BioDate 2018 MSc Project Proposal

Optimal control of combined chemo-radiation therapy treatments for improving cancer care

Researcher #1	Researcher #2
Name: Zoltán Perkó	Name: Giulia Giordano
E-mail: Z.Perko@tudelft.nl	E-mail: G.Giordano@tudelft.nl
Department/Faculty: TNW/RST	Department/Faculty: DCSC/3mE
Expertise for the Project: Treatment planning, radiotherapy fractionation and chemotherapy modelling	Expertise for the Project: Systems and control theory, dynamical systems, optimal control, optimisation

Introduction. In the treatment of cancer patients, 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. At the same time, cancer treatments advance in numerous aspects, such as the increasing use of significantly shorter treatments (e.g. 5 treatment fractions instead of traditional 30/35 fraction treatments), or our increasing understanding of the importance of drug and/or radiation resistant cell sub-populations in tumor recurrence.

Scientific challenge. The main goal of this project is to explore how *methods from systems and control theory can aid the planning and optimization of single modality radiotherapy, as well as of combined chemo-radiotherapy treatments*. While some preliminary work exists in pure chemotherapy application, 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), application to the *temporal optimization of radiotherapy or chemo-radiotherapy* is an entirely new idea. With the growing emphasis on shortening treatments and measuring tumor and normal tissue response (by quantitative imaging during treatment), this approach could be vital for *effective treatment adaptation* by choosing optimal times to switch between chemotherapy drugs, or to use radiotherapy in combination or as boosts to certain chemotherapy resistant areas, in order to *achieve tumor control with minimal side effects*.

Specific research plan. As this project aims to *lay down the basics of a completely new research line*, the primary goal is the investigation of how *treatment efficacy can be optimised using control-theoretic methods together with temporal radiotherapy models*, such as the biologically effective dose model and different tumor growth and dose response models, *as well as combined chemo-radiotherapy models*. Different problem formulations will be studied as well as several approaches and algorithms to find their optimal solutions, including Pontryagin's Principle, Hamilton-Jacobi-Bellman equations, and convex and non-convex optimization. For each type of model representing possible combination therapies, the expected outcome is a *systematic approach to suggest clinically viable treatments able to minimize the tumor mass over a finite (time) horizon and minimize the side effects*, by prescribing the optimal starting time and optimal duration of each phase of the therapy.

Student profile. The project offers excellent opportunities for an enthusiastic *math or applied physics student*, keen on both theoretical and numerical work, to perform *interdisciplinary research* and to *learn about current radiotherapy and chemotherapy practices, modelling approaches in medical physics* as well as *optimization methods and approaches from systems and control theory*.

Time planning for the MSc project. *M1-2:* Literature study on radiotherapy and chemotherapy modelling, and on optimal control theory. *M3-5:* Radiotherapy temporal optimization (varying tumor response, growth). *M6-8:* Combined chemo-radiotherapy optimization (additive effects, interplay between chemo and radiotherapy, e.g. radiosensitization). *M9:* Write thesis.

Collaboration benefits and impact. *Integrating state-of-art therapy models* and *control approaches tailored to design optimal treatments is a first step* allowing us to study and demonstrate the benefits of this novel, systematic approach. The *BioDate funding would enable discussing and disseminating the results* of this joint project with the wider clinical research community (e.g. at conferences), *thus initiating a long-lasting collaboration that* combines the complementary expertise of the two groups with practical insight of clinical experts, and *can ultimately improve the life of cancer patients*.