of the avalanche; the $z$-coordinate is determined by the time of arrival of the charge on the pixel.

4.2.1 Track finding

The first step in tracking is the identification of tracks in events. This is done by a simple algorithm looking for peaks in the projection of all hits on the $x$-axis (image 4.6). Only events containing a single track in both detectors are kept. In this way, 42\% of events are rejected:

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|c|}
\hline
 & TPC 1 & TPC 2 & Total \\
\hline
No tracks & 18.5\% & 35.4\% & 40.1\% \\
\hline
>1 Tracks & 1.5\% & 1.5\% & 2.9\% \\
\hline
Outliers & 7.0\% & 8.3\% & 14.4\% \\
\hline
\end{tabular}
\caption{Fraction of events containing less or more than 1 track. Fraction of non-rejected events is thus 49\%}
\end{table}

4.2.2 Diffusion model

As explained in section 3.1.5, electrons diffuse as they drift, which gives an uncertainty on their original position. Additional uncertainty is caused by binning, and in case of the time resolution, also by timewalk.

- $x,y$ resolution

The $x,y$ resolution (in the chip plane) comes from the transverse diffusion ($\sigma_{\text{dif}}$) and the pixel size ($\sigma_0$), so the total uncertainty is given by

$$
\sigma_x^2 = \sigma_y^2 = \sigma_0^2 + \sigma_{\text{dif}}^2(\text{trans}),
$$

(4.1)
with
\[ \sigma_0 = \frac{55}{\sqrt{12}} \text{mm}, \]  
(4.2)
and
\[ \sigma_{\text{diff}}(\text{trans}) = D_t \sqrt{z}, \]  
(4.3)
with \( D_t \) the transverse diffusion coefficient and \( z \) the drift height. The \( \sqrt{12} \) denominator in (4.2) comes from the standard deviation of a flat distribution: consider a flat probability distribution of height 1 from \( x = -1/2 \) to \( x = 1/2 \). The average of \( x \) is 0. The standard deviation is then given by:
\[
\sigma^2 = \lim_{N \to \infty} \frac{1}{N} \sum_{i=1}^{N} (x_i - \bar{x})^2 = \int_{-1/2}^{1/2} x^2 \, dx = 1/12
\]  
(4.4)

- **z resolution**

The errors in \( z \) similarly come from the (longitudinal) diffusion and binning, but there is an extra factor due to timewalk:
\[
\sigma^2_z = \sigma_0^2 + \sigma_{\text{diff}}^2(\text{long}) + \sigma_{\text{timewalk}}^2.
\]  
(4.5)
In this case, the binning is in 10 ns steps, so to get a positional error, we multiply by the drift speed, \( v_{\text{drift}} \).
\[
\sigma_0 = v_{\text{drift}} \cdot \frac{10}{\sqrt{12}} \text{ns}.
\]  
(4.6)
The diffusion factor is similar to (4.3), except with the longitudinal drift coefficient, \( D_l \):
\[
\sigma_{\text{diff}}(\text{long}) = D_l \sqrt{z}.
\]  
(4.7)
Addition uncertainty in the reconstruction of the \( z \)-coordinate comes from two effects:

- There are differences in the way the electrons generate avalanches, and the position of the avalanche compared to center of a pixel causes different pulse distributions in a pixel.
- Especially due to different pulse heights there can be an offset in time between the start of the pulse and the point where it crosses the threshold (see image 4.7). This effect is called timewalk and it dominates the \( z \)-resolution. The timewalk distribution is slightly asymmetrical, but for simplicity we assume a symmetric error of \( \sigma_{\text{timewalk}} = v_{\text{drift}} \cdot 17 \) ns as an initial guess.
4.2.3 Fitting

To reconstruct a track, the points of the previously selected events have to be fitted with a straight line. To do this, we do two 2-dimensional fits, one in the projection of hits on the x,y-plane, and one in the z,y-plane. Combining the two fits, we obtain a 3-dimensional straight line equation. The fitting method used is the one described by York [12]. It is an iterative method that deals with asymmetric errors of hits (which is the case in the z,y-plane). From this method we obtain the center of gravity, slope and their respective errors.

4.2.4 Hit resolution

The errors obtained from the diffusion model are not the whole story; the actual hit errors can be obtained from the residual distribution after the initial fit. Since the errors are a function of drift height, we take slices of $z$, and using the fit calculate the residual for each hit. A better estimate of the coordinate errors as a function of drift height is then obtained from the standard deviation of a gaussian fit to the residuals in each slice (see figure 4.8a). For the $z$ error, this is still just an approximation since the error is not gaussian. As to why the data differs from the pure diffusion model, there can be several effects; such as non-zero initial velocity of the ionization electrons or an inhomogeneous electric field. The residual distribution for both the x,y and z,y projections are given in figure 4.8.

As can be seen in figure 4.9, a function in the shape of $\sigma = A + B\sqrt{z}$ is fitted through the errors obtained from the slices in figure 4.8, thus obtaining a proper empirical function describing hit errors as a function of drift height. The tracks are re-fitted with the newly obtained errors; this process is then iterated until it
(a) Residual distribution in x,y projection  (b) Residual distribution in z,y projection

Figure 4.8: Distribution and gaussian fits of residuals for tracks between 12.0 mm < z < 12.5 mm. On the right the wider and non-gaussian shape as a result of timewalk is very clear.

(a) Standard deviation of gaussian fit to x,y residuals vs height  (b) Standard deviation of gaussian fit to z residuals vs height

Figure 4.9: Standard deviation of gaussian fits as in image 4.8, as a function of height. The points are fitted with a square root function, and the results are used as new estimates for the uncertainty of hits.

4.2.5 Track parameter resolutions

The position resolution (of the center of gravity of the track) is given by [12] as

$$\sigma_{pos}^2 = \frac{1}{\sum_i W_i} + \tilde{y}^2 \sigma_{slope}^2, \tag{4.8}$$

with $W_i = \frac{\omega(Y_i) \omega(Y_i)}{\omega(X_i) + b^2 \omega(X_i)}$, where $\omega(X_i, Y_i)$ are the weights of each point, given by $\frac{1}{\sigma_{x_i}}$ and $\frac{1}{\sigma_{y_i}}$, $b$ the slope and $\tilde{y}$ the weighted average of $y$, $\tilde{y} = \frac{\sum_i W_i y_i}{\sum_i W_i}$, $y_i$ are actually the least-squares adjusted positions, given by York as

$$y_i = \bar{Y} + \beta_i, \tag{4.9}$$

stabilizes.
with
\[ \beta_i = W_i \left( \frac{Y_i - \bar{Y}}{\omega(X_i)} + \frac{b(X_i - \bar{X})}{\omega(Y_i)} \right) . \] (4.10)

We can simplify these equations by putting the slope to 0 \((b = 0)\), which is possible because this is actually the case in the zy-plane, and because of symmetry in the xy-plane \((\sigma_x = \sigma_y)\). We can also translate to a center of gravity coordinate system so that \(\bar{y} = 0\). This means that \(\beta_i = Y_i - \bar{Y}\), so that \(y_i = Y_i\), and simply
\[ \sigma^2_{\text{pos}} = \frac{1}{\sum_i W_i} = \frac{1}{\sum_i \frac{1}{\sigma_x^2}} = \frac{\sigma^2_x}{n} . \] (4.11)

The resolution of the slope is given by
\[ \sigma^2_{\text{slope}} = \frac{1}{\sum_i W_i} u_i^2 . \] (4.12)

With
\[ u_i = y_i - \bar{y} = Y_i , \] (4.13)
this means that
\[ \sigma^2_{\text{slope}} = \frac{1}{\sum_i \frac{1}{\sigma_x^2} y_i^2} . \] (4.14)

In our situation, the resolution of each hit depends on the drift height, but the protons’ trajectories are parallel to the read-out plane so the resolution is the same for each hit, so
\[ \sigma^2_{\text{slope}} = \frac{\sigma_x^2}{\sum_i y_i^2} . \] (4.15)

Looking at the expected value, \(E(y^2) = \frac{1}{n} \sum y_i^2\), and using \(\sigma(y)^2 = E(y^2) - E(y)^2\), where \(E(y) = 0\) (we’re in the center of gravity), and \(\sigma(y)^2 = \frac{l^2}{12}\) (as in (4.4)), this reduces to
\[ \sigma^2_{\text{slope}} = \frac{12\sigma_x^2}{nl^2} , \] (4.16)
with \(n\) the number of hits and \(l\) the length of the track.

Since the position resolution of the tracks is quite accurate, we can determine the actual angle of the beam using both TPCs without a phantom in between. As can be seen from figure 4.12, the average angular spread of the beam is 6.8 mrad in the xy and 6.1 mrad in the zy plane.

In the zy-plane, the standard error on the angle, as obtained by York’s method is in disagreement with the width of the angular distribution. A better estimate of the error on the fit parameters can be made using the bootstrap method, where the error is obtained from the RMS of the fit parameters from random resamples of the collection of hits. The difference is shown in figure 4.10. The underestimation of the errors on fit parameters with York’s method is most likely due to its assumption of gaussian errors, which in the yz plane is a bad approximation because of the assymetric timewalk.
Figure 4.10: Errors on angle reconstruction, from York’s method (black) and bootstrap (red)
4.3 Phantom reconstruction

4.3.1 Proton path

Ideally the information from the TPCs results in the locations and angles of the entry and exit points of protons in the phantom. The path of the proton through the phantom can then be approximated with a most likely path formalism, as in [13]. However, in our case, the typical scattering angle is much smaller than the resolution. See for example image 4.11, where for a 3 cm tissue-equivalent phantom the average scattering angle is in the order of 1 mrad. When comparing this to the angular resolution in 4.10, it is clear that the resolution prevents a proper path reconstruction in the phantom. We therefore have to fall back to a more basic method. One possibility is to simply extrapolate the tracks as measured before and after the phantom to a point in the center of the phantom. A problem is that the low angular resolution then also leads to an uncertainty in this position. We can do one of two things to improve on this:

- The spread of angles in the beam is quite low (see figure 4.12), so that we can take a weighted average of zero and the measured angle.

- For a phantom where we expect low scattering, we can simply disregard the measured angle, and take as the reconstructed proton track a straight line through the centers of gravity in TPC 1 and 2, which we know to high accuracy.

The low scattering angles means the second method leads to the smallest uncertainty. We divide the plane in the center of the phantom into bins and determine for each event the bin that the proton track goes through. For each bin, a single energy value is then extracted from the energy distribution in the bin. The energy distribution

![Figure 4.11: TOPAS simulation of scattering angle distribution for a 3 cm tissue equivalent phantom, thanks to [21].](image)
4.3.2 Energy radiographs

Each phantom was illuminated for 2.5 hours each at a low rate proton beam at AGOR, obtaining an acquisition rate of about 40 Hz. About 50% of events were rejected, leading to approximately 180,000 events per phantom. We used a 60x60 binning grid, so that each bins area is 0.5 mm \( \times \) 0.5 mm, contains an average of 50 events. From figure 4.15, we can see that the occupancy is not evenly distributed, should ideally look landau-shaped, however typically a bin will contain several peaks in the energy loss value, especially near the border between materials. A landau shaped fit is therefore not appropriate so instead we look for a peak in the histogram (see figure 4.13).

We now have a binned image plane with energy values in each bin. This we call an energy radiograph and these images are the final result of our work. Results from actual proton data at AGOR are given in the next section, and results from preliminary experiments are given in the appendix (7.1.1).
Figure 4.14: Phantom: 2.5 cm long cylinder (diameter 2.5 cm) of solid water (Gammex 457 \( \rho = 1.015 \text{ g cm}^{-3} \)), with 8 mm inserts: PMMA \( (\rho = 1.18 \text{ g cm}^{-3}) \), Fat (Gammex adipose 453, \( \rho = 0.92 \text{ g cm}^{-3} \)) and bone (Gammex cortical bone 450, \( \rho = 1.82 \text{ g cm}^{-3} \)).

most notably a deficit in the center - a result from the large dead area between the chips in each TPC.

Another interesting observation is that the outline of the phantom can be seen in the occupancy plot. This is probably due to a 'lensing' effect, the protons that travel along the border between two materials of high density difference are curved towards the higher density material. As can be seen from figure 4.14a, the experimental results are in agreement with expectations from TOPAS simulations and the different materials are well resolved. Figures 4.16 - 4.20 show the energy radiographs of the other phantoms under study.

Figure 4.15: Occupancy per bin corresponding to image 4.14a.

(a) Experimental data, from 150583 events.  (b) TOPAS simulation [21]
Figure 4.16: Phantom: 2.5 cm long cylinder (diameter 2.5 cm) of solid water, with inserts: air, Water and glycerol ($\rho=1.26 \text{ g cm}^{-3}$). 183948 events.

Figure 4.17: Phantom: same as in figure 4.16, but rotated 90 degrees. 181706 events.
Figure 4.18: Phantom: same as in figure 4.14a. 230776 events.

Figure 4.19: Phantom: same as in figure 4.16. 155433 events.
Figure 4.20: Phantom: Copper wedge with PMMA insert. 62071 events.
Chapter 5

Similar experiments

Several groups have recently published their work on proton radiography, with individual proton tracking capabilities. The most state of the art by the LLUMC collaboration (section 5.1).
5.1 LLUMC Collaboration

A collaboration from the Loma Linda University has presented their findings of a proton imaging setup in [14]. Their setup uses silicon strip detectors (SSDs) for tracking and an array of CsI scintillating crystals for residual energy measurements. A pair of two rotated planes are required to gain a single x,y position of a proton; therefore to reconstruct a track two sets of planes, spaced apart to form a telescope are necessary. There are telescopes like this before and after the phantom, giving a total of eight SSD planes. Each plane being 400 µm thick; the material causes unwanted scattering of protons in the tracking system.

The current setup is able to collect events at a rate up to 100 kHz. In their article they present an energy radiograph of a hand phantom (image 5.1a). This is made using 1.7 million 200 MeV proton tracks, averaging 40 tracks per pixel.

Furthermore they present a scattering radiograph (image 5.1b).
5.2 PRIMA Collaboration

A second proton radiography experiment with SSD tracking is the PRIMA Collaboration [16][17]. Their tracking area is 5x5 cm², and can operate at 10 kHz. They have made an actual CT-reconstruction by irradiating the phantom from 360°. They were able to reconstruct a PMMA phantom with holes of 4 and 6 mm diameter. 5.2.
5.3 TERA Foundation

The TERA foundation also uses a gas drift chamber for the tracking of protons [15]. Instead of a pixel chip they use orthogonal strips for readout and GEM-foils for electron amplification. The proton tracks however go through the read-out plane. For residual energy measurements a plastic scintillator plate stack is used. Their current system has a 10x10 cm$^2$ imaging area and is able to collect data at a rate of 10 kHz. Results of the imaging of a 20 mm thick PMMA plate, with holes of diameter 1 to 10 mm and 5, 10, 15 and 20 mm depth are given in 5.3.
Chapter 6

Conclusion and suggested improvements

We have succeeded in getting a basic proton radiography system running. However, our current system has a few shortcomings, as compared to other groups in this field and with respect to actual practical applications. These are the following:

- **Rate.** Our current setup has a very limited acquisition rate of about 50 hertz. The groups described in chapter 5 all have rates of about 10 kHz, and are planning to go towards MHz.

- **Spatial resolution.** One of the advantages of using gas TPCs for tracking is the low scattering on the equipment itself. However this potential advantage is mitigated by the current low angular resolution. It prevents a proper reconstruction of proton tracks. Also, besides energy loss, there is information in the amount of scattering that is currently unavailable.

- **Size.** The 9cm$^2$ size of the system should for practical purposes be increased to get a bigger imaging plane.

The next generation of Timepix chips (Timepix 3) allows for a much higher rate. It is data-driven instead of event-driven and allows up to 80 MHits/s, which is a great improvement from using Timepix. Currently work is being done to create Timepix 3 based TPCs for proton radiography. The HiSPARC II system that is now used for readout of the PMTs of the $BaF_2$ crystal is the next limit. Readout can take up to 20 ms and it has some problems when its buffer fills. So a faster ADC system is also necessary. The slow signal from $BaF_2$ has a 0.6 µs decay time, so at rates up from 10 kHz pile-up will become an increasing problem.

So, with Timepix 3 and a faster ADC a great increase in the rate performance can be achieved. Timepix 3 has one more advantage: it can simultaneously measure time of arrival and time over threshold. The time over threshold information can be used to decrease the timewalk, improving the z-resolution. To really take advantage of the extra information from scattering and increased spatial resolution from a proper most likely path reconstruction this is not enough; angular resolution should be increased by using a different gas with more ionizations and lower diffusion, and/or
by measuring tracks over a longer distance, for example by using two sets of TPCs in front of and behind the sample.

TPCs with a 4x larger imaging plane are also currently being developed, using a double TPC with the cathode in the center, and a row of four Timepix chips on the top and bottom.
Chapter 7

Appendix

7.1 Data set 2013

The data set from 2013 contained a few problems:

- The ToA clock was mistakenly set to 100 ns instead of 10 ns. This causes a big uncertainty in ToA.

- Synchronization between TPCs and calorimeter events was quickly lost. The biggest cause was that data was being written to disk in series with the read-out from the devices. Disk operations can take a significant amount of time, which can lead to a data acquisition thread not being ready in time and thus events being skipped. Furthermore a write buffer wasn’t properly emptied after writing, causing some HiSPARC events to be written multiple times.

Luckily, each event was timestamped; in the case of the HiSPARC events the trigger time with high precision, but in the case of the TPC events only the moment of disk writing, causing these timestamps to have a big uncertainty, in the order of the time between two events. This complicated offline synchronization using the timestamps. However, about 90% of the data could be restored using the following procedure:

- Choose two events from TPC and HiSPARC as initial alignment.

- Minimize the average difference between neighbouring events by shifting one timeline.

- Choose a new alignment as in step 1 and repeat.

- Use the alignment with the lowest average difference in time between events.

- Iterate all events; synchronization is lost when the average time difference increases above a threshold. In this case start again from step 1.

The data thus restored resulted in the energy radiographs in the following section.
7.1.1 Energy radiographs

Figure 7.1: Phantom: Solid copper block, covering half of the beam. 16390 events.

Figure 7.2: Phantom: Solid copper wedge. 15530 events.
Figure 7.3: Phantom: same as in figure 4.20. 15799 events.

Figure 7.4: Phantom: Steel cylinder, diameter 1cm. 18798 events.
Figure 7.5: Phantom: Steel door key. 18706 events.
Bibliography


[12] Derek York, Norman M. Evensen, Margarita Lopez Martinez and Jons De Basabe


