Medical projects

Deep Learning Methods for Uncertainty Quantification in Proton Therapy (BEP)

Proton therapy is a promising method of radiotherapy in cancer treatment. One of the challenges in its most efficient application in practice is the inherent sensitivity of proton dose deposition in patients due to unavoidable uncertainties present during the treatment (such as proton range, patient positioning or organ motion errors). Thus, it is essential to accurately quantify the effects of such inaccuracies in a computationally feasible, preferably real-time fashion.

A promising method to do so is by utilizing reduced order modelling (ROM) methods and neural networks (NN). Reduced order modelling can capture the dominant modes in which uncertainties affect the dose distribution, while NNs can explore the connection between the errors and the strength of the different modes. Our group has recently demonstrated that such approaches are attractive, as a few modes can encode most of the error effects and simple neural networks can predict the low order ROM coefficients accurately. However, for the higher order coefficients (required for more complex errors and increased accuracy), the prediction by simple 2 layer neural networks breaks down, leading to inaccurate results. This project aims to employ deep learning methods to improve the prediction of higher order ROM coefficients, thus improve the coupled ROM-NN approach and the quantification of uncertainties in proton treatments.

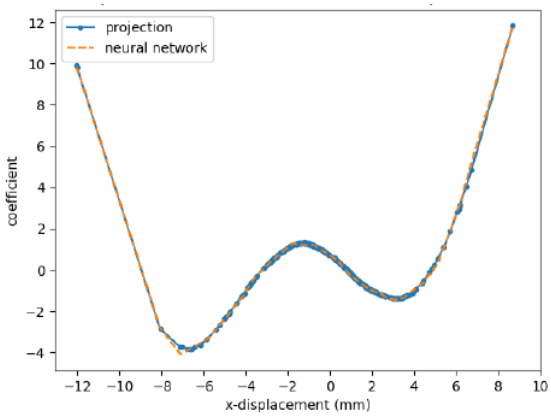

Figure 1 - Neural network prediction of low order ROM coefficient of dose distribution changed. The prediction is practically perfect.

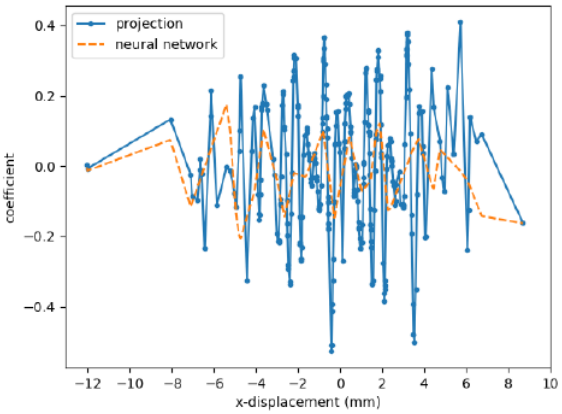

Figure 2 - Neural network prediction of higher order ROM coefficient. As the coefficients get more and more osciallatory, the NN prediction accuracy breaks down.

Info: Dr. Zoltán Perkó, **email:** Z.Perko@tudelft.nl

Uncertainty Quantification Methodologies for Monte Carlo Proton Dose Calculations (BEP)

Proton therapy is a new form of radiotherapy that can irradiate cancerous tumours with less side-effects than traditional photon therapy. Proton's special physical properties allow highly conformal irradiations, however this comes at the cost of high sensitivity to unavoidable uncertainties, such as patient alignment errors, anatomical changes or dose computational inaccuracies. Consequently, analysing the effects of uncertainties and ensuring that proton treatments are sufficiently robust against them is a key priority.

In clinical practice, proton dose distributions are typically calculated using “pencil-beam” algorithms. These methods are deterministic and fast; however, their accuracy is limited, especially in regions where large heterogeneities are present (e.g., a bone next to air filled lung tissues). Consequently, more accurate Monte Carlo (MC) dose engines are increasingly being employed. MC calculations can correctly handle heterogeneities; however, they are computationally expensive. Moreover, their results are stochastic, meaning that calculating the dose for the same patient twice results in slightly different dose distributions.

The aim of this project is to develop methods for the accurate and effective quantification of uncertainties in Monte Carlo proton dose calculations. The focus will be on two aspects. The first challenge is that since MC calculations are stochastic, it is difficult to separate variations caused by parametric uncertainties (e.g., an actual change in patient position) from the inherent MC variation. The second challenge is that very little is known regarding the effects of numerous decisions that must be made when setting up an MC proton dose calculation, such as the choice of voxel size or the particle step size. When successful, answering these two fundamental questions can directly improve clinical practice by providing treatment planners the currently missing knowledge about how to ensure the highest accuracy possible.

Info: Dr. Zoltán Perkó, Dr. Jeremy Brown, **email:** Z.Perko@tudelft.nl, J.M.C.Brown@tudelft.nl

Adjoint Methods for Beam Angle Selection in Radiotherapy (MEP)

Radiotherapy treatment planning is a high dimensional, complex multi-criterial optimization problem, where sophisticated algorithms are intensively used to derive the best treatment for each patient. While most of this process is highly automated already, the selection of the irradiation beams is still a largely manual procedure, which is based on clinical experience as well as the experience of the treatment planners. At the same time, the beam angle has a fundamentally important role in the quality of the derived treatment plan, thus finding the best angles is highly significant.

In this project adjoint methods will be investigated to reach this goal. Adjoint techniques are intensively used in neutron transport, but they are equally applicable to all radiation transport problems encountered in radiotherapy. The huge advantage of adjoints is that they allow deriving “importance maps”, signalling how strongly different parts of the phase space contribute to a response of interest. Thus, defining such response as the overall quality of the plan, adjoint techniques hold the promise of enabling a computationally cheap, yet accurate determination of the best beam angles, which could significantly improve current treatment planning approaches ultimately.

Info: Dr. Zoltán Perkó, Dr. Danny Lathouwers, **email:** Z.Perko@tudelft.nl, D.Lathouwers@tudelft.nl

Handling Delineation Uncertainties in Radiotherapy (MEP)

Radiotherapy (RT) is a dominant treatment modality for cancer, with more than 50% of patients receiving radiation treatments throughout their disease. Typically, radiation treatments are delivered in so called fractions, i.e. daily treatments over the course of several weeks. To ensure the best chance for cure without causing detrimental side effects, irradiations are planned in a complex, time consuming process known as treatment planning, ensuring that the treatment plans are personalized for every patient. This process starts with a high quality CT/MRI image of the patient, providing the basic information about the internal anatomy, such that the radiation can be aimed at the tumor

avoiding healthy organs as much as possible. To do so, the CT/MRI images have to be delineated, meaning that a medical professional has to draw contours on each image slice to annotate which parts of the image belong to which organs and structures.

This delineation process is of pristine importance, as the resulting treatment plan heavily depends on it. Yet, delineation is also the source of significant uncertainties. There are two major sources. First, CT/MRI images typically only show the visible tumor, known as the Gross Target Volume (GTV), whereas it is also known that invisible, microscopic extensions of the tumor are also typically present beyond the boundaries of the GTV. To account for these, the standard practice is to irradiate a larger, so called Clinical Target Volume (CTV), which contains the GTV with some margin around it. However, since there is little information about the exact spread of the microscopic disease, determining margins is difficult and is subject to significant inter-observer variability. Second, current RT trends increasingly favour adaptive treatments, where the irradiation plan is adapted each day to the exact anatomy of the patient on that day. Such adaptive treatments however necessitate the quick imaging, delineation and re-planning of treatments, which is infeasible with standard manual planning methods within the short available timeframe. Thus, automation is key, and one aspect of automated plan adaptation is the quick, algorithmic delineations of organs on the daily CT/MRI images, based on the previous delineated images of the patient. This process - known as contour propagation – however is also subject to non-negligible uncertainties which need to be accounted for.

This project aims at developing appropriate computational methods to analyse the effects of these 2 main sources of delineation uncertainties. We will expand our unique methodology for handling positioning and range uncertainties, as well as develop new methods specifically for the simulation of delineation uncertainties. Subsequently, the effects of these uncertainties on real patient treatment plans will be evaluation, and ultimately the effectiveness of robust optimization methods will be studied to ensure successful treatment under delineation uncertainties.

Info: Dr. Zoltán Perkó, Dr. Danny Lathouwers, **email:** Z.Perko@tudelft.nl, D.Lathouwers@tudelft.nl

Neural network based reduced order modelling for proton therapy applications (MEP)

Proton therapy is a new form of radiotherapy that has the ability to accurately deliver dose to the tumor, with much less dose to healthy tissues than traditional radiotherapy using photons. This high dose conformity however also makes proton treatments very sensitive to uncertainties, which are always present during the treatment. To counteract this sensitivity, so called robust treatment optimization can be used that takes into account possible error scenarios in the planning process itself, ensuring plan quality under uncertainties.

For proper accounting of the uncertainties however many such error scenarios need to be considered, which necessitates fast dose calculation methods for these deviations from the nominal circumstances. We have recently demonstrated that Reduced order modelling (ROM) methods are an attractive approach to achieve this goal, since the change in the dose distribution is highly correlated, making it possible to reduce model complexity. Such ROM models can be built by calculating the dose under different error scenarios, constituting a training set, then performing a singular value decomposition (SVD) to find the most important modes of change. Since these eigenmodes are orthogonal however, the dependence of their presence in any given scenario is an increasingly oscillatory function of the input errors. Thus, this project focuses on a different approach by using auto-encoder neural networks

to build ROM models. Since neural networks allow highly non-linear mapping from inputs to outputs, it is expected that they can outperform the SVD based approach which yields a linear model.

Info: Dr. Zoltán Perkó, **email:** Z.Perko@tudelft.nl

In vivo efficacy study of irradiation dose rate effects in Zebrafish (MEP)

The primary mechanism of radiotherapy is to induce cell death at a faster rate in cancerous cells than in non-cancerous cells. This differential effect was traditionally achieved by geometrical sparing and fractionation, i.e. giving the treatment over the course of weeks. Recently however, due to improved geometrical sparing, the rationale for fractionated radiotherapy is increasingly being re-evaluated. Hypofractioned treatments, with only 3-20 fractions, are used routinely in the clinic. The latest idea in this paradigm is FLASH radiotherapy, suggesting giving ultrahigh dose-rate treatments in a matter of seconds. While some rodent experiments show promising results, further experimental validation is needed, for which Zebrafish may be ideal.

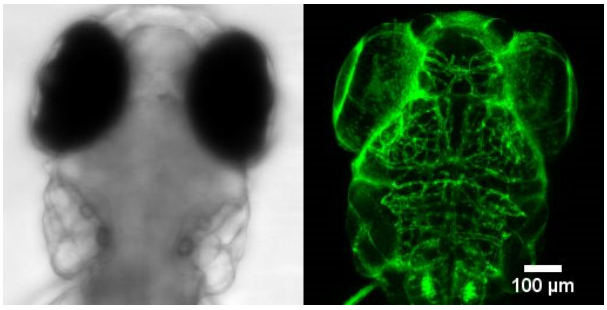

Figure 3 - Left: Brightfield image of 5 day of zebrafish head. Right: Intravital fluorescence image of blood vessels expressing GFP

Zebrafish present a novel small animal model for investigating the biological effects of radiation exposure. Relative to rodent models, zebrafish have high fecundity (spawning hundreds of eggs) and lower cost (1 euro per fish vs 60 euro per mouse). Vertebrate physiology and small size make zebrafish embryos particularly attractive for high-throughput pharmacological and toxicological screens. Optical transparency and ability to genetically introduce fluorescent labels, make zebrafish an increasingly popular vertebrate model for organogenesis, haematopoiesis, immunology, and developmental biology. Zebrafish cancer models are currently used for research on tumor development, cancer genetics, and drug discovery.

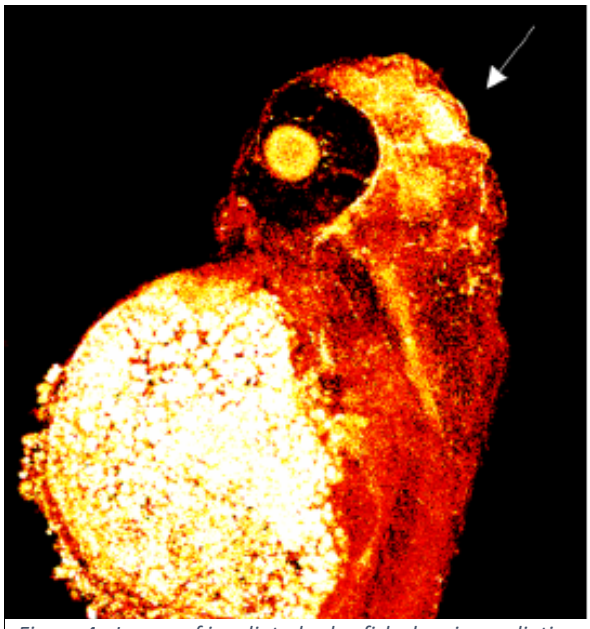

Figure 4 - Image of irradiated zebrafish showing radiation damage in the brain

The goal of this MEP project is to continue our pilot study to explore the radiobiological effects of different irradiation dose rates, and establish a basis for future radiotherapy experiments with the use of Zebrafish. The study will be performed to test the effects of high and low dose-rate irradiations in zebrafish embryos, as assessed by a combination of intravital imaging and analysis of tissue damage.

We are looking for a highly creative, enthusiastic student with both good experimental and computational skills, who is interested in designing and building an experimental setup from almost scratch, as well as performing and evaluating measurements with his/her own device.

Info:

Dr. Zoltán Perkó, Z.Perko@tudelft.nl (Radiation Science & Technology), Dr. Elizabeth Carroll, E.C.M.Carroll@tudelft.nl (Imaging Physics)

Optimization methods for combined chemo-radiotherapy treatments (MEP)

In cancer treatment, chemotherapy and radiotherapy both play fundamental roles, either as standalone modalities, or - in many cases - in combination. For *planning radiotherapy treatments*, the development of sophisticated computational models and computer algorithms has long been a focus to *maximize the therapeutic effect* of using radiation to kill tumor cells, while sparing healthy tissues as possible. Comparatively, the *modelling and optimization of chemotherapy treatments* is largely unexplored, while the clinical application of algorithmic planning methods for individualized chemotherapy is practically non-existent. Similarly, *combined chemo-radiotherapy treatments* are routinely prescribed as a separately optimized radiotherapy treatment with the addition of generic chemotherapy regimen.

The goal of this project is to explore *optimization methods to aid the planning of single modality chemotherapy and combined chemo-radiotherapy treatments*. We will build on our previous work regarding the optimal dosage of a set of chemotherapy drugs to control heterogeneous tumors (consisting of multiple species of cancer cells having varying drug resistance, mutation rate and spatial migration rate) and preliminary results from optimizing combined chemo-radiotherapy treatments (investigating different formulations and algorithms). Focus will be on extending the developed algorithms to better take into account the interplay effects between chemotherapy and radiation therapy, and testing the performance of different algorithms on experimental and/or clinical data.

Info: Dr. Zoltán Perkó, **email:** Z.Perko@tudelft.nl

Probabilistic treatment planning for clinical target volume uncertainties in radiotherapy (MEP)

Radiotherapy (RT) is primary treatment option for the majority of cancer patients. To achieve the best outcome, it is essential to irradiate all cancer cells sufficiently, without overdosing healthy tissues causing decreased quality of life due to side effects. One of the main sources of uncertainties in the planning of all RT treatments is that on the CT images typically used to plan irradiations, only gross tumors are visible, while it is well known that small microscopic tumor extensions are also present outside the bulk tumor. The traditional approach to account for this is to extend the gross tumor with a fixed margin, and consider this bigger volume (called the clinical target volume or CTV) as the true target of the treatment.

This project focuses on improving the definition of the clinical target volume by correctly taking into account the uncertainty of the tumor extension. By treating the margin of the tumor extension, as well as the tumor cell densities as random variables or as random fields instead of fixed values, we will formulate the treatment optimization problem in a probabilistic sense, optimizing the expected values or other probabilistic metrics. The research will include both searching for the best problem formulation and algorithmic solution approaches, as well as the practical application and clinical performance of the developed methods. This project is a collaboration between Erasmus Medical Center and Delft University of Technology, and the student will split their time between the institutes.

Info: Dr. Zoltán Perkó, Dr. Danny Lathouwers, **email:** Z.Perko@tudelft.nl, D.Lathouwers@tudelft.nl

Use of machine learning for quality control of radiotherapy treatment planning (MEP)

The departments

Radiotherapy uses ionizing radiation to irradiate tumour tissue to a high dose while sparing the surrounding normal healthy tissue as much as possible. The cluster radiotherapy of the Antoni van Leeuwenhoek hospital uses the most modern techniques to irradiate its patients. Due to the synergy between clinic implementation groups and medical physics research, we are able to quickly implement state of the art techniques in daily clinical practice. Because of this, the Antoni van Leeuwenhoek hospital belongs to the (inter)-national forefront of clinical radiotherapy.

The Radiation Science and Technology department of TU Delft is specialized in ionizing radiation and its medical use (among others). In the Medical Physics and Technology section we specifically focus on developing fundamentally novel computational methods and algorithms to improve treatment planning supporting state-of-the-art of radiotherapy practice. Close collaboration with the Antoni van Leeuwenhoek hospital, Erasmus Medical Center and the new Holland Proton Therapy Center ensures fast practical implementation of our work.

Knowledge based treatment planning

A key step in the radiotherapy process is treatment planning where, before treatment, an individualized irradiation plan is optimized for each patient. This optimization is typically a time consuming, iterative, manual process. In order to streamline the workflow, we are actively working on the full automation of this process.

This brings however new challenges: How do we know that the automatically generated treatment plan is the best possible treatment (in terms of dose delivered to the tumour, while sparing the healthy tissue) for the particular patient? In order to resolve this question we are working on an approach known as knowledge based planning (KBP). In this approach a database of patients treated in the past is used to predict the best dose distribution for the new patient at hand. This prediction is based on geometrical information of the patient - like volume of the tumour and the distance between the tumour and the organs at risk – and machine learning algorithms that correlate the optimal dose distributions with the geometrical information.

The project

In this collaborative project you will work on improving the prediction models for prostate cancer treatment using a variety of machine learning methods, including support vector machines and random forests. You will extend our currently used set of geometrical input parameters, with the aim of making a clinically applicable decision on the quality of the individual, automatically planned treatment plan. Apart from the application of machine learning to treatment planning, you will have the opportunity to experience daily practice at a medical physics department with a strong focus on research and innovation.

Interested?

For further information please contact dr. Tomas Janssen, Medical physicist, +31 (0)20 512 2164, t.janssen@nki.nl or dr. Zoltán Perkó, z.perko@tudelft.nl.