AARHUS UNIVERSITY

# Individualized treatment margins through improved proton range uncertainty estimations

## Introduction

The number of facilities treating cancer patients worldwide with proton therapy has increased rapidly over the last couple of years and more are either under construction or in the planning stage [1]. The Danish Centre for Particle Therapy (DCPT) started treating patients in January 2019 and has completed over 100 cases.

Proton therapy can be used to reduce the dose to healthy tissue and organs at risk (OARs) due to the physical characteristics of the depth dose curve, with a low entrance dose followed by a steep dose increase and a sharp fall-off at the end of the range (Bragg Peak) [2]. Protons have a restricted penetration depth in tissue and will not deposit any dose at greater depths. The high-dose area for protons is very narrow and located at the end of the depth-dose curve, which enables the targeting of the high-dose region to the tumor, while sparing the surrounding normal tissue.

The sharp fall-off of the protons is a key advantage of proton therapy, but it also makes it very sensitive to range uncertainties [3]. If not taken into account in treatment planning, the range uncertainty can potentially cause a considerable degradation of the deposited dose to the tumor and an increase in dose to the surrounding normal tissue, leading to a risk of missing the tumor or causing severe side effects (Figure 1 [4]). Uncertainties in range arise from variations in patient setup, imaging, beam delivery, organ motion and the estimations of the proton range. The latter contributes mainly to a systematic uncertainty resulting in the same dosimetric error in each treatment fraction why this is of great importance [5]. By reducing the uncertainties, it would be possible to reduce the treatment volume and allow a better utilization of the advantages of protons. Many proton centers take all these uncertainties into account by adding safety margins around the tumor, typically 3.5% of the beam range plus 1 mm [3, 6]. Many factors contributing to the systematic range uncertainty are dependent on center- or patient-specific parameters, such as the CT scanner, the dose calculation algorithm or the complexity of the patient anatomy. Nevertheless, the margins used are almost always standardized. Some investigations into patient specific range calculations have been made but are not clinically implemented [7].

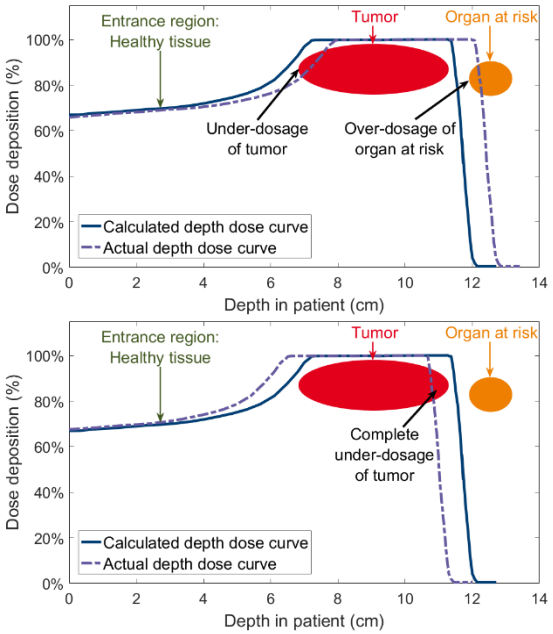


**Figure 1:** The impact of range uncertainties in proton therapy. a) Under-estimation of proton range causing over-dosage to organs at risk. b) Over-estimation of proton range causing complete under-dosage of the distal part of the tumor. From Taasti [4].

To account for the range uncertainties, setup errors and motion in delivering proton therapy, robust optimization methods have been developed. In robust optimization, the uncertainties are incorporated

in the optimization of the dose distribution by taking the different errors into account and creating a treatment plan where the target coverage is ensured in each scenario [8].

The accuracy of the determination of the range is essential in proton therapy. Pencil beam algorithms for calculation of the proton range require accurate estimations of the stopping power ration (SPR) relative to water. SPR is a key constituent to the range calculations and is typically based on data from computed tomography (CT) scans [9]. Estimation of SPR is most often performed using empirical piecewise linear calibration curve, a so-called Hounsfield Look-up Table (HLUT) [10]. However, Dual energy CT (DECT) has been shown to improve SPR determination used for proton treatment planning compared to the use of standard single energy CT [11, 12, 13, 14, 15].

When protons move through the patient, some protons will scatter away from their straight-line path. In standard analytical dose calculation algorithms, this is only approximately taken into account, which is of particular concern when the beam passes through large tissue heterogeneities. In Monte Carlo based treatment planning this issue is addressed more accurately leading to a more precise dose calculation [16]. Monte Carlo calculations require knowledge on the elemental composition and the density of the tissue which are estimated based on CT images [17]. DECT may increase the accuracy of this estimation [18, 19].

All treatment planning methods rely on accurate dose calculations that in turn rely on accurate proton range estimation. A way to verify proton range estimation is by using *in vivo* range verification which could be valuable in the pursuit of improving the accuracy in proton therapy [5]. Several methods have been proposed where validations are performed either prior, during or after treatment [20, 21, 22, 23, 24]. One of these methods is called proton range probe. This is a 1D range measurement where the patient is irradiated with a single proton beam of energy sufficient to pass all the way through the patient and the Bragg Peak is measured with a multi-layer ionization chamber (MLIC) placed on the other side of the patient [25, 26]. Range probing can potentially both verify patient positioning as well as validate the estimated proton range.

In this project, a strategy for determining individualized range uncertainty margins will be developed. To accomplish the goal of improving range uncertainty estimations, the project will investigate different treatment planning methods for proton therapy and propose an improved method that can be clinically implemented. Range uncertainty contributors and the resulting necessary margins will be calculated and compared to ground-truth measurements using a controlled experimental setup. Ultimately, the proton range estimations are to be validated *in vivo* for head-and-neck patients receiving proton therapy at DCPT.

## Overall aim

The overall aim of this project is to develop a strategy for determining individualized range uncertainty margins with improved proton range estimations and validate these in patients. This will result in assurance of target coverage, less dose to OARs and thereby a reduction of the risk of side effects. The results of the project are to be implemented in the clinical workflow at DCPT. The project fits well into the overall aim of DCPT and the expected amount of proton patients that will be treated at DCPT.

## Study 1: Coherent experimental testing setup for different treatment planning methods (May 2020-March 2021)

### Background

At present time, several suggestions to improve proton range estimations exist, where some of these would be difficult to implement in routine treatment and a few are already used [1]. The suggested methods often differ in the selected parameters and the experimental setup, making comparison difficult. However, studies where some parameters are compared have been made e.g. SECT vs. DECT-based methods [13, 27] and Monte Carlo based calculations vs. pencil beam algorithms [16]. In addition, studies with DECT as input to Monte Carlo based calculation have been performed [18, 19]. A full examination of all range estimation methods with a coherent experimental setup needs to be done to be able to compare these and eventually optimize the clinical dose calculation strategy. Furthermore, combinations of different methods should be considered since they could potentially supplement each other.

### Hypothesis and aim

The aim of this study is to find a clinical strategy for estimating the proton range in order to reduce the range uncertainty margins. An experimental setup is suggested which can be used to test a large variety of different methods on the same set of parameters and the same experimental setup. The hypothesis is that combining different treatment planning strategies will reduce the uncertainty in the estimated proton range.

### Research plan

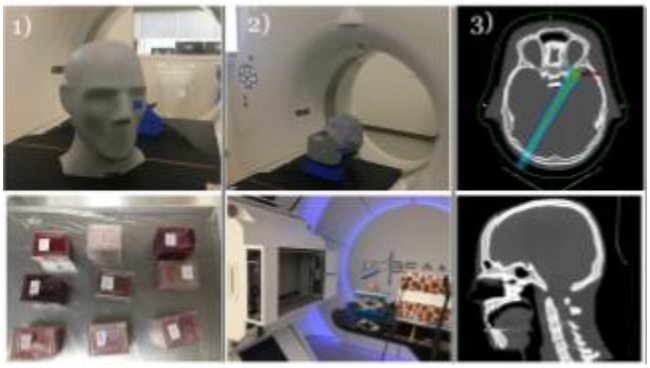


**Figure 2:** Outline of the workflow for the full study: 1) Anthropomorphic head phantom, and animal tissue samples. 2) DECT scanner, and proton measurement setup with MLIC. 3) Dose distribution for a single proton spot, and a CT scan of the head phantom.

An anthropomorphic head phantom (CIRS, Inc. Norfolk USA) with a known ground-truth SPR map will be scanned with a DECT scanner, SOMATOM Definition Edge (Siemens Healthineers, Erlangen, Germany), and afterwards proton range estimations will be performed using different methods. The following methods will be tested: The two dose calculation algorithms implemented in the Eclipse treatment planning system (Varian Medical System, Palo Alto, CA, USA), namely the pencil beam algorithm, proton convolution superposition (PCS), and the MC based AcurosPT; DECT for SPR estimation; and pencil beam algorithms with improved proton scattering calculations (FRoG (Fast Recalculation on GPU) [28]). In addition, robust optimization will be used when calculating the proton dose distribution. The calculated proton range from the abovementioned methods will be compared to ground-truth calculations. Testing will also be completed on biological (animal) tissues where SPR measurement will be performed by irradiating the tissues with several proton spots and measured with an MLIC (IBA Dosimetry, Schwarzenbruck, Germany). An outline of the workflow for the full study is shown in Figure 2.

## Study 2: Determination of site-specific range uncertainty margins (April 2021 – March 2022)

### Background

A reduction in the treated volume could reduce irradiation of healthy tissues, if the range uncertainties are properly understood following a decrease in range margins. Several studies have examined animal tissues and with different calculation methods investigated the range uncertainties [13, 14]. Bony materials as well as lung tissue often have the largest errors due to the high density or air cavities, respectively. Site-specific range uncertainty could give a more realistic estimation of the range uncertainty since only the tissues and tissue transitions in the anatomical site of the treatment volume would be considered in the calculation. Site-specific range uncertainties have been proposed and investigated in prior studies and a reduction in margins compared to the generic margin could for some sites be reached [29]. For head-neck as well as lung and breast regions the case was opposite and larger margins were suggested. This is due to the large heterogeneity and complexity of the sites, e.g., bone-air transitions. Further investigations into range uncertainty contributions based on specific tissues and compositions of tissues would give even better site-specific uncertainty margin estimations. If tested on a cadaver of an animal this would give a more realistic picture of the heterogeneity of the different sites.

### Hypothesis and aim

This study aims to find range uncertainty margins that are site-specific based on the tissue composition in different anatomical regions. It is foreseen that margins can be reduced compared to the generic margins for most patient groups however, margins might have to be increased for patients with very heterogeneous geometries around the tumor sites.

### Research plan

This study will estimate the range of proton beams through a cadaver of an animal (sheep or porcine) using the strategy found in study 1. This will be carried out by scanning the animal in a DECT scanner and afterwards irradiate it with proton spots at different positions. The proton range will be measured with a MLIC and the estimated and measured range will be compared. The range uncertainties from the different positions can now be estimated and the contributions to the range uncertainty from different tissues and tissue transitions can be defined. Ultimately, a strategy for determining site-specific range uncertainty margins will be proposed.

## Study 3: Clinical implementation of *in vivo* range validation and optimized range calculations (April 2022 – May 2023)

### Background

A reduction in margins is desirable in proton therapy and *in vivo* measurements of proton range could further improve the accuracy of the proton range estimations. The concept of proton range probe has been suggested for *in vivo* proton range verification and preliminary studies have shown that range probe could be feasible for range verification [25] as well as for patient positioning and reduction in setup errors [26]. The concept has not yet been clinically implemented and suggestions to a clinical workflow have to be made and tested in order to exploit the full potential of *in vivo* proton range verification. Potentially, this could reduce range uncertainties and decrease the treatment volume, sparing healthy tissues as well as ensuring target coverage.

### Hypothesis and aim

The aim of this study is to clinically implement an *in vivo* proton range validation strategy on a group of head-and-neck cancer patients. The evaluation of these will be used to estimate the proton range, and

to optimize the clinical treatment calculation of the range and the range uncertainty margins. It is hypothesized that patients with large heterogeneity around the tumor will benefit the most from these optimizations and an *in vivo* range validation could be especially important for these patients.

**Research plan**

In study 3, the results from study 1 and study 2 will be applied to a group of head-and-neck cancer patients that are selected for proton therapy at DCPT according to the guidelines from The Danish Head and Neck Cancer Group (DAHANCA). DAHANCA 35 is the protocol describing which head-and-neck patients should be treated with proton therapy. This project will be carried out by measuring the range *in vivo* using the range probe technique, and a protocol for implementing range probe in a clinical workflow will be made. An MLIC will be used to measure the proton range from each proton spots irradiated through the patients at certain positions. The measured range will be examined and compared to the calculated range from the clinically used treatment planning system at DCPT (Eclipse PCS) and the range estimated using the method found in study 1 with uncertainty margins calculated as suggested from study 2. An evaluation based on the differences between measured and estimated range will be made and according to this, changes to the clinical workflow will be proposed.

**Perspectives**

Improved range estimations methods will lead to a reduction in range uncertainties and this will further open for the opportunity to treat patients with individualized margins. With an *in vivo* verification of the proton range, patients will get an advanced proton treatment optimized for their specific anatomy. Verified proton range will also open for the opportunity for further refinement of proton therapy, i.e., treatments for patients with OARs close to the distal end of the proton beam. Potentially, range probe cannot only verify proton range but also optimize patient positioning. This study will investigate clinical implications for head-and-neck cancer patients but could eventually be applied for other patient groups.

**Research environment**

This PhD project will be performed at the DCPT, giving access to three clinical proton treatment gantries with beam energy 70-230 MeV and an experimental room with a fixed horizontal beam line, dedicated for biology and physics research. Furthermore, there is access to a DECT scanner (Siemens SOMATOM Definition Edge). At Aarhus University Hospital several different DECT scanners are available. The PhD student will have access to these facilities. The treatment planning system Eclipse PCS and AcurosPT will be available for use in this study as well as access to the dose calculation engine FRoG. It is expected that 300 patients with head-neck cancer will be treated at DCPT during the first three years, starting April 2019. The research will take part in a dynamic interdisciplinary environment with close collaboration with both clinicians and researchers affiliated to the Danish Centre of Particle Therapy, the Department of Oncology and Medical Physics and Clinical Experimental Oncology.

In addition, some part of Study 1 will be performed at Maastro Clinic, Maastricht as per agreement with Wouter van Elmpt, Phd, Assistant Professor and Program Manager of the Physics Innovation Team, see attached agreement.

## The PhD student's contribution and supervisor team

The PhD student will be performing all parts of the described project. All theoretical calculations, CT scans, measurements and treatment planning studies will be performed by the applicant herself. She will be supervised by the following research group:

- Kenneth Jensen, MD PhD, Danish Centre for Particle Therapy (main supervisor)
- Vicki Trier Taasti, Innovation Physicist, Maastro Clinic, Maastricht, The Netherlands (supervisor)
- Maria Fuglsang Jensen, Medical Physicist, Danish Centre for Particle Therapy (supervisor)
- Ludvig Paul Muren, Professor, PhD, Danish Centre for Particle Therapy / Dept. of Medical Phyisics, Aarhus University Hospital (collaborator)
- Ole Nørrevang, Chief Physicist, Danish Centre for Particle Therapy (collaborator)

## Biography

[1] The Particle Therapy Cooperative Group (PTCOG), "Particle therapy facilities in clinical operation https://ptcog.ch/index.php/facilities-in-operation".

[2] W. D. Newhauser, R. Zhang, "The Physics of Proton Therapy," *Phys. Med. Biol. 60,* p. R155, 2015.

[3] H. Paganetti, "Range uncertainties in proton therapy and the role of Monte Carlo simulations," *Phys. Med. Biol. 57,* pp. R99-R117, 2012.

[4] V.T.Taasti, "Improving proton range determination using new x-ray computed tomography principles".*PhD Thesis.*

[5] A.C. Knopf and A. Lomax, "In vivo proton range verification: a review," *Phys. Med. Biol. 58,* pp. R313-R160, 2013.

[6] V. T. Taasti, C. Bäumer, C. V. Dahlgren, A. J. Deisher, M. Ellerbrock, J. Free, J. Gora, A. Kozera, A. J. Lomax, L. De Marzi, S. Molinelli, B.-K. K. Teo, P. Wohlfahrt, J. B. B. Petersen, L. P. Muren, D. C. Hansen, and C. Richter, "“Inter-centre variability of CT-based stopping-power prediction in particle therapy: Survey-based evaluation," *Phys in Imaging Radiat Oncol 6,* pp. 25-30, 2018.

[7] C.-A. Collins-Fekete, S. Brousmiche, D. C. Hansen, L. Beaulieu, and J. Seco, "“Pre-treatment patient-specific stopping power by combining list-mode proton radiography and x-ray CT," *Phys. Med. Biol. 62,* pp. 6836-6852 , 2017.

[8] J. Unkelbach, M. Alber, M. Bangert, R. Bokrantz, T. C. Y. Chan, J. O. Deasy, A. Fredriksson, B., "Robust radiotherapy planning," *Phys. Med. Biol. 63,* p. 22TR02, 2018.

[9] M. Yang, G. Virshup, J. Clayton, X. R. Zhu, R. Mohan, and L. Dong, "Theoretical variance analysis of single- and dual-energy computed tomography methods for calculating proton stopping power ratios of biological tissues," *Phys. Med. Biol. 55,* pp. 1343-1362, 2010.

[10] U. Schneider, E. Pedroni, and A. Lomax, "The calibration of CT Hounsfield units for radiotherapy planning," *Phys. Med. Biol. 41,* pp. 111-124, 1996.

[11] V. T. Taasti, J. B. B. Petersen, L. P. Muren, J. Thygesen, and D. C. Hansen, "A robust empirical parametrization of proton stopping power using dual energy CT," *Med. Phys. 43,* pp. 5547-5560, 2016.

[12] V. T. Taasti, G. J. Michalak, D. C. Hansen, A. J. Deisher, J. J. Kruse, B. Krauss, L. P. Muren, J.B. B. Petersen, and C. H. McCollough, "Validation of proton stopping power ratio estimation based on dual energy CT using fresh tissue samples," *Phys. Med. Biol. 63,* p. 015012, 2018.

[13] C. Möhler, T. Russ, P. Wohlfahrt, A. Elter, A. Runz, C. Richter, and S. Greilich, "Experimental verification of stopping-power prediction from single- and dual-energy computed tomography in biological tissues," *Phys. Med. Biol. 63,* p. 025001, 2018.

[14] P. Wohlfahrt, C. Möhler, C. Richter, and S. Greilich, "Evaluation of stopping-power prediction by dual- and single-energy computed tomography in an anthropomorphic ground-truth phantom," *Int J Radiation Oncol Biol Phys 100,* pp. 244-253, 2018.

[15] W.V. Elmpt, G. Landry, M. Das, F. Verhaegen, "Dual energy CT in radiotherapy: Current applications and future outlook," *Radiotherapy and Oncology 119,* pp. 137-144, 2016.

[16] H. Paganetti, H. Jiang, K. Parodi, R. Slopsema, and M. Engelsman, "Clinical implementation of full Monte Carlo dose calculation in proton beam therapy," *Phys. Med. Biol. 53,* pp. 4825-4853, 2008.

[17] W. Schneider, T. Bortfeld, and W. Schlegel, "Correlation between CT numbers and tissue parameters needed for Monte Carlo simulations of clinical dose distributions," *Phys. Med. Biol.,* pp. 459-478, 2000.

[18] N. Hünemohr, H. Paganetti, S. Greilich, O. Jäkel, and J. Seco, "Tissue decomposition from dual energy CT data for MC based dose calculation in particle therapy," *Med. Phys. 41,* p. 061714, 2014.

[19] I. P. Almeida, L. E. J. R. Schyns, A. Vaniqui, B. van der Heyden, G.Dedes, A. F. Resch, F. Kamp, J. D. Zindler, K. Parodi, and G. Laundry, "Monte Carlo proton dose calculations using a radiotherapy specific dual-energy CT scanner for tissue segmentation and range assessment," *Phys. Med. Biol. 63,* p. 115008, 2018.

[20] H. M. Lu, "A potential method for in vivo range verification in proton therapy treatment," *Phys. Med. Biol. 53,* pp. 1413-1424, 2008.

[21] H. M. Lu, "A point dose method for in vivo range verification in proton therapy," *Phys. Med. Biol. 53,* pp. N415-423, 2008.

[22] H. M. Lu, G Mann, and E. Cascio, "Investigation of an implantable dosimeter for single-point water equivalent path length verification in proton therapy," *Med. Phys. 37,* pp. 5858-5866, 2010.

[23] P. Farace, R. Righetto, and A. Meijers, "Pencil beam proton radiography using a multilayer ionization chamber," *Phys. Med. Biol. 61,* pp. 4078-4087, 2016.

[24] C. H. Min, C. H. Kim, M. Y. Youn, and J. W. Kim, "Prompt gamma measurements for locating the dose fall-off region in the proton therapy," *Appl. Phys. Lett. 89,* p. 183517, 2006.

[25] M. Mumot, C. Algranati, M. Hartmann, J. M. Schippers, E. Hug, and A. J. Lomax, "Proton range verification using a range probe: definition of concept and initial analysis," *Phys. Med. Biol. 55,* pp. 4771-4782, 2010.

[26] A. Hammi, L. Placidi, D. C. Weber, and A. J. Lomax, "Positioning of head and neck patients for proton therapy using proton range probes: a proof of concept study," *Phys. Med. Biol. 63,* p. 015025, 2018.

[27] V. T. Taasti, L. P. Muren, K. Jensen, J. B. B. Petersen, J. Thygesen, A. Tietze, C. Grau, and D. C. Hansen, "Comparison of single and dual energy CT for stopping power determination in proton therapy of head and neck cancer," *Physics and Imaging in Radiation Oncology 6,* 2018.

[28] K. Choi, S. B. Mein, B. Kopp, G. Magro, S. Molinelli, M. Ciocca, and A. Mairani, "FRoG – A New Calculation Engine for Clinical Investigations with Proton and Carbon Ion Beams at CNAO," *Cancers 10,* p. 395, 2018.

[29] J. Schuemann, S. Dowdell, C. Grassberger, C. H. Min, and H. Paganetti, "Site-specific range uncertainties caused by dose calculation algorithms for proton therapy," *Phys. Med. Biol. 59,* pp. 4007-4031, 2014.

[30] The Particle Therapy Cooperative Group (PTCOG), Particle Therapy facilities in clinical operation, https://ptcog.ch/index.php/facilities-in-operation.