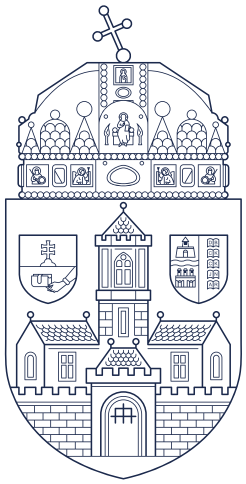
Óbuda University

PhD Thesis summary



Model based control of cancerous diseases

by

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Contents

Nomenclature

DMS Direct Multiple Shooting

FIE Full Information Estimator

IO Input-Output

MHE Moving Horizon Estimation

NMPC Nonlinear Model Predictive Control

PLD pegylated liposomal doxorubicin

RFPT Robust Fixed-Point Transformations

1 Background of the Research

Cancerous diseases pose a significant challenge from a medical perspective in our current society. In 2022, approximately 1.25 million people die from some variant of this illness in the European Union [1]. While the numbers are decreasing due to better screening procedures, there has not been a single effective treatment that can stop the illness completely. The most commonly available treatment options are still surgery, radiotherapy, and chemotherapy. In the case of chemotherapy, the treatment process can often involve side effects which can range from mild symptoms to even severe, life threatening scenarios. Furthermore, drug resistance can occur during the treatment, where the tumor adapts to the effect of a given drug and is no longer sensitive to each consecutive treatment. The objective of the current thesis was to provide individualized protocols for chemotherapeutic treatments, through which these side effects can be mitigated. Individualization of the treatment could also prolong the effectiveness of a given drug which also justifies my current research [2]. Personalized treatment protocols can be attained through using optimal control methods which can account for both the reduction of the tumor and the amount of chemotherapeutic agent that was given to the patient.

Literature on chemotherapy optimization dates back to the beginning of the 1970s. Initial effort was put in the development of simulational models based on in-vitro experiments and first principle assumptions [3]. These models were utilized in the context of optimal control, for example as can be seen in [4]. A survey on the results of the first ten years in the domain of optimal control of tumor growth models can be found in [5]. These initial results heavily relied on explicit formulations of the optimal control problems, without the use of sophisticated numerical solvers. With the development of computational resources, researchers started to use numerical nonlinear optimization algorithms to solve these optimal control problems. Moreover, soft computing techniques, and heuristics were also employed, which, together with the classical approaches, can be found in the survey by [6] and [7]. Some of the most recent results involve the use of Nonlinear Model Predictive Control (NMPC), Moving Horizon Estimation (MHE), and impulsive differential equations as can be seen in [8] and [9]. From a medical perspective, most of the current research focus on the optimization of metronomic chemotherapy, where smaller doses are given to the patient more frequently, as opposed to conventional treatment schemes [10]. Metronomic therapy might also be a viable option to delay (or even avoid) drug resistance during the treatment, as reported in [11].

2 Goal of the current research

Throughout my dissertation, I aimed to solve the optimal control problem for breast cancer treated by pegylated liposomal doxorubicin (PLD). The effect of PLD on the tumor growth was previously modelled in [12] based on experimental data from [13]. The model uses three states that describe the tumor dynamics, pharmacokinetics and pharmacodynamics of the drug, derived using a formal reaction kinetics analogy. The model was further improved in [14] and [15], where an additional compartment was in-

troduced to account for additional effects in the pharmacokinetic model. Using these models, I was able to design various control algorithms that can account for optimality and robustness during treatment. An additional goal was to test and validate the control strategies with in vivo mice experiments, so that the effectiveness of the optimal metronomic based approach can be demonstrated beside numerical results.

In Thesis 1., I investigated the application of the Robust Fixed-Point Transformation (RFPT) based nonlinear control algorithm, which is able to deal with inherent parametric uncertainties during its operation. Moreover, I connected the methodology to the classical Input-Output (IO) linearization scheme to provide a basis for further stability analysis in a general sense. In Thesis Group 2., I have developed various NMPC solutions which can provide an optimal therapy protocol using the previously introduced tumor growth models. In order to account for the personalization of the therapy, I also augmented the design with an MHE, which is also able to estimate the possible time-varying parameters of the model. The Thesis Group also includes a detailed description on the tuning process of both algorithms in conjunction with in silico validation. In Thesis Group 3., I present the in vivo validation of the algorithm through mice experiments.

3 Materials and methods

Two different nonlinear control techniques were used in the dissertation. Initially, the RFPT method was chosen, which was motivated by previous results in dealing with uncertain systems using this algorithm. The second approach was the use of the NMPC, which is a standard technique in nonlinear optimal control. The NMPC was also augmented with an MHE to provide state and parameter estimates for the dynamical model, thus increasing the accuracy of the tumor volume predictions.

3.1 The Robust Fixed-Point Transformations based control approach

The Robust Fixed-Point Transformations based control method originates from the article [16], where the authors developed the algorithm on the basis of classical results in nonlinear control. The core idea of the approach is to eliminate parametric and structural discrepancies, emerging in the theory of IO linearization, via fixed-point iterations. Each consecutive iteration is produced by a so-called *deform function*, which alters the control signal in each time step to the end of retaining the IO linearization of the system. Several different deform function were elaborated in [17, 18, 19], and extensions were presented in [20, 21] and [22] for multiple-input multiple-output systems. A number of examples for its application can be found in [23, 24, 25, 26, 27], where the algorithms were designed for the control of quadcopters, robot manipulators, DC motors and physiological systems.

The discrete time control loop of the RFPT algorithm can be seen in Figure 1. The controller tries to eliminate the error between the reference signal r and the output signal y of a dynamical system in each time step $k \in \mathbb{N}$. A linear controller (LQR for example)

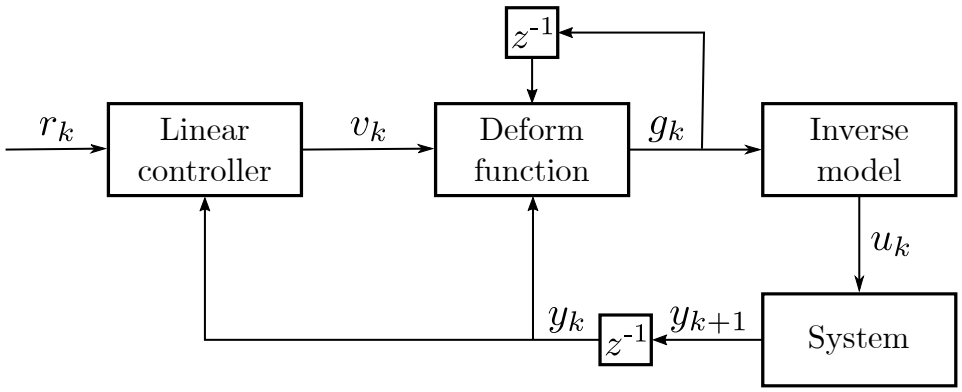

Figure 1: Block diagram of the RFPT method in discrete time

produces a control signal to the IO linearized system through the virtual input v, which is manipulated by the deform function. The corrected signal g is then used to calculate the input signal u using the *inverse model* of the underlying system that is the input equation obtained by the IO linearization.

3.2 Nonlinear Model Predictive Control

I also investigated the use of Nonlinear Model Predictive Control in my dissertation. The general algorithm uses a dynamical model to predict the future evolution of the controlled variable which is dependent on a sequence of control inputs [28]. By using a cost function that both incorporates the control goal and the overall control effort in a prediction horizon, an optimization problem can be formulated that balances these two quantities. The problem is then solved using nonlinear programming algorithms, which results in a vector containing the optimal control actions on the given prediction window. The first element of this vector is then applied on the actual system and the procedure is repeated in the next control cycle. During the optimization, constraints can be enforced on the solution space which can be used to limit the maximum dosages and enforce physiologically reasonable behavior of the model.

The algorithm is illustrated in Figure 2. At time t_k, the controller simulates the dynamical model of the system, using the measurement y_k, and produces a tumor volume prediction $\hat{y}(t)$ in the time window $t \in [t_k, t_{k+N}]$. The prediction is dependent on the input sequence $\boldsymbol{u} = [u_k, u_{k+1}, \ldots, u_{k+N}]$, which is the subject of the optimization. During the optimization, each successive iteration of the nonlinear optimizer results in a different control sequence, which changes the prediction, denoted by $\hat{y}_1(t)$ and $\hat{y}_2(t)$. At the end of the optimization, an optimal input vector $\boldsymbol{u}^*$ is obtained, from which the first element u_k^* is applied on the system. In my case, the considered input signals are also impulsive such that they resemble Dirac delta type input action in order to model drug delivery through injections.

There are a number of different technical approaches to solve the optimization problem in the NMPC [29]. In my dissertation, I have used both single shooting and multiple

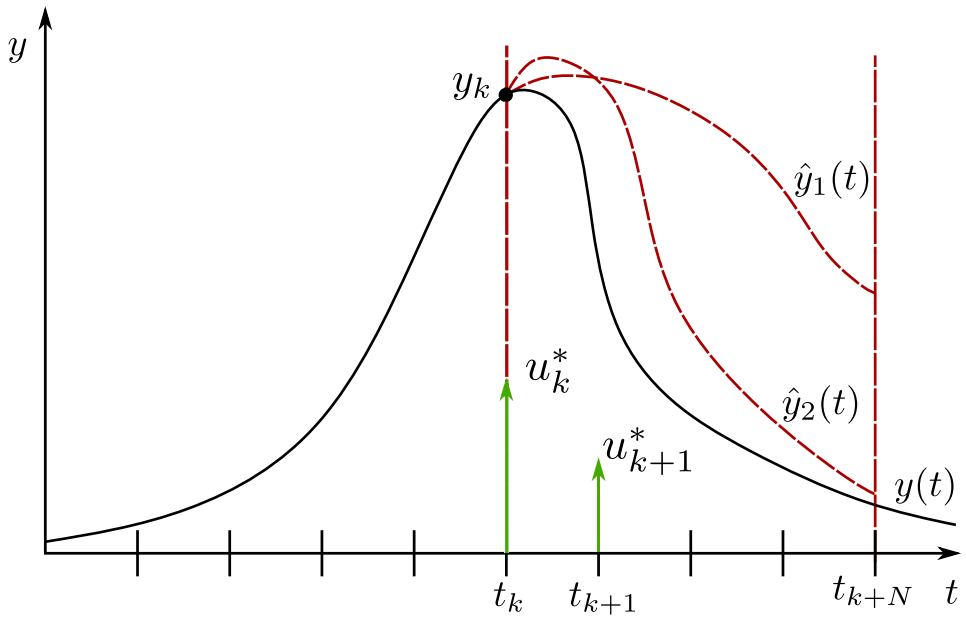

Figure 2: Visualization of the NMPC strategy for impulsive systems

shooting techniques. The single shooting case was previously discussed and was shown in Figure 2. Using the Direct Multiple Shooting (DMS) paradigm, the system can be simulated in parallel by introducing artificial initial values in the optimization, as shown in Figure 3. The prediction horizon is cut into N pieces and an artificial initial value s_k is associated with each slice, which is also subject of the optimization.

In order to simulate the system at each control cycle in the NMPC, one needs an estimate of the full state vector of the underlying dynamical system at time step k. This can be achieved using an estimator that takes the measurement y_k and produces the state estimate $\hat{x}_k$.

3.3 Moving Horizon Estimation

Moving Horizon Estimation is a state estimation technique for nonlinear systems, which can be considered as a dual problem of the NMPC. It is both capable of estimating time-varying model parameters and calculating their corresponding state estimates [28]. Akin to its counterpart, MHE is also an optimization based technique that uses the dynamical model of the system to provide additional insight on its behavior. Optimization of the parameters is performed on a given time window by considering the prediction error between the estimation, which originates from the simulation of the dynamical model, and the actual measurements. The strategy is also capable of providing time-varying parameters of a given model, thus proving to be a reasonable candidate for capturing the adaptation strategy of the disease to the drug.

Figure 4. visualize the operation of the MHE on a given time-series, where the measurements and control instances can be temporally separated. At time instance t_k, we

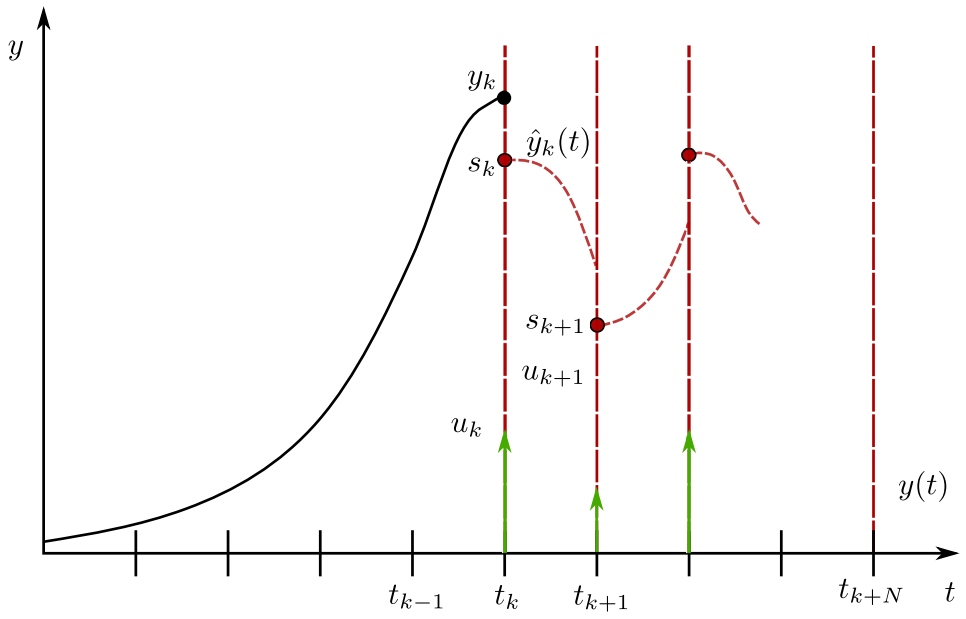

Figure 3: Schematic diagram of the Direct Multiple Shooting approach

record the past W measurements in a vector, denoted by $\boldsymbol{y}_k^W = [y_k, y_{k-1}, \ldots, y_{k-W}]$ and all the input signals $\boldsymbol{u}_k^W$ that are present in the time interval $[t_{k-W}, t_k]$. During the first few measurement, i.e. $k < W$, we simulate our system from a fixed initial condition at time t_0. When $k > W$, we set the initial condition of the dynamical model at t_k to be equal to the solution of the same model at t_k from the previous optimization, associated with t_{k-1} (red dashed lines in the figure). By iterating the process, a full state estimate can be obtained at each measurement time instance.

I have also used the extension of the MHE principle, called the Full Information Estimator (FIE). In the FIE, the window size grows with the number of measurements in the time-series. The FIE is then able to iteratively find an optimal set of parameters that can be used to simulate the system from t_0, where the output of the simulation is close to the measurements in a least squares sense. By iteratively incorporating each new measurement, I was able to robustly find the model parameters for each time-series, as opposed to the direct approach, where all the measurements are simultaneously considered. The identified model parameters can also be used to support initial parameter estimates for the SAEM algorithm.

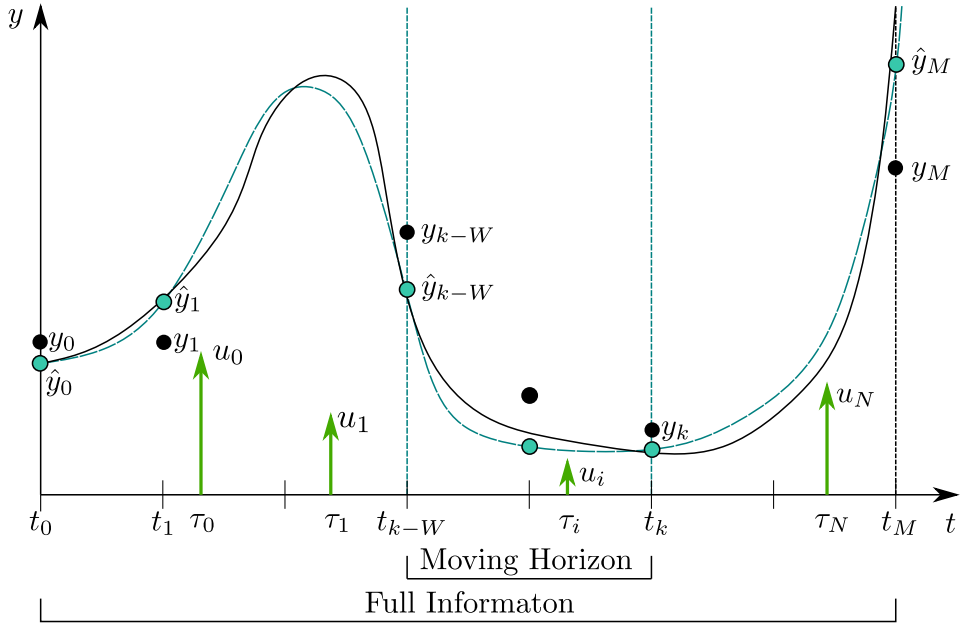

Figure 4: Visualization of the estimation process

4 New Scientific Results

Thesis 1: Model-based control using the RFPT approach

Thesis 1
I contributed to the theoretical description of the RFPT method by connecting it with the Input-Output (IO) linearization principle. Moreover, I developed a functional fixed-point iteration based variant of the algorithm in conjunction with a purely discrete time version. I also tested the viability of each different strategy in silico.

Publications relevant to the theses: [30, 31, 32].

Thesis Group 2: Chemotherapy optimization using NMPC and MHE

Thesis 2
I designed an impulsive NMPC to compute individualized chemotherapy protocols for mice. The controller was augmented with an MHE and the combined robustness of the method was tested in silico using a virtual population that was generated from previous mice experiments.

Publications relevant to the theses: [33, 34, 35, 36].

Thesis 2.1
I implemented an impulsive NMPC using Direct Multiple Shooting with Dirac delta approximations in the input action. The results were demonstrated in silico, assuming full state observability and no uncertainties. The simulations showed that the algorithm is capable of providing an optimal administration sequence for the tumor growth model.

Thesis 2.2
I developed a purely impulsive NMPC that uses an impulsive differential equation as the prediction model. I also developed a virtual population that was used for the tuning and testing of the proposed algorithm. Furthermore, I showed that numerical errors in the optimization problem can be avoided by introducing transformations on the state variables and the cost function. Numerical results showed that the numerical stability of the proposed scheme is superior to the DMS based implementation.

Thesis 2.3
I have developed a Moving Horizon Estimator that is able to simultaneously estimate the states and the parameters of the underlying tumor growth model. I also presented the tuning process of the estimator. In silico results on previous experimental data indicated that the algorithm is effective in solving the estimation task.

Thesis Group 3: In vivo validation of the control algorithms

Thesis 3
I tailored the algorithms for in vivo experimental validation using mice. The first two iterations of the algorithm were tested in separate mice experiments, which indicated that the proposed schemes can also be viable in practice.

Thesis 3.1
I generated both open and closed loop therapy protocols of the first iteration of the NMPC algorithm for in vivo validation. Results showed that the closed-loop approach is able to achieve remission in the subjects without using excessive amount of drug during the therapy.

Thesis 3.2
I implemented the second iteration of the NMPC controller for closed loop in vivo validation. During the experiment, I have generated the optimal dosages for the mice using the algorithm. Results showed that mice treated with the algorithm had similar mean survival as the conventionally treated subjects, however, some mice reached significantly longer survival.

Publications relevant to the theses: [34, 35, 37].

5 Application of the results

Theoretical results obtained in Thesis 1. can be immediately applied to general control design of nonlinear systems. By connecting the method with the IO linearization, the derivation of the inverse model can be automated using a Computer Algebra System. Moreover, the purely discrete time variant can be employed in cases, where the sampling time is significant and continuous design leads to unsatisfactory results.

The control algorithm introduced in Thesis Group 2 was designed to generate the optimal dosing scheme for breast cancer, treated with PLD. Since the underlying model captures essential mechanisms present in a wide variety of cancerous diseases, only the model parameters have to be tailored for each new drug-disease interaction. This entails that the algorithms presented in the dissertation are also applicable for other cancer types as long as the model structure can adequately describe the underlying process. Furthermore, the presented FIE algorithm can be especially powerful to estimate model parameters of nonlinear systems, where the number of measurements are limited and additional constraints are present, e.g. positivity of the system.

In Thesis Group 3., the in vivo results indicate that the overall survival of mice can be prolonged by using the model-based approach. This can be considered a significant progress on the field, since there is no existing literature in chemotherapy optimization where a sophisticated control algorithm was tested in vivo. Since the mice model used in the dissertation mimics the behavior of the tumor in humans, the algorithm can be adapted for medical use if one can obtain reliable measurements on the tumor volume. Ultrasound imaging of the malignant disease can provide such measurements without any major adverse effect for example.

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