Prototyping of a Proton Computed Tomography System for Treatment Planning and Real-time Monitoring of Dose Deposition in Particle Therapy

A proposal submitted to Bergen Research Foundation for strengthening the research and education consortium in medical physics and technology in Bergen

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Project duration	4 years
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Abstract

In October 2012, the Minister of Health and Care Services initiated a National planning project for preparations for particle therapy in Norway. In September 2013 the Ministry of Health and Care Services (HOD) instructed the boards of all the 4 Norwegian health regions to start preparations for implementation of particle therapy in each health region with the aim for clinical startup around 2020-22. The HOD outlined a regional model for proton therapy carried out at the main regional university hospitals in Oslo, Bergen, Trondheim and Tromsø respectively. An option with a future national carbon ion therapy facility was also included in the 2013 HOD outline for particle therapy in Norway.

Thus, Haukeland University Hospital (HUS) is presently planning the establishment of a regional proton therapy center in Bergen while not loosing sight of the possibility of also incorporating a national carbon ion therapy facility at HUS. The facility is expected to be operational within the next 5-6 years, leaving a time window of about five years that is to be used for gaining the required expertise in the field of particle therapy.

The objective of the current proposal is to strengthen regional research, education and innovation within the fields of medical physics and technology by including HiB in the established HUS-UiB consortium in these fields. This facilitates a broader approach to the required technology and to implementing future solutions to particle therapy generated challenges through science and engineering performed at UiB and HiB. The consortium will benefit from the existing national and international collaboration partners at each institution.

In order to include HiB into the UiB-HUS consortium in a timely and effectively fashion, a research project on the development of a prototype proton computed tomography (CT) system for treatment planning and real-time monitoring of the beam position in particle therapy, is proposed. The research objective and the related activities have due overlap with ongoing projects at UiB and HUS. One example of this is the 3D microdosimetry project at Department of Physics and Technology at UiB, recently funded by Bergen Research Foundation and UiB. The activities proposed in this project will be aimed to both enhance the effort in existing projects and to broaden the regional platform for research and development within particle therapy. The complementary nature and integration of the ongoing and proposed activities is seen as a key component in the establishment of the consortium. Coordinated research at UiB, HiB and HUS will serve as an important basis both to provide the desired scientific results and also to strengthen the research and educational activities related to medical technology at HiB, in particular within the fields of electrical and electronic engineering and software engineering.

In addition to the complementary science - engineering approach, inclusion of HiB in the HUS-UiB consortium will increase the total volume of the activity to a level that would be difficult and perhaps not possible to achieve for UiB alone. In addition HiB will also add experience from industrial gamma-ray tomography to the activity. Further, HiB's strategy is to strengthen the bridge between fields of engineering and health in general by introducing medical technology (diagnostics and therapy), to the curriculum of the engineering students. This will benefit HUS within (and beyond) particle therapy so that the result of the proposed project will be a larger competence base in Bergen on bachelor-, master- and PhD level. This will add value to Bergen's position within particle therapy.

1. Introduction

Radiation therapy using particle beams, i.e. protons and lighter ions such as ^{12}C (carbon) beams, is emerging as a frequently utilized cancer therapy modality. This is a direct consequence of the fact that radiation therapy with particle beams is known to be superior to more conventional X-ray based radiation therapy as charged particles deposit lower doses in the entrance channel and exhibit a steep increase and a sharp fall-off of the deposited dose towards the end of their range in tissue, i.e. the Bragg peak. Thus, irradiation of a patient using charged particles has the potential to deposit a lethal dose to a tumor whereas at the same time, the dose to the surrounding healthy tissue can be reduced significantly [1,2]. The significant difference between the dose deposition characteristics of X-ray, proton and carbon beams is also illustrated in figure 1.

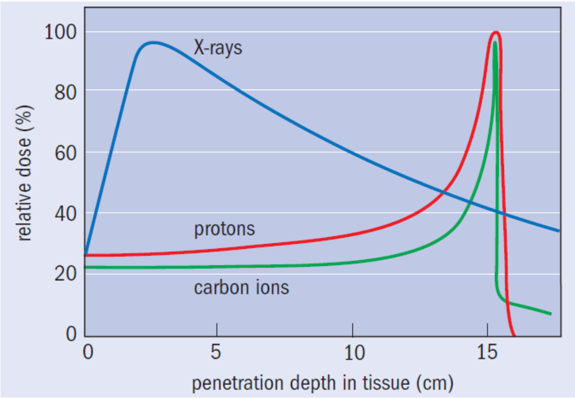

Figure 1. Depth-dose profiles of X-rays, protons and carbon ions in tissue [3].

As shown in figure 1, X-rays deposit a significant dose just below the surface of the structure they penetrate with significant doses deposited also beyond a given target area. On the other hand, protons and carbon ions exhibit a much more favorable depth-dose characteristic curve with most of the dose deposited in a limited area under the Bragg peak. The depth of the Bragg peak is determined by the initial energy of the particle beam for a given material.

Within radiation therapy, the ultimate goal is to minimize the radiation dose to healthy tissue and to maximize the dose to tumorous tissue to reduce the risks of secondary tumor growth following the treatment. This is an important issue with respect to increasing the reliability and robustness of radiation therapy, especially in pediatric patients. Thus, the above mentioned characteristics of charged particle beams make them an attractive alternative to conventional therapy by X-rays. However, the depth-dose characteristics of charged particle beams, i.e. the sharp increase and fall-off of the deposited dose in tissue, necessitates accurate measurements and monitoring of the beam range and the position of the Bragg peak to exploit the full potential of the particle beam therapy modalities. Even small uncertainties in the calculated beam range or the estimated position of the Bragg peak may translate into insufficient coverage of the tumor volume and unwanted dose to healthy tissue.

In light of these observations, efforts are underway also in Norway for the establishment of regional proton beam therapy centers with the possible addition of a national carbon ion therapy center; the decision for the initiation of regional proton therapy centers being made in 2013 [4]. One of these centers will be located in Bergen and this will have an estimated clinical start-up within the next 5 years. There is a significant need to build-up necessary competence in the pertinent particle beam therapy modalities and the use and development of related technologies both at a regional and national level. Considering the case of Bergen, this goal can be achieved through relevant research and development efforts with a solid research and educational consortium among key regional institutions; including the University of Bergen (UiB), Bergen University College (HiB) and Haukeland University Hospital (HUS). Therefore, the present proposal has the twofold objective:

1. Establishment of a regional research and education consortium among the three key regional institutions; UiB, HiB and HUS, aiming at enhancing the capabilities and competence with relevance to medical physics and in particular, within particle beam therapy at each institution.

2. Initiate and support research and development efforts with focus on measurements of the position of the Bragg peak, i.e. the distribution of dose deposition for treatment planning and real-time monitoring of dose deposition and beam position through the development of a proton computed tomography (CT) system and auxiliary equipment for real-time dose deposition measurements.

The current proposal is organized such as to give a brief description of the proposed development of the proton CT system. Next, a section is devoted to the description of the proposed research and education consortium followed by a project summary, a brief implementation plan showing the main activities and milestones of the project and the proposed budget.

2. Proton CT for treatment planning and real-time monitoring of dose deposition

The common practice as a first step within treatment planning and dose calculations for particle beam therapy has up to now been the use of conventional X-ray CT where images of the patient obtained through X-ray CT scans are used to define the gross tumor and clinical target volumes (GTV and CTV) as well as organs at risk (OARs) [1]. For treatment planning and dose calculations in particle beam therapy, the attenuation maps obtained through X-ray CT need to be converted into stopping power values in tissue to be irradiated as stopping power is the single most important parameter that determines the overall range of charged particles in tissue, i.e. the position of the Bragg peak [2]. However, the use of X-ray CT for dose calculations and treatment planning is an inherently inaccurate approach due to fundamental differences in physical interactions of protons and photons with tissue [5]. Thus, ideally, it would be most appropriate to obtain the tissue stopping power values directly using a computed tomography system based on measurements of pertinent particle beams.

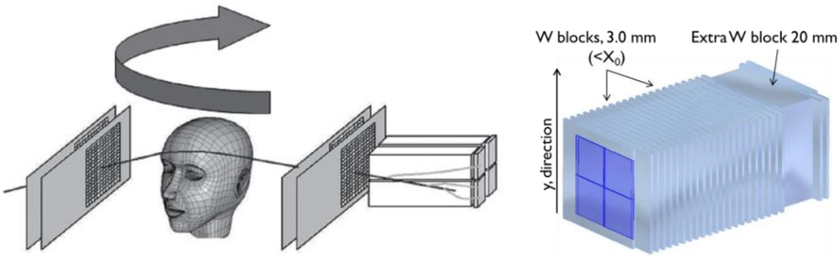

Figure 2. Left: A schematic of the concept of proton CT for clinical applications showing two tracker planes upstream of the patient and another two downstream of the patient in addition to an energy detector where incident protons are stopped and their residual energies are measured[1]. Right: The current geometry of the digital tracking calorimeter prototype [6].

For proton therapy, the use of proton CT has been proposed [7, 8]. Proton CT relies on the use of high energy protons that can penetrate the patient and detection of these downstream of the patient on an individual proton basis. For a successful utilization of a proton CT for the reconstruction of stopping power maps in the volume of interest, it is necessary to track the most probable path traversed by the individual protons through the patient as well as knowing their initial position and energy and detecting their position and residual energies on the distal side. Figure 2 (left) summarizes the general concept of proton CT.

Generally, the accuracy of the position measurements should be better than the image pixel size, i.e. better than about 1 mm whereas the accuracy of the measurements of the residual energies of protons should be better than about 1% [8]. Position measurements with sub-millimeter accuracy and measurements of residual energy with accuracy better than 1% are not trivial tasks. For the position measurements, silicon strip detectors used as vertex detectors in high-energy physics have been proposed whereas crystal calorimeters are proposed for energy measurements [1, 8]. However, routine clinical applications of these systems are yet to be realized as there is still a need for research towards faster and more accurate measurements of the position and residual energy of protons.

In addition, a major advantage of proton CT is reported to be the reduction of imaging dose by a factor of 10-20 as compared to X-rays [2]. Proton CT systems can also provide important real-time feedback on the beam range in the patient through detection of protons scattered out of the incident beam as well as energetic secondary particles produced in nuclear interactions. Reconstructed secondary or primary particle tracks can be extrapolated back to their origin allowing on-line monitoring of beam size and position [1, 9]. Also, primary beam energy and intensity can be monitored in this way.

The nuclear physics group at UiB has had significant activity within development of proton CT for treatment planning and dose calculations for radiation therapy with protons in collaboration with HUS. The focus has been on the use of a high granularity digital forward tracking calorimeter originally developed as a possible upgrade to the ALICE detector at CERN in collaboration with the University of Utrecht (UU) [10]. This is a sampling calorimeter consisting of 24 alternating layers of 120 um thick silicon sensors and 3 mm thick tungsten absorbers. A schematic of the current geometry is given in figure 2 (right). To achieve the required high granularity, the use of CMOS pixel sensors with digital readout is considered. In recent MSc theses, the individual particle tracking capabilities as well as energy resolution of the calorimeter in a proton CT context have been investigated through MC simulations and experiments with promising results [11, 12]. The use of the pertinent calorimeter represents a novel development within proton CT as it combines energy measurements with tracking capabilities. The previous work [11, 12] concludes the proof-of-principle studies of the calorimeter as well as the conceptual design of a clinical prototype. Further work is, however, needed before a final design with potential clinical applicability can be developed.

This project focuses on; (a) verification of the key estimates from the previous design studies through the development of a dedicated clinical prototype of the digital sampling calorimeter for proton CT measurements and (b) MC studies toward the design and development of a clinical imaging system utilizing the prototype calorimeter also for real-time proton beam range monitoring. One of the main goals of the project is to ensure substantial increase in the research and development activities with regards to the planned proton therapy center in Bergen. More importantly, it will form the basis to initiate the consortium among UiB, HiB and HUS for research and education toward the upcoming center and medical physics in general.

In close collaboration with UiB, HUS and UU, it is proposed to design and develop a small scale, clinical prototype device utilizing four sensors already made available to the project. The energy resolution of the detector impacts the density resolution of images reconstructed using proton CT systems whereas the tracking resolution will have a direct impact on the spatial resolution. The tungsten layers of the existing prototype lead to a degradation of both the energy resolution and the tracking resolution. A new updated version of the detector with fewer layers will be constructed using aluminum or polymethyl methacrylate (PMMA) as the absorber layers. For the development of the readout circuitry, existing expertise at UiB will be required. Existing detector readout architecture can be applied for the proposed device whereas the focus will be on increasing the readout cycle frequency and also to reduce the amount of raw data required [13]. During the initial design stage, Monte Carlo (MC) simulations of radiation transport through relevant media and geometries will be required. MC simulations provide a degree of flexibility to disentangle the relevant parameters that may be difficult and, in many cases, impossible to achieve through experiments alone. The PI's experience with general purpose as well as specific purpose MC simulation software will be required for providing the necessary progress in the project. MC simulations will be performed to determine the optimal detector configurations. Based on the results of MC simulations, a prototype device will be constructed. Further beam tests of the device will be performed to determine the tracking and energy resolutions experimentally. It is foreseen that the beam tests can be carried out at proton treatment facilities with which the project partners have established contact; these include CNAO in Pavia, Italy, and the Svedberg Laboratory in Uppsala, Sweden. Data from MC simulations of the detector will be compared with experimental data. This represents benchmarking of the MC simulations. In addition, the experimental and MC data will be used to verify the parameter estimates previously obtained on the conceptual design of the prototype device.

Furthermore, the MC simulations will be performed for the technical design of a clinical system. This spans challenges related to image reconstruction as well as real-time monitoring of the incident beam position and size. Benchmarked MC simulations can be used to generate data on proton CT scans of various phantoms to study image reconstruction algorithms taking also into account the curved internal paths of protons [14]. Depending on the availability of beam time, the intention is to also perform proton CT scans of phantoms of known geometry and density to establish the spatial and density resolution that can be expected from such a system. In addition, the real-time monitoring of the beam position can be achieved through measurements of large angle scattered primary protons or secondary particles produced in nuclear interactions. Especially in the case of carbon ions, correlation between secondary fragments and the primary beam have been studied through experiments and MC simulations whereas more work is needed to show the feasibility of this approach for proton beams [9]. Initial studies will be initiated through MC simulations. Making assumptions on the performance of the detector system and through MC simulations, questions related to the accuracy with which incident beam position and size can be reconstructed, the degree of correlation with incident beam intensity and energy can be answered to a first approximation. MC simulations can also be used to estimate the design parameters such as the timing requirements of such a system through simulations of time-of-flight (TOF). Finally, relevant experiments can be performed at existing proton and ion therapy facilities when a device is ready to be tested. The results of these experiments can also be used to benchmark MC simulations which are known to show some deviations from experimental distributions especially at large angles [15].

3. The triangular collaboration

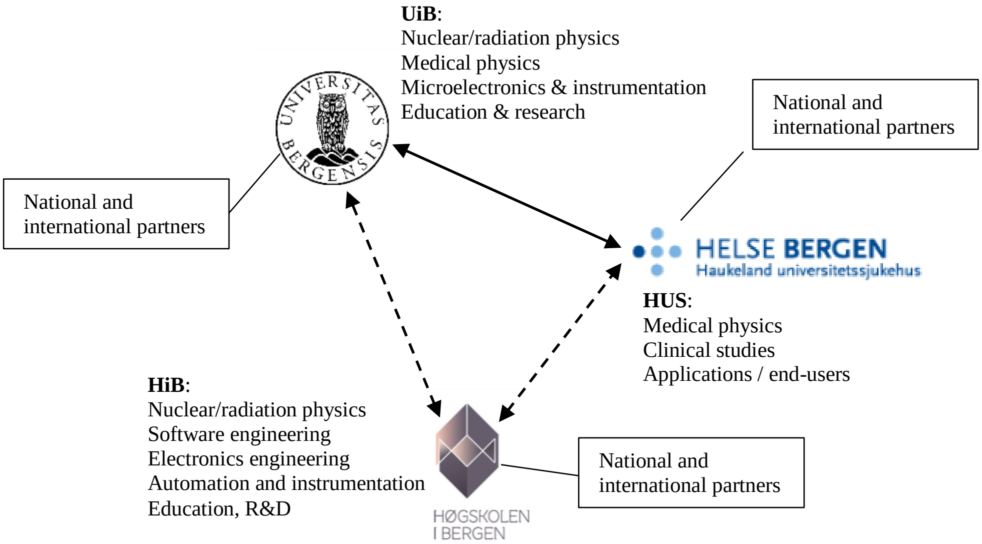

Figure 3. A diagram of the triangular collaboration among UiB, HiB and HUS forming the core of the proposed research and education consortium. The existing ties between UiB and HUS and the proposed contribution from HiB are shown explicitly (the solid and dashed lines). The arrows indicate the mutual exchange of knowledge and expertise. Note that HiB readily collaborates with UiB and HUS in other fields whereas collaboration within particle therapy is yet to be realized.

The proposed project is seen as a unique opportunity to combine the existing knowledge and expertise within the three institutions in a complementary manner to achieve the above objective. In this regard, combination of dissimilar traditions found at these three institutions should be seen as a mechanism through which identification of new synergies is made possible. Such an extensive collaboration will be of utmost importance with respect to enhancing capabilities and knowledge building. A diagram of the proposed triangular collaboration is given in figure 3 emphasizing also the existing ties between UiB and HUS and the proposed contribution from HiB; also given in the figure are the complementary expertise areas at each institution. The arrows in figure 3 indicate the mutual exchange of expertise and knowledge within the consortium with extensions to include national and international partners.

HiB will benefit from the existing expertise and knowledge within medical physics and particle therapy at UiB and HUS. The proposed project will further utilize the existing expertise and knowledge within industrial radiation and radioisotope measurement systems and MC simulations at HiB as these complement the areas of expertise at UiB and HUS. The proposed project has some overlapping aspects with the ongoing activities at UiB and HUS, one of which is funded by the Bergen Research Foundation [16, 17]. This is a clear advantage as these aspects will allow integration of proposed activities into the existing ones at UiB and HUS. The activities proposed in this project complement the existing ones. The complementary nature of these ongoing and proposed activities is seen as a key component in the establishment of the consortium. The consortium will also take advantage of the current national and international partners of each institution where deemed necessary for both research and educational purposes. The three Bergen based institutions will, however, form the core of the consortium at any given time.

The education aspect of the project is of high priority as education of technical personnel and engineers with proper background and skills within medical technology will be of crucial importance for ensuring proper operation of the planned facility. Also, increasing medical physics activities will necessarily imply an increasing demand for engineers within medical technology. Ensuring a sustainable supply of engineers and technical personnel with the proper background in the field will also help reduce Bergen's dependence on the required expertise from abroad or other regions within Norway. At this initial stage, the educational aspect will be accounted for through seminars and workshops organized at HiB with the aim of introducing engineering students to the concepts of proton beam therapy and other aspects of medical physics where the results and status update on the proposed proton CT activities will also be presented. These seminars will be to a greater extent organized in collaboration with scientists and other relevant personnel from UiB and HUS. Through these seminars and workshops, students will be encouraged to enroll in an MSc program within medical physics and technology offered at the Department of Physics and Technology (IFT) at UiB. Overall, the project activities will be an important component of the ongoing planning of the joint MSc program between HiB and UiB within medical technology with focus on bringing the engineering aspect into a theoretical medical physics teaching environment and vice versa.

4. Project summary

Radiation therapy using particle beams such as protons and carbon ions is emerging as an invaluable alternative to conventional radiation therapy with X-rays. This is mainly due to the fact that particle beams have the potential to deposit much of the prescribed dose in the tumorous regions whereas the dose to healthy tissue is reduced significantly. Motivated by these observations, the commissioning of a proton therapy center in Bergen located at HUS is being planned. It is anticipated that the facility would be operational within the next 5-6 years. This time window is crucially important to enhance capabilities and competence with relevance to medical physics and in particular, within particle beam therapy. Therefore, the objective of the project at hand is twofold. Firstly, research on the development of a proton CT system is proposed where research collaboration among UiB, HiB and HUS will be crucial. Proton CT systems will be an important component of proton therapy centers as these will allow accurate treatment planning and dose calculations. The results of this work will be published in scholarly journals, popular science journals, PhD theses and presented at relevant conferences. Secondly, the project has focus on establishment of a regional research and education consortium among the three key regional institutions; UiB, HiB and HUS, with the aim of enhancing the capabilities and competence with relevance to medical physics and in particular, within particle beam therapy at each institution. A goal of the consortium will be education of engineers and technical personnel within medical technologies. Students at both UiB and HiB will be made well aware of the consortium activities and encouraged to pursue medical physics and technology studies. This will be achieved through seminars and workshops where also the results of research activities related to proton CT will be disseminated.

5. Activities and milestones

			2016				2017				2018				2019		
Activity	Milestone?	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Employment of PhD 1	No																
Initial MC design study	No																
Design parameters set	Yes																
Design and development of readout circuitry	No																
Employment of PhD 2	No																
Assembling detector components	Yes																
Beam tests for detector characterization	No																
Detector characterization	Yes																
Evaluation of image reconstruction algorithms	No																
Initial MC simulations for beam range monitoring	No																
Laboratory tests for beam range monitoring	No																
Analysis of laboratory data	Yes																
Beam tests for beam range monitoring	No																
Reporting / PhD theses	Yes																
Seminars / workshops	No																

6. Proposed budget

Type of costs	2016	2017	2018	2019	Sub-total [1000 NOK]
Doctoral fellowships	1 004	2 078	2 140	2 200	7 422
Grants for overseas researchers	-	120	120	120	360
Researcher positions	1 004	1 039	1 070	1 100	4 213
Hourly-based salary including indirect costs	504	521	539	558	2 122
Procurement of R&D services	200	400	200	218	1 018
Equipment	400	600	1 000	-	2 000
Other operating expenses	300	300	300	300	1 200
Total	**3 412**	**5 058**	**5 369**	**4 496**	**18 335**

7. Proposed funding plan

Type of costs	2016	2017	2018	2019	Sub-total [1000 NOK]
Bergen Research Foundation	1 904	3 498	3 760	2 838	12 000
HiB doctoral fellowship	604	1 039	1 070	1 100	3 813
HiB in-kind (professors and engineers)	504	521	539	558	2 122
HiB equipment	400	-	-	-	400
Total	**3 412**	**5 058**	**5 369**	**4 496**	**18 335**

In addition, attempts will also be made to attract funding from public national and international sources during the project period - in collaboration with UiB and HUS.

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