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Personalized physiological modeling and control by robust control methods

by

Levente Kovács

Physiological Controls Research Center
John von Neumann Faculty of Informatics
Budapest

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"I believe that pure scientific research is the true source of progress"

Marie Curie

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List of abbreviations

Abbreviations	Meaning
LTI	Linear Time Invariant
LTV	Linear Time Variant
NLTV	Nonlinear LTV
LPV	Linear Parameter Varying
qLPV	quasi LPV
TP model	Tensor Product model
SS	State Space
PS	Parameter Space
PB	Parameter Box
DM	Diabetes Mellitus
CHO	Carbohydrate
LMI	Linear Matrix Inequality
LQR	Linear Quadratic Regulation
MVS	Minimal Volume Simplex
SVD	Singular Value Decomposition
HOSVD	Higher-Order SVD
AP	Artificial Pancreas
T1DM	Type 1 DM
T2DM	Type 2 DM
MPC	Model Predictive Control
PDC	Parallel Distributed Compensator
TMT	Targeted Molecular Therapy

List of mathematical notations

Notation	Meaning
$a, b, ...$	scalars
$\mathbf{a}, \mathbf{b}, ...$	vector
$\mathbf{A}, \mathbf{B}, ...$	matrices
$\mathbf{a}_i, \mathbf{b}_i, ...$	ith row vector of $\mathbf{A}, \mathbf{B}, ...$ matrices
$a_{i,j}, b_{i,j}, ...$	jth elements of the $\mathbf{a}_i, _i, ...$ row vectors
$\mathbb{R}, \mathbb{C}$	sets
$\mathcal{A}, \mathcal{B}, ...$	tensors
$\mathcal{S} \bigboxtimes_{n=1}^{N} \mathbf{w}_n$	multiple tensor products,
	e.g. $\mathcal{S} \times_1 \mathbf{w}_1 ... \times_N \mathbf{w}_N$

1. Introduction

In the case of any scientific research field, the key to success lies in interdisciplinary. Especially by taking into account nowadays complex coupled systems and the approaching era of the cyber-physical world. In recent years, a new viewpoint, the cyber-medical systems came into the focus of research in the domain of biomedical engineering. This means that the medical treatments and issues should be handled by using strong cybernetical background, which means that the decisions should be supported in a computer-aided way. This includes the design of simple or unique therapies or even the development of complex medical devices.

From this viewpoint, medical treatments are in the front of this fast-evolving field. The processes which lead to a successful therapy are so complex that professionals of physiology, biology, engineering, and other fields have to work together, to find more effective ways of healing and helping the recovery of the patients. Such problems also require a strong background in complex cyber-medical systems so that a satisfactory result can be obtained.

Applying appropriate modeling and control is crucial in the regulation of physiological processes [1]. A serious problem is that handling such processes is highly non-trivial with several notoriously difficult challenges: most of the problems are nonlinear, coupled with complex effects and there may be significant time delay present in such systems [2]. From the modeling perspective, another challenge is where should we draw the line between accuracy and complexity. Complex models are hard to handle mathematically, but simple models might be inaccurate or inadequate.

In the recent years of my research activities, I have focused on two prominent and ubiquitous illnesses: diabetes mellitus (DM) and cancer. Both of them are serious diseases that are the leading cause of death around the globe. I am interested in the research of DM and the related problems for many years. During my investigations, I have found that most of the concepts that are employed in the case of DM can be adapted to tackle the tumor growth regulation issue.

During the course of my career, I always hoped that I will be able to provide better therapeutic solutions by applying advanced methods of control engineering so that the

quality of life of the patients can be significantly improved. In this thesis, I will show the results related to control of DM and tumor growth which have been born in this spirit.

1.1. Motivation and background

Diabetes mellitus is a chronic disease that can endanger the lives of those who suffer from it in both the short and long term. The disease affects the metabolic system of the body. More precisely, DM connects to given conditions of glycemia and the insulin hormone. It occurs when the production or the effect of the insulin is insufficient [3]. The insulin hormone is produced by the pancreas in its β-cells which can be found in the islets of Langerhans [3]. The main rule of the hormone in the metabolic system is to allow the glucose molecules to enter into cells. Most of the cells use glucose as a primary energy source, but there are cell types that do not require insulin to take the glucose from the bloodstream. Such an example are cells that belong to the neural system [4].

According to the latest estimation of the International Diabetes Foundation (IDF), the number of diagnosed and undiagnosed diabetic patients is around 425 million, and it is expected to reach 629 million by 2045 [5]. These numbers indicate that further progress must be achieved in the domain of DM research to cope with these numbers. One can see the worldwide distribution of DM patients in Figure 1.1.

One can distinguish between different types of DM. Besides T1DM and T2DM, which are the most infamous versions of DM, one can also mention Genetic DM, Gestational DM, Double DM, and other types of this disease. The most dangerous condition is T1DM in short term, but T2DM and other types can result in life-threatening conditions, especially in the long term [5, 6].

T1DM occurs when the patient's pancreas is not able to produce insulin. This condition emerges after an intense autoimmune reaction in which the β-cells are destroyed by the immune system of the patient. The reasons for this reaction are still not completely understood, unfortunately. The occurrence of T1DM is around 10% in the diabetic population [6]. The glucose influx will be very limited in those body cells for which the insulin induces the glucose uptake. This means that the cells of the patient are in serious need of energy, while the concentration of glucose in the plasma is high. This state can lead to life-threatening conditions even in the short term which makes it the most dangerous type of DM.

T2DM is the most common type of DM [5]. The evolution of the disease in the body takes a longer time compared to other DM types and it is highly dependent on the lifestyle of the patient. In this case, the body can produce insulin, but the sensitivity to

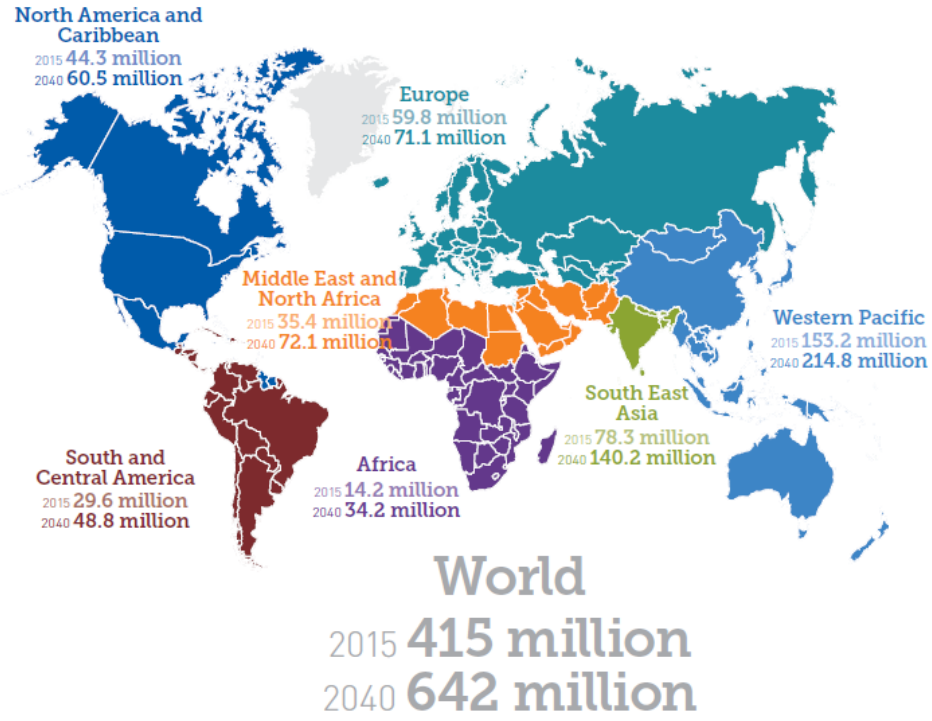


Figure 1.1.: Estimated number of diabetic patients worldwide between 2017 and 2045 (20-79 years) [5]

the hormone decreases over years. Thus an elevated level of insulin is needed to reach the same blood glucose (BG) level as years earlier, which causes higher blood glucose levels eventually.

In this thesis, I mostly investigated methods applicable in the case of T1DM, since this is the most dangerous condition and it requires robust, accurate, and (possibly) optimal insulin administration to maintain the diabetic state of the patient in short term and prevent the serious side-effects in long term. The required therapies that handle the diabetic state are dependent on the type of DM. In the case of T1DM, the patients need exogenously administered insulin due to the lack of internally produced hormones. In the case of T2DM, the regular therapy starts with gluconeogenesis inhibitors, which obstruct the daily glucose production of the liver and decrease the insulin resistance [4]. Although, over time externally administered insulin can be required to keep the blood glucose level in a healthy range.

The common therapy is external insulin administration, which is delivered via subcutaneous injections. There are different devices with which diabetic patients can manage insulin delivery. Usually, it is done by using an insulin pen, which is a small pen shape mechanical device that consists of a dispenser, insulin reservoir, injection mechanics, and thin needle parts. With this device, the patients can manage their blood glucose levels on their own. The dosage is manual and based on preliminary rules laid down by the doctors, which is dependent on the food intake, physical activities, or other factors. During the self-administered therapy, the patients can use rapid-acting insulin (bolus insulin to handle the food intake) and slow-acting insulin (to keep the basal insulin rate), as well [6, 7].

Another solution for insulin administration is the semi-automatic or automatic insulin pump or Continuous Subcutaneous Insulin Infusion (CSII) devices, which can be used in both DM cases as well [8–12]. The pump or injection system contains an insulin reservoir that connects to the subcutaneous regions by a thin catheter. These electromechanical devices can deliver insulin boluses automatically based on predefined rules. The pumps use rapid-acting insulin and the delivery protocols are varying based on the state of the patient. The long term goal from an engineering perspective is to develop the so-called Artificial Pancreas (AP) concept. This development consist of three major parts [13–19]:

1. An insulin pump or insulin pump completed with external insulin injection system, which stores and injects the rapid-acting insulin;

2. A Continuous Glucose Monitoring System (CGMS) for continuous blood sugar level measurement and transmit;

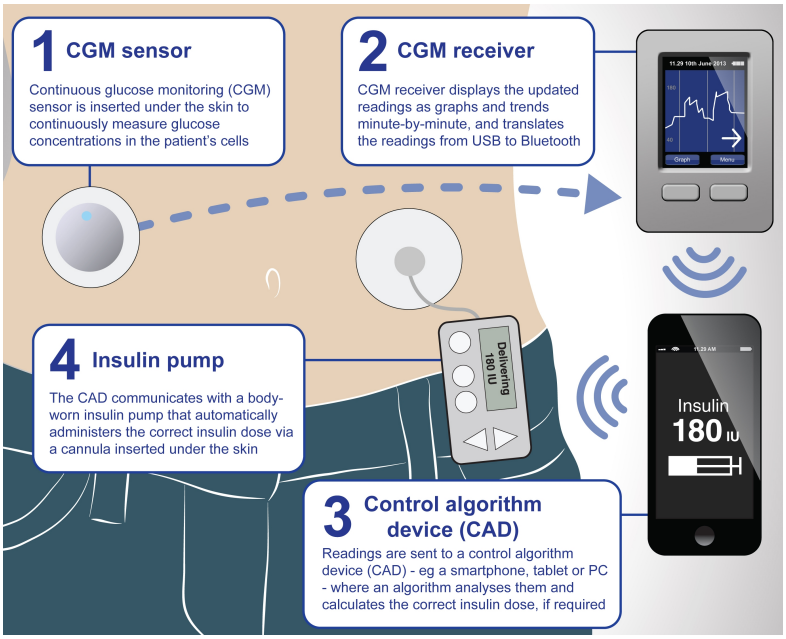


Figure 1.2.: The AP concept and its physical components [21]

3. Appropriate software components including control algorithms, user interfaces, and drivers.

The CGMS system is used in parallel with the insulin pump. The operation of CGMS is based on various principles. In practice, the most widely used systems are external devices fixed on the abdominal skin surface and connected to the subcutaneous level through a thin catheter. The most frequent measuring principle is enzymatic based which uses Glucose Oxidase (GOx) for detection. Besides its several benefits, CGMS has also some disadvantages which arise mostly from the control engineering perspective; the sensor measurements are provided only every 5 minutes. Implantable CGMS have also been developed, but these are not available on the market, yet [20].

The leading AP solutions integrate the benefits of the available smart devices, smartphones for example [17]. In this way, the control algorithms which may need high computational capacity can be exported to the smart device instead of the compact insulin pumps. Figure 1.2. shows the schematic representation of the latest AP concept. As mentioned earlier, the third necessary component to realize the AP is the appropriate software elements, which includes the control algorithm. Since insulin pump therapies are used mostly in the case of T1DM, the advanced control algorithms developed inside AP

researches focus on this DM form. The main expectation from an AP control algorithm is the automatic glucose regulation to keep the blood glucose concentration in the normal glycemic range, i.e. 70-110 mg/dL (3.9-6 mmol/L). The ultimate goal is to avoid the dangerously low blood glucose levels that could directly endanger the life of the patient.

Besides my research on DM, I have also focused on the optimization of cancer therapies. In the EU, the total estimated number of cancer casualties for 2021 is 1.267 million [22]. In clinical practice, there are general protocols for cancer therapies (such as chemotherapy, radiotherapy). However, these treatments have many side effects and tumor cells can become resistant to chemotherapy drugs which on the one hand makes the usage of new drugs necessary, and on the other hand, increases the treatment cost. That is the reason why a new dynamically developing therapeutic group called Targeted Molecular Therapies (TMTs) has emerged [23]. These therapies have gained significant attention as they specifically fight against different cancer mechanisms, being more effective and having limited side effects compared to conventional cancer therapies.

Nevertheless, protocols for cancer treatments are determined empirically which could hinder their effectiveness. Physiological modeling and control aim to study, understand and model biological processes, then apply identification and control strategies to them. By designing closed-loop control systems, the treatment protocols could become tailored to individual patients. Model-based design enables the automated treatment of cancer diseases by the personalized administration of TMT drugs. In this way, more effective solutions can be found in healing and offering individualized treatment for the patient. Optimizing cancer treatments would improve efficiency, decrease treatment cost and minimize the side effects of cancer therapy (i.e. improves the patient's quality of life), thus analysis and synthesis of cancer therapies from an engineering point of view are beneficial.

A promising targeted molecular therapy that arose in the last decade is antiangiogenic [24, 25], which aims to stop tumor angiogenesis (i.e. forming new blood vessels). By blocking the formation of new blood vessels to the tumor, it stops growing since it has no nutrients to do so. A clinically validated tumor growth model under angiogenic inhibition was developed at Harvard University by Hahnfeldt et al. [26]. The model describes the evolution of tumor volume based on endothelial reduction. The Hahnfeldt model and its simplified form have been used by most researchers working in the field of antiangiogenic control to design controllers and perform simulations.

The original theoretical concept of angiogenesis was endothelial sprouting which means that new blood vessels sprout from existing ones [27]. Endothelial cells undergo disorganized sprouting, proliferation, and regression, and become dependent on the

vascular endothelial growth factor (VEGF), one of the most important proangiogenic factors in tumor growth. Hence, by inhibiting VEGF in tumors, one can stop sprouting angiogenesis. Most of the angiogenic inhibitors act in that way and this is the key point in angiogenic inhibition studies. However, later on, it has become clear that VEGF inhibition leads to apoptosis (the process of programmed cell death) only in newly-built vessels in tumors, but does not have an effect on vessels that have already existed [28]. This implies that there is a strong need to revise the existing tumor growth model, since, according to the Hahnfeldt model, every blood vessel can be eliminated by the drug. Nevertheless, controllers that work on the Hahnfeldt model could be readily adapted to other kinds of treatment options (chemotherapy, radiotherapy) which makes its control scientifically plausible.

The solution of this tumor control problem was actually the primary goal of the ERC grant, 'Tamed Cancer', that was carried out by my research group and myself [29]. The ultimate goal of the grant was to theoretically prove the possible benefits of creating optimal therapies for antiangiogenic treatment options in cancer.

1.2. Relevant control engineering methods in the domain of DM and tumor control

In this section, I introduce the most important control design techniques from the DM literature and the field of tumor therapy optimization. The soul of the AP concept is the usage of appropriate control algorithms. Over the last decades, most of the available control concepts have been tested in this field, but no de-facto standard has been evaluated. Figure 1.3 shows the AP concept completed with the most frequently used control algorithms. The most important directions focus on model predictive control (MPC), fuzzy rule-based and other soft computing techniques, classical, robust and fractional Proportional-Integral-Derivative (PID) control techniques [13–16, 19, 30].

It can be said that every control algorithm considers similar principles which is the fulfilment of prescribed quality and quantity properties. The first attempts in this area were related to PID control which is still being the most widely used classical control technique in the industry. Although the basic principle of PID control is not too sophisticated, highly advanced variants like robust PID [13, 31] or switching PID [32, 33] have been applied for the AP concept aside from the basic algorithm. There is also an example regarding the application of fractional PID in the research field, [34] for example, but the usage as a common technique is not dominant.

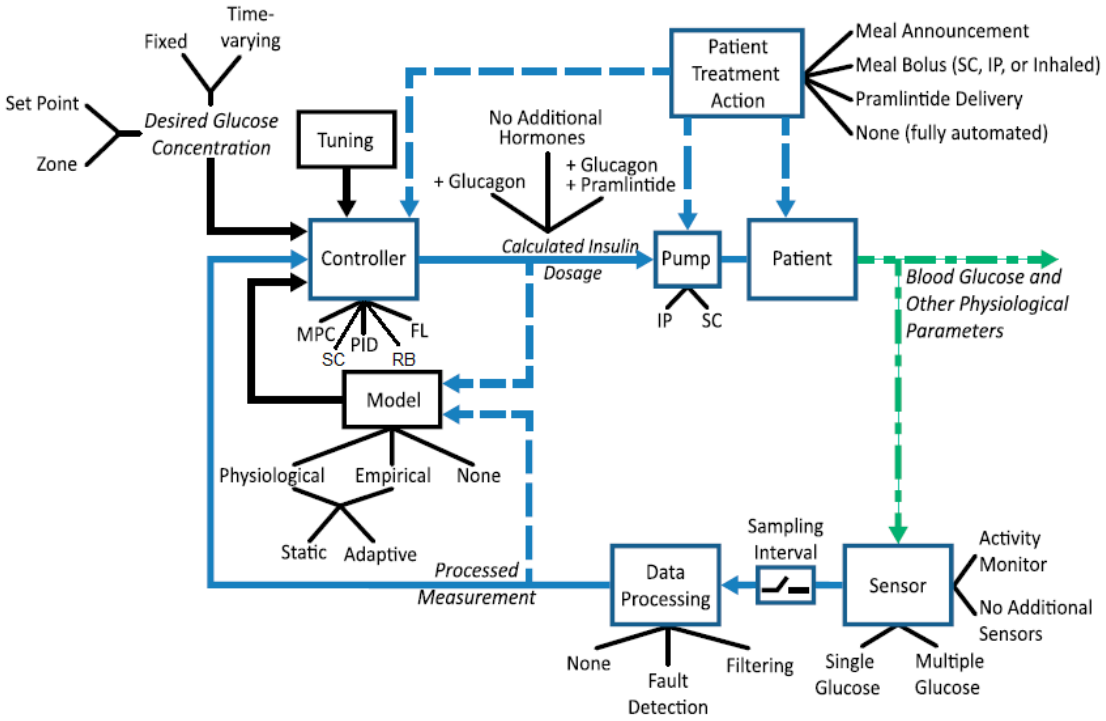


Figure 1.3.: Schematic representation of the AP concept [13], including each practical subsystems

MPC-based approaches have been successfully used in physiological controls, reported in [35–37], which is a more advanced approach than PID control. Since it can handle processes with large time delays and constraints, it is better suited for such biological systems. This entails that MPC represents probably the mostly used advanced control method in the AP concept, but it is susceptible to intra- and inter-patient variabilities and external noises. MPC is a model-based approach which means that an appropriate model that describes the physiological process is essential for its operation. In particular, MPC algorithms produce the best results in individual therapy if the model parameters are known beforehand. Several, highly developed MPC based control solutions appeared in the recent years like Robust MPC (RMPC), Nonlinear MPC (NMPC), Robust-Nonlinear MPC (RNMPC) [38–41]. A significant issue in the MPC literature is the tuning of the controller, which is not well understood at the present. One possible solution to overcome this issue is the MPC design by using soft computing tuning tools [42]. Soft computing alone has also been applied several times in the AP concept, but only in recent years have been investigated in clinical trials [43–45].

Modern robust control methods like $\mathcal{L}_2$- or $\mathcal{H}_\infty$-based ones were introduced in the

AP researches to tackle the parametric uncertainties coming from inter- and intra-patient variability. Supplemented by the Linear Parameter Varying (LPV) methodology, modern robust control successfully deals with the quality and quantity requirements [46–49]. Another useful direction in this domain proved to be the combination of LPV methodologies with concepts from the Linear Matrix Inequalities (LMI) based principles [49–51].

The idea of the optimization of cancer therapies has been around for the past century. Initial approaches considered the optimization of chemotherapy, and radiotherapy using PID controllers and simple logistic models [52, 53]. The problem with such approaches was that the size of the tumor must be measured continuously, which is yet infeasible since there is no such device that can provide measurements with such frequencies (as opposed to the CGMS sensor in the AP concept). While continuous dosage could be solved by using a similar device as the insulin pump, it is still not present in the market. These issues have hindered the interest in tumor control until the emergence of antiangiogenic therapy, which provided an additional basis for further research. The Hahnfeldt model was a foundation for many control strategies that were designed for antiangiogenic therapies and is still popular in the field [54–56]. While the measurement issue is still unsolved, recent developments aim to overcome this by using techniques from estimation with less frequent measurements, and discontinuous dosing [57, 58].

1.3. Aims of the thesis

The thesis aims to provide state-of-the-art control techniques in the domain of physiological control. Moreover, the presented methodologies are also illustrated on DM and tumor control problems:

- **Robust control of physiological systems.** The sensitive tuning of H_∞ control is presented that can handle parametric uncertainties, which is crucial in designing successful control strategies for physiological systems due to the inherent variability between each individual. The controller is based on the LPV representation of a well-known T1DM model, which is then validated in an FDA-approved simulator. The goal is to show the validity of this combined LPV-H_∞ approach in the case of complex systems.

- **Robust Fixed Point Transformation based control.** A novel nonlinear control strategy is also presented, which can adapt to the individual dynamics of each patient over time by using an approximate model. The approach is not only able

to handle the parametric uncertainties but is also capable of handling considerable disturbances acting on the model as well. My goal here is to show how this novel method can be beneficial in controlling physiological systems since the most application of the method concerns mechanical or electrical models.

- **Tensor Product based LPV control with LMI constraints.** A general description of the TP approach is also presented which utilizes a number of reference models to ensure safe operation in every dynamical region of the presented models. The use of LMI conditions is also illustrated which can ensure that the poles of the closed-loop system lie in a feasible domain. Based on the fundamentals of the method, the goal is to show how its applicability can provide a robust alternative to conventional techniques.

1.4. Structure of this thesis

Chapter 2 presents the development of a new quality marker (”metric”) for LPV modeling and control based on a given norm, that is interpreted on the LPV parameter space. Further, a novel completed LPV controller and observer scheme for nonlinear systems is proposed, which can be used in the control of biomedical systems. Their applicability is demonstrated on nonlinear DM models. In Chapter 3, I introduce the latest results on the RFPT control method. The application of the controller is also illustrated on a T1DM, and a tumor regulation problem. Chapter 4 details the TP modeling possibilities regarding DM to realize control-oriented LPV-TP models, which will be the subjects of the controller design later. LMI based design is also shown as an alternative way to characterize safe zones for the closed-loop poles of a system. In Chapter 5, the results of the work are summarized and the thesis group points are formulated. There are two Appendixes that contain information on the biological background of the DM and tumor control problems. Appendix A.1 shows the pathophysiology of DM, while Appendix A.2 describes the scientific background of TMT-s.

2. Robust Control of Diabetes Mellitus and Tumor Growth

In this chapter, I introduce a robust control approach that can handle the parametric uncertainty that is present in the control of T1DM. The design steps of the approach are shown, and the ideas are validated on a benchmark system. I used MATLAB^{TM} during the design and simulation phase.

2.1. Robust control of T1DM

2.1.1. Modern robust control for T1DM

Most available T1DM models are complex nonlinear systems with slowly changing patient parameters over time. This means that the robustness of the controller must be guaranteed so that it can operate in every possible parametric configuration. Moreover, there are various constraints and specifications which the controller must address, complicating the design even further [59]. Modern robust control methods seek to provide safety and generalized usability in worst-case scenarios by providing guarantees on specific domains of parameters. Nevertheless, increasing the robustness can hinder tracking properties of the controller, hence a robust controller would be inferior to other model-based methods if one is in the possession of the true parameters of the patient [60].

For this reason, modern robust control, e.g. H_∞ robust controller design can be most effectively used when working with uncertain linear systems. In particular, the applicability of this methodology in the T1DM problem has been investigated in [59, 61–63] and the advantages have been highlighted in comparison with other control design methods [64–66]. However, a generally applicable method does not exist for nonlinear models, where even proving stability can be a difficult task, and the problem gets more complicated under parameter inaccuracies, uncertainties, and unmodeled dynamics.

2.1.2. The investigated model

The 11th order model introduced by [39] at Cambridge, UK, represents one of the most used T1DM model in the domain of artificial pancreas research. Later it was updated by [67] leading to the University of Cambridge SimEdu$^{\text{TM}}$ simulator, which is used in the current research as well. The model can be described by the following system of differential equations:

$$
\begin{aligned}
&\dot{C}(t) = -k_{a,\text{int}} C(t) + \frac{k_{a,\text{int}}}{V_G} Q_1(t) \\
&\dot{Q}_1(t) = -\left(\frac{F_{01}^s}{Q_1(t) + V_G} + x_1(t) \right) Q_1(t) + k_{12} Q_2(t) \\
&- R_{cl} \max\{0, Q_1(t) - R_{th} V_G\} \\
&+ EGP_0 \max\{0, 1 - x_3(t)\} + U_G(t) - Phy(t) \\
&\dot{Q}_2(t) = x_1(t) Q_1(t) - (k_{12} + x_2(t)) Q_2(t) \\
&\dot{x}_1(t) = -k_{b1} x_1(t) + S_{IT} k_{b1} I(t) \\
&\dot{x}_2(t) = -k_{b2} x_2(t) + S_{ID} k_{b2} I(t) \\
&\dot{x}_3(t) = -k_{b3} x_3(t) + S_{IE} k_{b3} I(t) \\
&\dot{I}(t) = \frac{k_a}{V_I} S_2(t) - k_e I(t) \\
&\dot{S}_2(t) = -k_a S_2(t) + k_a S_1(t) \\
&\dot{S}_1(t) = -k_a S_1(t) + u(t),
\end{aligned}
\tag{2.1}
$$

where the state variables are:

- $C(t)$ the glucose concentration in the subcutaneous tissue [mmol/L];
- $Q_1(t)$ and $Q_2(t)$ the masses of glucose in accessible and nonaccessible compartments [mmol];
- $x_1(t)$, $x_2(t)$ and $x_3(t)$ remote effect of insulin on glucose distribution, disposal and endogenous glucose production respectively [1/min];
- $I(t)$ insulin concentration in plasma [mU/L];
- $S_1(t)$ and $S_2(t)$ insulin masses in the accessible and nonaccessible compartments [mU].

The $u(t)$ injected insulin flow of rapid-acting insulin [mU/min] is the input of the system, while the $U_G(t)$ glucose flux from the gut [mmol/min], and the $Phy(t)$ effect of physical activity [mmol/min] are considered as disturbances. The parameters of the model are the following:

- $k_{a,\text{int}}$ transfer rate constant between the plasma and the subcutaneous compartment [1/min];
- V_G distribution volume of glucose in the accessible compartment [L];
- F_{01}^s parameter of the total non-insulin dependent glucose flux [mmol/min];
- k_{12} transfer rate constant from the non-accessible to the accessible compartment [1/min];
- R_{cl} renal clearance constant [1/min];
- R_{th} glucose threshold [mmol/L];
- EGP_0 endogenous glucose production extrapolated to the zero insulin concentration [mmol/min];
- k_{b1} and k_{b2} deactivation rate constants [L/(mU $\cdot$ min 2)], k_{b3} deactivation rate constant for the insulin effect on endogenous glucose production [L/(mU $\cdot$ min)];
- S_{IT}, S_{ID} and S_{IE} insulin sensitivities for transport, distribution and endogenous glucose production [L/(mU $\cdot$ min)] and [L/(mU)];
- k_a insulin absorption rate constant [1/min];
- V_I volume of distribution of rapid-acting insulin [L];
- k_e fractional elimination rate from plasma [1/min].

There are time-varying parameters of the model, in particular $k_{a,\text{int}}F_{01}^s, k_{12}, EGP_0, k_{b1}$, $k_{b2}, k_{b3}, S_{IT}, S_{ID}, S_{IE}, k_aandk_e$ can be regarded non-constant [67, 68]. Six parameter sets representing six different virtual patients were available in the SimEdu in-silico simulator version 2.2, and have been used in the paper for controller design and simulation. SimEdu represents one of the reference in-silico simulators in the artificial pancreas (AP) domain, and it was developed in accordance with FDA regulations [67].

2.1.3. Controller design

H_∞ control is a standard robust control technique in control engineering which has a well-established basis for linear systems. As T1DM models are nonlinear, an important issue is the direct applicability of the control scheme taking the parameter inaccuracies into consideration as well on the nonlinear system.

LPV modeling related to robust control

In this section, a brief introduction can be found regarding the LPV modeling which is related to the applied robust control techniques [59]. There are several ways to handle nonlinearity in the model equations. The classical nonlinear methodology focuses on the differential geometric approach which includes coordinate transformations, while a more recent methodology is the application of LPV systems, where nonlinearity is handled through the time-varying parameters [69, 70]. LPV is an acceptable compromise between the model's complexity and the developed control algorithm, as LPV systems can be seen as an extension of LTI systems. In the case of the LPV systems, the relations of the states are considered to be linear, but model parameters are assumed to be functions of time-varying signals [69]:

$$\begin{aligned} \dot{\mathbf{x}} &= \mathbf{A}(\rho(t))\mathbf{x}(t) + \mathbf{B}(\rho(t))\mathbf{u}(t) \\ \mathbf{y} &= \mathbf{C}(\rho(t))\mathbf{x}(t) + \mathbf{D}(\rho(t))\mathbf{u}(t), \end{aligned} \tag{2.2}$$

from which

$$\begin{aligned} \mathbf{A}(\rho(t)) &= \prod_{i=1}^{m} \rho_i(t)\mathbf{A}_i \quad \mathbf{B}(\rho(t)) = \prod_{i=1}^{m} \rho_i(t)\mathbf{B}_i \\ \mathbf{C}(\rho(t)) &= \prod_{i=1}^{m} \rho_i(t)\mathbf{C}_i \quad \mathbf{D}(\rho(t)) = \prod_{i=1}^{m} \rho_i(t)\mathbf{D}_i. \end{aligned} \tag{2.3}$$

It can be observed that (2.2) is an LTI system in the $\rho(t)$ scheduling parameters, thus nonlinearity can be hidden in the $\mathbf{A}, \mathbf{B}, \mathbf{C}, \mathbf{D}$ matrices ((2.3)). One approach could be the linearization around stable working points in the state-space, then creating a polytopic region of possible linear models, and using this information to determine the nominal model and uncertainty weighting functions. The current investigation can be considered as a rigorous and more complex extension and continuation of the article presented in [62]. In the original paper, only one particular scenario was analyzed to present the capability of LPV-modeling for T1DM control (i.e. for a given parameter set a robust controller

was designed), here I give a complex roadmap of the nonlinear robust control design for T1DM, analyzing different parameter possibilities and highlighting the sensitivity of uncertainty weighting function selection. Based on the gained knowledge from real patient data collected from insulin pump centers, (clinics and hospitals affiliated to the Hungarian Diabetes Association and considered the only legal entities in Hungary to work with CGMS and insulin pumps) one could formulate the weighting functions of the neglected uncertainties of the model.

Beyond the polytopic representation, which is applied in Chapter 4, the other most widely used LPV modeling approach exploits the affine representation (similar to quasi-affine LPV (qALPV)) of the nonlinear model [71]. Given a bounded vector $\rho(t)$ with bounded time-derivatives, the model can be treated as a linear model with parameter inaccuracies. For the model (2.1) all candidates $\rho(t)$ (named as scheduling parameters) are given in (2.4), being bounded by constants in (2.5)–(2.6) with additional bounds on their time-derivatives as well [66]. Numerical values were determined analytically and validated with Monte-Carlo simulations [66]. The scheduling parameter is given as

$$\rho(t) = \left(Q_1(t) \ \frac{F_{01}^s}{Q_1(t) + V_G} \ Q_2(t) \ x_1(t) \ x_2(t) \right)^T, \tag{2.4}$$

with bounds

$$\rho_{\min} = \left(Q_{1,\min} \ \frac{F_{01}^s - \Delta F_{01}^s}{Q_{1,\max} + V_G} \ Q_{2,\min} \ x_{1,\min} \ x_{2,\min} \right)^T \tag{2.5}$$

$$\rho_{\max} = \left(Q_{1,\max} \ \frac{F_{01}^s + \Delta F_{01}^s}{Q_{1,\min} + V_G} \ Q_{2,\max} \ x_{1,\max} \ x_{2,\max} \right)^T. \tag{2.6}$$

The existence of a qALPV model would make LPV-based control possible [59]. However, from the proposed members of $\rho(t)$ parameters none can be measured, therefore, an LPV-based controller cannot be implemented directly. Instead, the bounds should be used as parameter inaccuracies of a linear model leading to the two possible approaches:

- Define an uncertain model directly;
- Create input and output multiplicative uncertainties.

For the current T1DM model the latter option was chosen so that no further unstructured uncertainties must be introduced. Furthermore, the decision was influenced by the twelve aforementioned time-varying parameters of the model. Nevertheless, the choice of parameters for the qALPV-like description is not a trivial task. Finding the correct model can greatly reduce the burden on the controller while choosing the wrong

configuration could lead us to an overly complicated problem, where the performance of the controller could be similar to the performance of a classical control strategy. Introducing $\mu_i \in [0,1](i = 1,...,4)$ parameters to investigate different configurations, while $\delta_i \in [0,1]$ represent parameter inaccuracies, including the changing of scheduling parameter candidates, the state-space model of the system is given in (2.7).

Here Δ reflects the variation of the parameter uncertainties (a variation of 5% was considered in each case as suggested in [67]). After evaluating all possible scenarios the configuration $(\mu_1, \mu_2, \mu_3, \mu_4) = (0,0,0,0)$ was chosen. This means that state variables $x_1(t)$ and $x_2(t)$ are not considered to be a part of $\rho(t)$, while the switching effect of the endogenous glucose production ($x_3(t)$) is just a disturbance only. There are a few number of reasons which motivate such a choice:

- Although all of $Q_1(t), Q_2(t), x_1(t)$ and $x_2(t)$ states of the model (2.1) are bounded, the bounds of $Q_1(t)$ and $Q_2(t)$ only depend on the performance of the controller. If the controller can maintain a smaller glucose level region, that would lead to a smaller parameter inaccuracy in the model. On the other hand, $x_1(t)$ and $x_2(t)$ are bounded by the amount of injected insulin flow. Higher the maximal value of the possibly administered insulin, the faster the controller disturbance compensation. Moreover, to avoid hypoglycemia, zero insulin flow is a possible scenario as well. For better control properties, wider limits for the input are needed, but at the same time the effect of parameter inaccuracies will also grow;

- It can be easily demonstrated that $\mu_1 = 0$ will slow the dynamics of $Q_1(t)$ in the nominal model, but would lead to higher input commands. On the other hand, $\mu_1 = 1$ would mean that the insulin concentration has no direct effect on the plasma glucose levels;

- The reason behind choosing $\mu_3 = 0$ and the effects of insulin on $Q_2(t)$ is the same with μ_1 and $Q_1(t)$ as discussed previously;

- In case of μ_2, choosing $Q_1(t)$ as parameter over $x_1(t)$ will leave the insulin dynamics having an opposite effect on $Q_2(t)$ (the rise in $I(t)$ would increase the value of $Q_2(t)$). Choosing a nonzero value for μ_2 however will lead to complex conjugate pair of poles in the nominal model, with possibly unstable dynamics depending on the actual value of the $\rho(t)$ vector;

- Choosing $\mu_4 = 1$ would raise the effect of the injected insulin on the controller, but the inaccuracy of the model would also increase. Moreover, the controller has no

$$
\begin{aligned}
A_{1,1} =& -k_{a,\text{int}} - \delta_1 \Delta k_{a,\text{int}} \\
A_{1,2} =& \frac{k_{a,\text{int}}}{V_G} + \delta_2 \frac{\Delta k_{a,\text{int}}}{V_G} \\
A_{2,2} =& \frac{\rho_{4,\max} + \rho_{4,\min}}{2}\mu_1 - \frac{\rho_{2,\max} + \rho_{2,\min}}{2} - \frac{R_{cl}}{2} \\
& - \delta_3 \frac{\rho_{4,\max} - \rho_{4,\min}}{2}\mu_1 - \delta_4 \frac{\rho_{2,\max} - \rho_{2,\min}}{2} - \delta_5 \frac{R_{cl}}{2} \\
A_{2,3} =& k_{12} + \delta_6 \Delta k_{12} \\
A_{2,4} =& \frac{\rho_{1,\max} - \rho_{1,\min}}{2}(1-\mu_1) - \delta_7 \frac{\rho_{1,\max} + \rho_{1,\min}}{2}(1-\mu_1) \\
A_{2,6} =& -\mu_4 \frac{EGP_0 + \Delta EGP}{2} - \delta_8 \mu_4 \frac{EGP_0 + \Delta EGP}{2} \\
A_{3,2} =& \frac{\rho_{4,\max} + \rho_{4,\min}}{2}\mu_2 + \delta_3 \frac{\rho_{4,\max} - \rho_{4,\min}}{2}\mu_2 \\
A_{3,3} =& -k_{12} - \delta_6 \Delta k_{12} - \frac{\rho_{5,\max} + \rho_{5,\min}}{2}\mu_3 - \delta_9 \frac{\rho_{5,\max} - \rho_{5,\min}}{2}\mu_3 \\
A_{3,4} =& \frac{\rho_{1,\max} + \rho_{1,\min}}{2}(1-\mu_2) - \delta_7 \frac{\rho_{1,\max} + \rho_{1,\min}}{2}(1-\mu_2) \\
A_{3,5} =& -\frac{\rho_{3,\max} + \rho_{3,\min}}{2}(1-\mu_3) - \delta_{10} \frac{\rho_{3,\max} + \rho_{3,\min}}{2}(1-\mu_3) \\
A_{4,4} =& -k_{b1} - \delta_{11} \Delta k_{b1} \\
A_{4,7} =& S_{IT} k_{b1} + \delta_{12}(\Delta S_{IT} k_{b1} + \Delta S_{IT} k_{b1} + \Delta S_{IT} k_{b1}) \\
A_{5,5} =& -k_{b2} - \delta_{13} \Delta k_{b2} \\
A_{5,7} =& S_{ID} k_{b2} + \delta_{14}(\Delta S_{ID} k_{b2} + \Delta S_{ID} k_{b2} + \Delta S_{ID} k_{b2}) \\
A_{6,6} =& -k_{b3} - \delta_{15} \Delta k_{b3} \\
A_{6,7} =& S_{IE} k_{b3} + \delta_{16}(\Delta S_{IE} k_{b3} + \Delta S_{IE} k_{b3} + \Delta S_{IE} k_{b3}) \\
A_{7,7} =& -k_e - \delta_{17} \Delta k_e \\
A_{7,8} =& \frac{k_a}{V_I} + \delta_{18} \frac{\Delta k_a}{V_I} \\
A_{8,8} =& -k_a - \delta_{18} \Delta k_a \\
A_{8,9} =& k_a + \delta_{18} \Delta k_a \\
A_{9,9} =& A_{8,8} \\
B_{2,1} =& B_{2,9} = C_{1,1} = 1, \text{and the other non-defined elements are 0.}
\end{aligned}
\qquad . \qquad (2.7)
$$

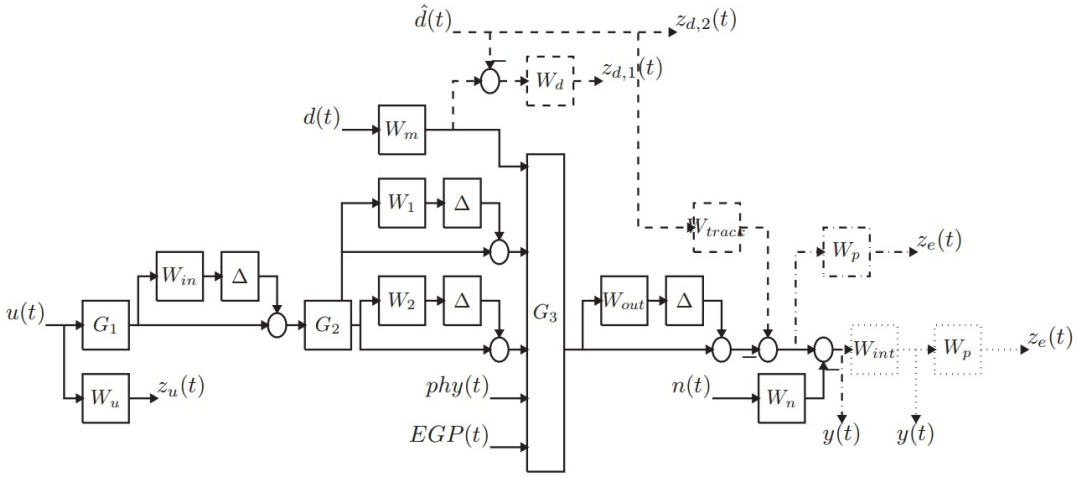


Figure 2.1.: Considered structures of the H_∞ controllers.

information on the fact that the state variable $\xi_3(t)$ and the endogenous glucose production are connected.

Weighting functions

Weighting functions and unstructured uncertainty blocks represent effective tools to incorporate our apriori knowledge of the controlled process into the model that is used for controller design. Unstructured uncertainty blocks represent linear systems with bounded norms (H_∞ norm ≤ 1) and unknown but stable and minimal phase dynamics [60]. Furthermore, various constraints can be represented with weighting functions, such as control signal limitations, tracking performance, and disturbance rejection. Once a model has been constructed in such a manner, computing the parameters of the corresponding controller becomes a convex optimization problem. This is one of the greatest advantages of modern robust controllers and it requires a deep understanding of the process dynamics (in our case the T1DM) obtained mostly from measurements. In our case, the gained knowledge and hence, the understanding of the diabetic patient behavior came from 83 patients' more than 200-week continuous glucose datasets analyzed throughout the years and collected from the insulin pump centers of the Hungarian Artificial Pancreas Working Group created in collaboration with the Hungarian Diabetes Association [69, 72].

Using the parameter inaccuracy information and the LPV-model constructed above, uncertainty weighting functions can be determined. There are altogether four of these functions: $W_{in}(s), W_1(s), W_2(s)$ and $W_{out}(s)$. The transfer functions were determined

Table 2.1.: Parameters of performance weighting functions.

Controller	T	τ	K
Regular (low γ)	300	9.6774	0.031
Regular (high γ)	350	7.7778	0.045
Integral (low γ)	400	40	0.01
Integral (high γ)	300	30	0.05
2DoF (low γ)	400	16	0.025
2DoF (high γ)	300	30	0.05
Integral 2DoF (low γ)	400	40	0.01
Integral 2DoF (high γ)	300	30	0.05

Table 2.2.: Parameters of performance weighting functions for switching controllers.

Controller	T	τ	K
Regular ($4.5 < Q_1(t)/V_G \leq 5.5$) (low γ)	300	37.5	0.04
Regular ($5.5 < Q_1(t)/V_G \leq R_{th}$) (low γ)	300	50	0.03
Regular ($R_{th} < Q_1(t)/V_G$) (low γ)	300	33.33	0.045
Regular ($4.5 < Q_1(t)/V_G \leq 5.5$) (high γ)	300	6	0.05
Regular ($5.5 < Q_1(t)/V_G$) (high γ)	300	5	0.06
Integral (low γ)	400	40	0.01
Integral ($4.5 < Q_1(t)/V_G \leq 5.5$) (high γ)	300	30	0.05
Integral ($5.5 < Q_1(t)/V_G \leq R_{th}$) (high γ)	300	25	0.06
Integral ($R_{th} < Q_1(t)/V_G$) (high γ)	300	21.43	0.07
2DoF ($4.5 < Q_1(t)/V_G \leq 5.5$) (low γ)	300	9.375	0.032
2DoF ($5.5 < Q_1(t)/V_G \leq R_{th}$) (low γ)	300	10	0.03
2DoF ($R_{th} < Q_1(t)/V_G$) (low γ)	300	8.57	0.035
2DoF (high γ)	300	12	0.05
Integral 2DoF ($4.5 < Q_1(t)/V_G \leq 5.5$) (low γ)	300	30	0.01
Integral 2DoF ($5.5 < Q_1(t)/V_G \leq R_{th}$) (low γ)	400	40	0.01
Integral ($R_{th} < Q_1(t)/V_G$) 2DoF (low γ)	300	12	0.025
Integral 2DoF ($4.5 < Q_1(t)/V_G \leq 5.5$) (high γ)	300	30	0.05
Integral 2DoF ($5.5 < Q_1(t)/V_G \leq R_{th}$) (high γ)	300	7.5	0.04
Integral 2DoF ($R_{th} < Q_1(t)/V_G$) (high γ)	300	23.077	0.065

based on a gridding technique and upper approximation of the frequency responses obtained, similar to [62]. The results are based on the simulations of six patients in the in-silico simulator of SimEdu. $W_{in}(s)$ represents the uncertainty of the dynamics of the subsystem (denoted as $G_1(s)$ later) of (2.1) consisting of the state variables $S_1(t), S_2(t)$ and $I(t)$. Its transfer function is presented in (2.8). At smaller frequencies, the uncertainty remains 5.5%, while it rises up to 22% for frequencies larger than 0.1 rad/min [62].

$$W_{in}(s) = 0.055\frac{101.01s+1}{25.31s+1} \tag{2.8}$$

$W_1(s), W_2(s)$ represent the uncertainty of $x_1(t)Q_1(t)$ and $x_2(t)Q_2(t)$ output of the subsystem containing state variables $x_1(t), x_2(t)$ and $x_3(t)$ (referred to as $G_2(s)$). This includes the effect of the changing parameters and the change of the selected scheduling parameters. The chosen transfer functions of these weights are presented in (2.9). All values were determined by the same gridding technique [62], except that here both model parameter and scheduling parameter changes were considered. $W_2(s)$ is significantly larger than $W_1(s)$ since $x_2(t)$ varies in a wider range. Furthermore, the parameters of $W_2(s)$ are different for each of the six patient, while one common $W_1(s)$ is used. K, T and τ are additional parameters.

$$\begin{aligned} W_1(s) &= 0.536\frac{714s+1}{624s+1} \\ W_2(s) &= K\frac{\tau s+1}{Ts+1} \end{aligned} \tag{2.9}$$

Finally $W_{out}(s)$ was chosen as presented in (2.10). In the subsystem ($G_1(s)$) consisting of state variables $C(t), Q_1(t)$ and $Q_2(t)$ there are various uncertain parameters, including a scheduling variable, as well as a kind of switching effect because of renal clearance: $R_{cl} = \max\{0,\ Q_1(t) - R_{thr}V_G\}$. The other switching component representing endogenous glucose production ($EGP_0 = \max\{0,\ 1 - x_3(t)\}$) is treated as noise in accordance with what was presented earlier as gained knowledge about the nominal model. On higher frequencies, the amplitude goes up to one, which represents 100% uncertainty. This represents the assumption that no reliable information on the behavior of the system is present on frequencies close to the sampling frequency.

$$W_{out}(s) = 0.15\frac{100s+1}{15s+1} \tag{2.10}$$

The disturbances also require weighting functions. $W_m(s)$ for the glucose flux from the gut is created using the meal absorption model presented in [67]. Although it is nonlinear

in the original model, a worst case representation is possible with a second order linear system:

$$W_m(s) = \frac{U_{G,ceil}}{(t_{max}s + 1)^2}, \tag{2.11}$$

where $U_{G,ceil}$ is the maximum glucose flux from the gut [mmol/kg/min], while t_{max} is the time-to-maximum appearance rate of glucose in the accessible compartment [min]. The effect of physical activity does not need an additional component aside from a corresponding input. The measurement noise has a constant weighting function $W_n = 0.5$, representing 0.5 [mmol/L] standard deviation of the measurement noise. The constraints on the control signal can also be captured with a weight. It can be either constant with value $W_u = u$, or one can also restrict fast changes with a transfer function. Limiting the control signal on higher frequencies can prevent rapid oscillations.

Finally, one have to define the desired tracking performance with a weighting function denoted as $W_p(s)$. Our choice in this particular case is presented by a first-order system given in (2.12). The numerical values are different for every controller, but the structure remains the same in the sense that the requirements are different for lower and higher frequencies. The former drives the glucose concentration towards the normoglycemic range, while the latter gives more relaxed bounds on rapid changes. This is in accordance with the uncertainty of the model in high-frequency regions. Furthermore, oscillations and hypoglycemic episodes can be reduced at the cost of longer hyperglycemic events.

$$W_p(s) = K\frac{\tau s + 1}{Ts + 1} \tag{2.12}$$

The numerical values for each controller are summarized in Table 2.1. Note that there are two versions for each controller. The reasons will be explained later in Section 2.1.3. As an example, choosing 0.5 for low frequencies means that the residual tracking error should be lower than 2 [mmol/L] even in the most extreme case.

In classical control theory, PID control or controllers containing an integrator can effectively eliminate residual error, which is a useful property when dealing with uncertain systems. However, in H_∞, control performance weighting functions cannot contain integrator, for it has infinitely large H_∞ norm, but one can make it part of the model in a different manner. In this case, the additional $W_{int}(s)$ component could be defined with a transfer function given in (2.13), determined on the responses of the virtual simulator. The output of $W_{int}(s)$ must be made available for measurement.

$$W_{int}(s) = \frac{1000s + 1}{1000s} \tag{2.13}$$

Furthermore, a two degree of freedom (2DoF) control structure is also possible. To achieve this, the reference system is required to be $W_{track}(s)$. Instead of following a reference signal directly, the aim was to match the behavior of the controlled system to the reference system. In the case of a classical 2DoF control, the controller consists of a feedforward and feedback component, where the former acts as a filter of the reference signal. Since the reference signal, in this case, is constant, the feed-forward component is not needed.

Moreover, an adequate estimation of the disturbances affecting the model is required, for which the reference model responds with the desired behavior. Hence, the controller in the 2DoF model will provide an estimation of the output of $W_m(s)$ with estimation error constrained by weighting function $W_d(s)$. Only the meal disturbance was considered since this has the most significant impact on the blood glucose levels among the processes that always elevate the glucose concentration. Endogenous glucose production is assumed to change rapidly because of the switching effect, hence it is difficult to observe in these settings. The transfer functions of $W_{track}(s)$ and $W_d(s)$ are presented in (2.14) and determined by responses from simulations in SimEdu. Note that the output of $W_m(s)$ is divided by U_G before entering $W_d(s)$.

$$\begin{aligned} W_{track}(s) &= \frac{76500s}{3000s^2 + 310s + 1} \\ W_d(s) &= 0.75\frac{2.86s + 1}{215s + 1} \end{aligned} \tag{2.14}$$

Controller structure

The controller structures for regular controller, integral control, 2DoF control and 2DoF with integrator are presented on Fig. 2.1 including all the uncertainty weighting functions determined above. The components with solid line are common for all types and the weighting functions described above. In case of 2DoF control, the elements drawn with dashed line should be also taking into account, including the tracking performance weighting function $W_p(s)$, the $W_d(s)$ for output estimation of $W_m(s)$ and the reference system $W_{track}(s)$. Dotted line marks the parts that belong to integral control ($W_{int}(s)$ and a separate tracking performance function $W_p(s)$), as opposed to the semi-dotted elements that are present only in the absence of the integrator.

The components $W_{in}(s), W_1(s), W_2(s), W_{out}(s), W_m(s), W_n(s), W_u(s), W_p(s), W_{int}(s)$, $W_d(s)$ and $W_{track}(s)$ were introduced previously. $G_1(s), G_2(s)$ and $G_3(s)$ stand for the subsystems described when the uncertainty weighting functions were presented. The

controller provides the injected insulin control signal $u(t)$ and estimated disturbance $\hat{d}(t)$ in the 2DoF case. The disturbances are the ingested meal $d(t)$, effect of physical activity $phy(t)$, sensor noise $n(t)$, and the disturbance resulting from endogenous glucose production $EGP(t)$. $z_e(t)$ and $z_u(t)$ are outputs of the performance weighting functions, while $z_{d1}(t)$ and $z_{d2}(t)$ keep the disturbance estimation in check. $y(t)$ is the measured output of the system. Note that the reference signal cannot be found in Fig. 2.1. The reason is that the reference signal is constant, and no constant input of the model has significance when designing a linear dynamic system. The offset caused by the reference signal, or other elements of the model is compensated by the integrator if present, otherwise an additional constant input is needed.

An additional safety feature has been included in all controllers. Whenever the measured blood glucose concentration reaches a certain lower limit (4.5 [mmol/L]), the control signal will be set as zero. This is a frequently used method in recent insulin pumps avoiding or reducing certain hypoglycemic episodes. The controller could be tuned to avoid these episodes without using this feature, if the uncertainty of the model would not be this high. However, the reason of high uncertainty used in this paper was to iterate on the possibilities in modern robust controller design, giving a roadmap to it.

The current case study highlights the difficulties in order to assert proper robust performance (RP). This can only be satisfied by defining weak tracking performance, inadequate to keep the plasma glucose concentration of the patient in the normoglycemic range. Therefore, two different versions were considered for each controller; one where RP is met and one where only robust stability (RS) is assured. The latter has stricter performance specifications, which are not met, but closed loop stability is still ensured (it is needless to say, a true solution would reduce the uncertainties of the system, but this cannot be done solely with a linear controller). One very important feature of this control strategy is that no information regarding the occurrence and size of meals is provided, unlike many other methods found in the literature. This certainly leaves a great burden on the controller, but makes it significantly less dependent from the compliance of the patient and approaches better the real life situation of a diabetic patient.

Switching control

A more effective approach can take into consideration the switching nature of the model. Endogenous glucose production (EGP) and renal clearance (R_{cl}) represent linear dependencies in certain working points, and non-existent in others. Treating each case separately four different models can be defined requiring four different controllers. Each model has slightly different dynamics, but individually they impose less burden on the

respective controllers. Furthermore, based on the blood glucose levels more models can be defined, similar to [73]. The six considered models are:

- No $EGP(t)$ and $Q_1(t) \in [4.5 \cdot V_G, 5.5 \cdot V_G]$ (no renal clearance);
- $EGP(t)$ is active, $Q_1(t) \in [4.5 \cdot V_G, 5.5 \cdot V_G]$ (no renal clearance);
- No $EGP(t)$ and $Q_1(t) \in (5.5 \cdot V_G, R_{th}V_G]$ (no renal clearance);
- $EGP(t)$ is active, $Q_1(t) \in (5.5 \cdot V_G, R_{th}V_G]$ (no renal clearance);
- No $EGP(t)$ and $Q_1(t) > R_{th}V_G$ (renal clearance active);
- $EGP(t)$ is active, $Q_1(t) > R_{th}V_G$ (renal clearance active);

Unfortunately the state variables that could be used to perform the switching cannot be measured, only estimated. The structure of the nominal model and the controllers are the same as previously, except that $EGP(t)$ is not a disturbance any more, but rather a part of the system. This calls for an additional uncertainty weighting function $W_3(s)$ given in (2.15), which incorporates the parameter changes of k_{b3} and S_{IE}. Similarly to $W_1(s)$ and $W_2(s)$ the parameters of $W_3(s)$ were determined by the same gridding technique [62, 74].

$$W_3(s) = 0.0627\frac{17.7904s + 1}{11.468s + 1} \tag{2.15}$$

By the aforementioned considerations on switching, the uncertainty will be reduced for certain components of the model. Furthermore different weighting functions can be defined for different working points and also for different patients. $W_1(s)$ differs depending on the value of $Q_1(t)$ resulting in three different weights given as follows:

$$W_1(s|4.5 < Q_1(t)V_G \leq 5.5) = 0.15\frac{714.286s + 1}{515.724s + 1} \tag{2.16}$$

$$W_1(s|5.5 < Q_1(t)V_G \leq R_{th}) = 0.41\frac{714.286s + 1}{608.415s + 1} \tag{2.17}$$

$$W_1(s|R_{th} < Q_1(t)V_G) = 0.103\frac{714.286s + 1}{464.28s + 1}. \tag{2.18}$$

Based on the remarks given at the selection of $W_2(s)$, i.e. the parameters of $W_2(s)$ are different for each of the six patient (see Eq. (2.9)), for every switching case a corresponding frequency evaluation of $W_2(t)$ is required. On the other hand, based on (2.10), the $W_{out}(s)$ weighting function represents smaller uncertainty on lower frequencies.

$$W_{out}(s) = 0.02\frac{2.05s+1}{100s+1} \tag{2.19}$$

Three mostly different performance weighting function were determined for every controller depending on the value of $Q_1(t)$. The controllers could further be tuned by defining different W_p for every working point. The parameters are summarized in Table 2.2. The time constant (T) is selected on the model property (only in case of integral control is used a higher time due to meal absorption), K and τ are results of the weighting functions selected.

Similarly to the non-switching case, two different versions have been implemented for each type of controllers: one where RP is satisfied and one where only RS is true. The structures of all four switching controllers are presented in Fig. 2.2 (similar to Fig. 2.1, just that here the uncertainty weighting function $W_3(s)$ is included in addition to the endogenous glucose production part), where the line-style of the different elements is the same as in the nonswitching case. The components with solid line are common for all types. In case of 2DoF control, the elements drawn with dashed line should also be taken into account. Dotted line marks the parts that belong to integral control, as opposed to the semi-dotted elements that are present only in the absence of the integrator. All six controllers were implemented and ran in parallel. The control signal will be the weighted sum of all controller outputs. The weights are determined by using sigmoid functions to avoid rapid changes in the signal during switching. For a controller that is valid when $Q_1(t) \in [Q_{1,i}, \bar{Q}_{1,i}]$ and $x_3(t) \in [x_{3,i}, x_{3,i}]$ the weight $\tilde{w}_i$ will be determined as follows:

$$\begin{aligned} w_i = &\frac{1}{1+\exp(M(\underline{Q}_{1,i} - Q_1(t)))} + \frac{1}{1+\exp(M(Q_1(t) - \bar{Q}_{1,i}))} \\ &\times \frac{1}{1+\exp(M(\underline{x}_{3,i} - x_3(t)))} \frac{1}{1+\exp(M(x_3(t) - \bar{x}_{3,i}))} \end{aligned} \tag{2.20}$$

$$\tilde{w}_i = \frac{w_i}{\sum_{j=1}^{6} w_j}. \tag{2.21}$$

The control signal is considered zero when the lower threshold of the measured glucose concentration (4.5 [mmol/L]) is reached. Compared to the non-switching case, smaller γ values could be achieved for the same performance functions. On the other hand, the synthesis could become ill-conditioned when faster tracking properties are enforced. Consequently, balanced model reduction was necessary [60].

Table 2.3.: Parameters of performance weighting functions for switching controllers.

Meal type	Chance of occurrence	Amount (g CHO)	Time
Breakfast	100%	50 – 90 g	6:00 – 10:00
Snack 1	50%	10 – 50 g	8:00 – 11:00
Lunch	100%	60 – 120 g	11 :00 – 15:00
Snack 2	50%	10 – 30 g	15:00 – 18:00
Dinner	100%	35 – 95 g	18:00 – 22:00
Snack 3	50%	10 – 20 g	22:00 – 24:00

Table 2.4.: Summary of simulation results for all controller types.

Controller	Hypo <4 [mmol/L]	Norm 4–6 [mmol/L]	Mild hyper 6–7.8 [mmol/L]	Hyper 6–11.1 [mmol/L]	Severe hyper >11.1 [mmol/L]
without switching					
Regular (low γ)	6.68%	25.98%	10.11%	26.67%	40.66%
Regular (high γ)	13.40%	28.34%	12.51%	30.03%	28.23%
2DoF (low γ)	3.13%	23.24%	9.01%	23.00%	50.63%
2DoF (high γ)	10.75%	26.93%	11.87%	30.42%	31 .90%
with switching					
Regular (low γ)	5.35%	27.02%	8.14%	24.45%	43.17%
Regular (high γ)	11.39%	28.83%	9.13%	26.46%	33.33%
2DoF (low γ)	4.59%	25.49%	6.78%	21.28%	48.64%
2DoF (high γ)	10.41%	28.33%	8.32%	25.14%	36.13%

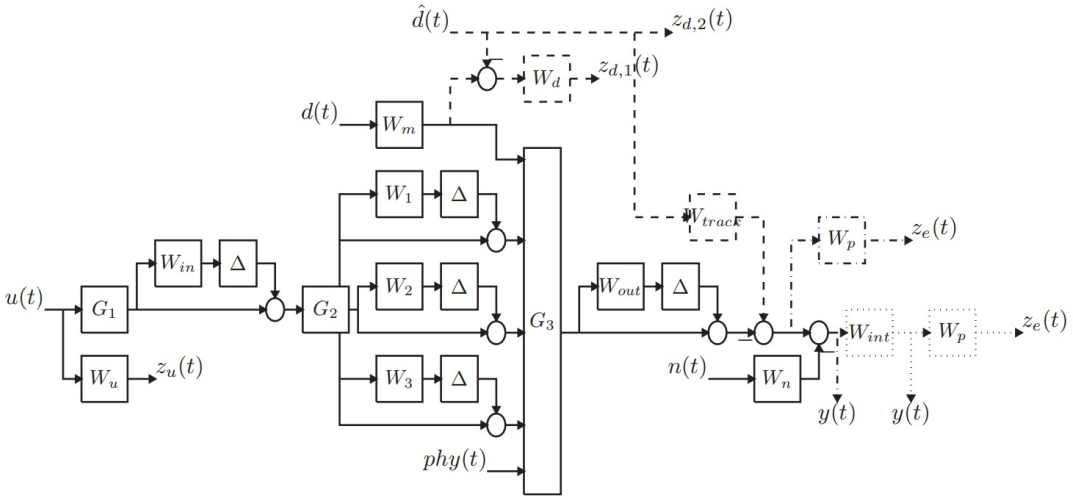
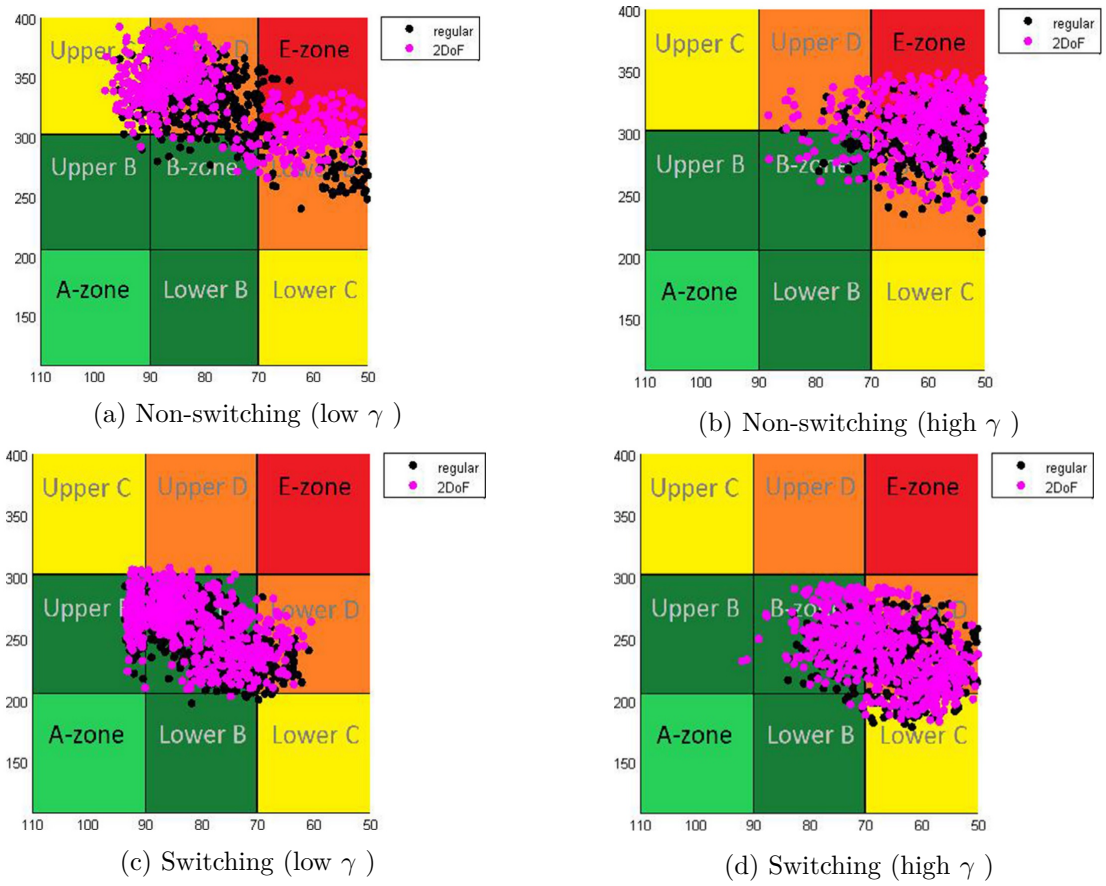


Figure 2.2.: Considered structures of the switching H_∞ controllers.



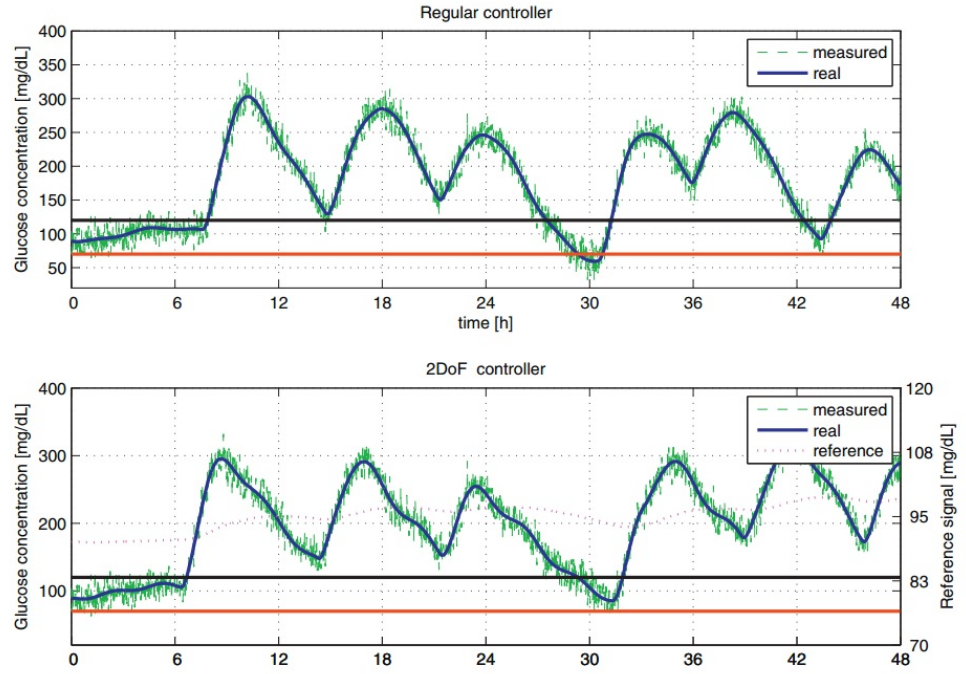
(a) Non-switching (low γ)

(b) Non-switching (high γ)

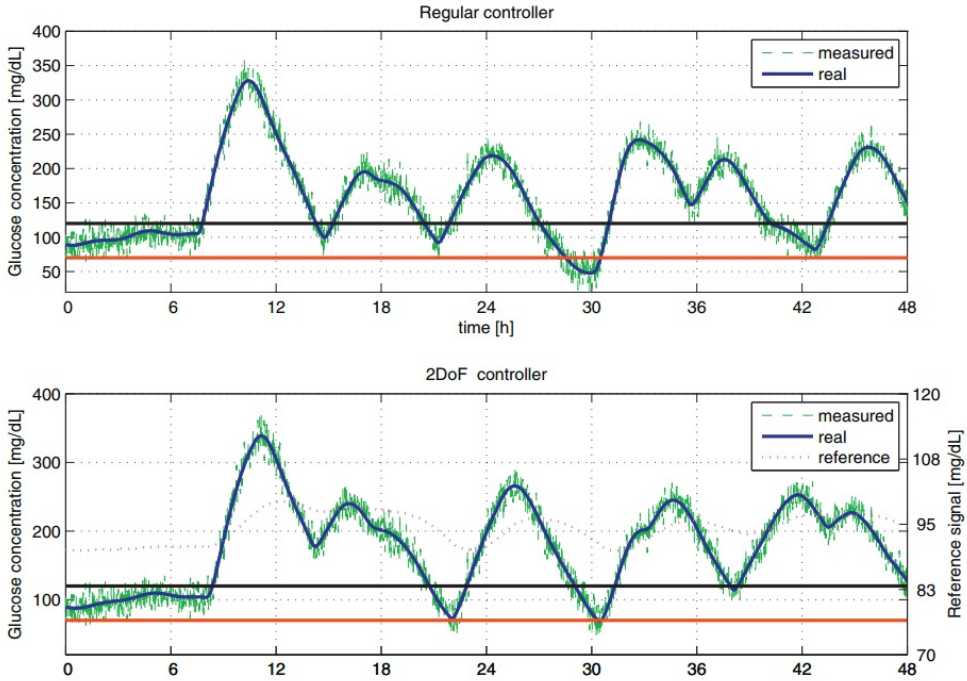
(c) Switching (low γ)

(d) Switching (high γ)

Figure 2.3.: CVGA analysis of the switching and non-switching cases.



(a) Low γ



(b) High γ

Figure 2.4.: Simulation over time for non-switching H_∞ controller (high and low γ). "Measured" represents the signal measured by the CGM sensor, "real" stands for the output of the system, while "reference" is for the output of the reference system W_{track}.

2.1.4. Simulation results

Altogether eight different controllers were implemented and tested using the University of Cambridge Simulator SimEdu version 2.2. In the case of integral control, RP was not possible to be achieved by merely reducing the weighting of the tracking performance, and not even RS could be ensured in certain cases. Results include massive hypoglycemic episodes during simulation, which suggests that unless the uncertainty is reduced, or additional information is made available regarding the disturbances, integral control is not favorable for H_∞ control of this model. However, for H_2 or L_1 control the idea might be more effective [60]. PID control is extensively researched for the AP problem [15], [75], therefore extending the controller with an integrator could be considered for robust methods as well.

Six virtual patients of the SimEdu in-silico simulator were used and 100 simulations were conducted for each patient with randomized initial states, parameter change, meal, and physical activity profile. Uniform distribution was used in all cases. Table 2.3 summarizes the parameters of meal intakes. Physical activity occurred 50% of the time starting between 9:00–12:00 and lasting for 1–4 hours. It can be seen from Table 2.3 that based on the relatively wide ranges of meal intake possibilities (simulating in this way the uncertain carbohydrate (CHO) estimation of the patients) even extreme meal intakes (400 g CHO) can occur. Moreover, by the uncertain time intervals, the idea was to deal with the uncertain registration of the meal periods as well.

For all simulations, a complete 48 hours simulation time interval was considered. The simulation results were evaluated based on the international standards of control variability grid analysis (CVGA) [76]. Figs. 2.3a–2.4b shows the analysis for the switching and non-switching cases separating the case when only RP (low γ) or when only RS (high γ) is satisfied. Instead of [mmol/L] the results are presented in the more widely used mg/dL format, for easier comparison. Fig. 14 reflects the non-switching robust control results. It can be seen that taking the uncertain meal intake or time recording into account, for scenarios presented in Table 2.3 efficient and generally robust control cannot be achieved.

This result presents the pros and cons of a modern robust control methodology. Only guaranteeing RP does not mean that one could obtain a suitable controller. It is true that the controller achieved is generally applicable, but in a physiologically unacceptable range which means large oscillations with a number of hypo- and hyperglycemic episodes that endanger diabetic patients' life. This remark is valid concerning RS as well (Fig. 2.3b). Moreover, results in Fig. 2.3b demonstrate illustratively that RS performs worse in quality requirements than RP. Simulations over time are exemplified by Figs. 2.4a

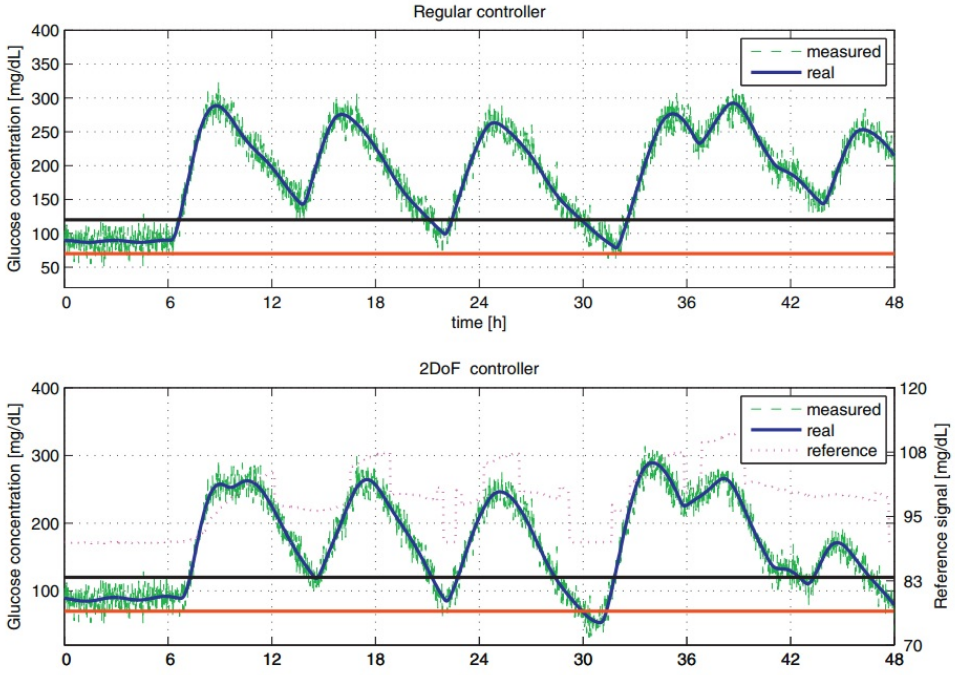
and 2.4b for both (RP and RS) cases.

By the switching control scheme (Fig. 2.3c) a qualitatively increased performance can be observed. RP is better matched with the physiological expectations due to the different working regimes where the controller can satisfy more adequately the physiological requirements. Besides the considered uncertain and extreme scenarios, the approach can avoid most of the hypoglycemic events (most dangerous for T1DM patients). In the remaining cases, the hypoglycemic episode is mild and does not pose a general threat to the patient. Regarding hyperglycemia, a considerable drop in CVGA can be observed in Figs. 2.3a and 2.3b. Moreover, due to the high meal intake scenarios, it is expected to have high glucose levels for T1DM patients. Focusing only on RS (Fig. 2.3d), the same remarks can be concluded as in the non-switching cases. Although RS can be guaranteed, without satisfying the nominal performance requirements (in this case minimizing hypoglycemia) the control quality is worse. In the switching cases, simulations over time are exemplified by Figs. 2.5a and 2.5b again for both (RP and RS) cases. In the case of 2DoF control, the reference signal is also displayed. Table 2.4 summarizes the simulation results for all the eight considered controller structures. Analyzing these results, the following remarks can be made:

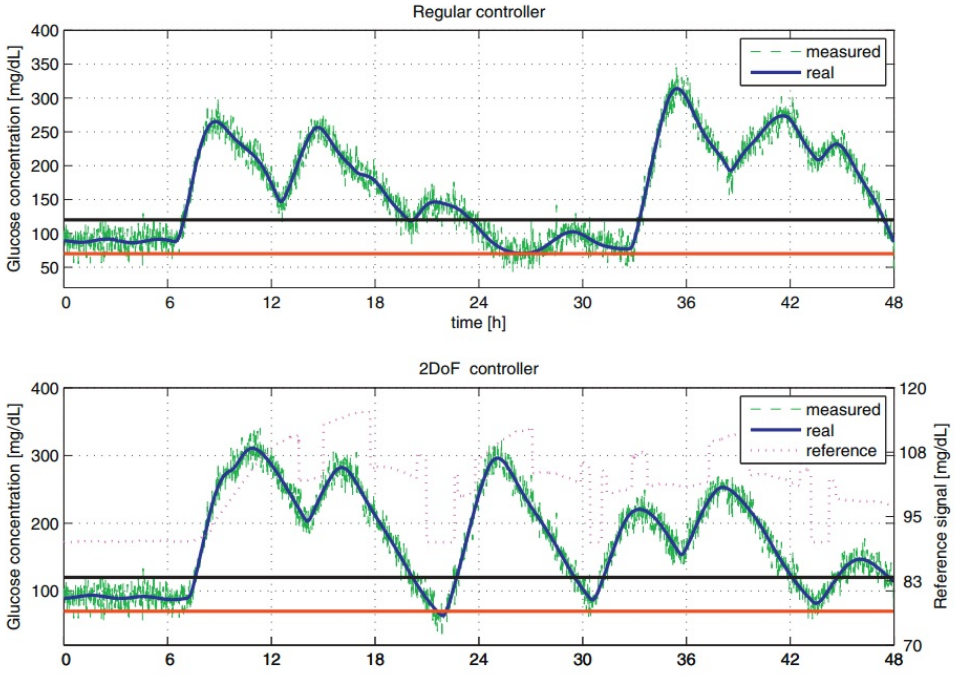
- While the proposed controllers are not ideal, they can prove their robust characteristics. With the extreme scenarios considered here, they can guarantee RP (or RS). In this way, a hierarchical control solution with individualized control adapted to the patient's physiology placed in a robust control framework to guarantee RP even in the worst cases can be a real alternative for the AP problem.

- For higher γ values, when only RS is met, blood glucose levels usually do not go as high when RP is satisfied. However, this comes at the cost of a higher possibility for hypoglycemic episodes. 2DoF control can slightly shorten the duration of hypoglycemic episodes. It might be more favorable to provide disturbance estimation with a more capable tool, e.g.: Kalman filters or their extensions on sigma-point filtering [77], [78].

- Switching control could considerably improve the results by defining different working regimes where the controller could focus only on a part of the complete dynamics. In this context, I have designed the corresponding controller used in this robust control framework. Results were presented in [77] and Fig. 2.6 illustrates a simulation result of the system, where the shortcomings presented in the above roadmap were avoided.



(a) Low γ



(b) High γ

Figure 2.5.: Simulation over time for switching H_∞ controller. *Measured* represents the signal measured by the CGM sensor, *real* stands for the output of the system, while *reference* is for the output of the reference system W_{track}.

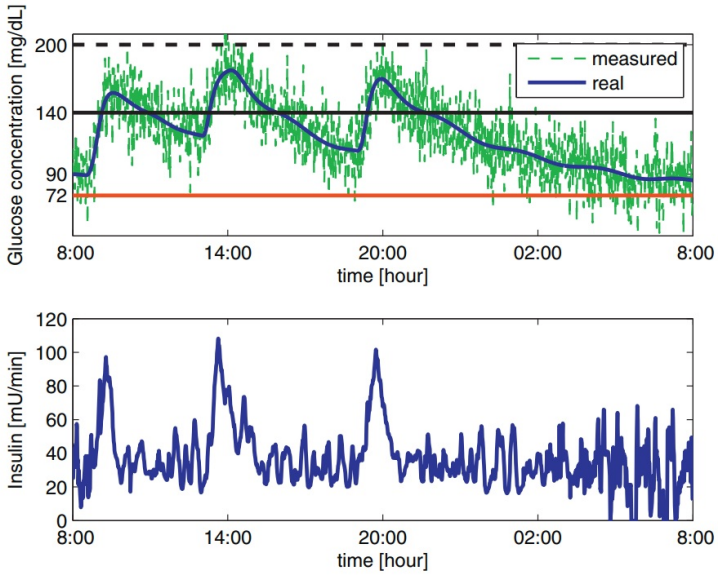


Figure 2.6.: Simulation over time for switching H_∞ controller (low γ). "Measured" represents the signal measured by the CGM sensor, "real" stands for the output of the system.

Summary

In this chapter, the implementation of H_∞ controllers was investigated for the widely known and used T1DM model published in [39] and later updated in [67]. From the nonlinear model, a nominal linear system was constructed with weighting functions representing the nonlinearity and parameter inaccuracies. These weights were identified either from real diabetic patient measurements or from simulations of the validated SimEdu virtual simulator. Using this configuration, regular, integral, 2DOF, and integral 2DOF H_∞ robust controllers were implemented, both for switching and non-switching cases. Simulations were conducted using 6 virtual patient data.

The study intended to show the possible issues appearing in the H_∞ controller design for this particular artificial pancreas problem. The exact mathematical formulation of modern robust technique was combined with the empirical (knowledge-based) expertise gained from medical practice. The most practical issues have been addressed and results have been tested for extreme scenarios (high meal intakes and uncertain time recording). Switching control possibilities have also been presented. Besides the robust control design roadmap was given in the Chapter, the advantage of the research from a control engineering point of view is to present the sensitivity of uncertainty weighting function selection. It shows, that without given expertise (in this case medical knowledge) not

only robust, but even unstable solutions can be achieved. From the clinical point of view the clear advantage is that once a robust controller is designed, there is no need to tailor the controller to different patients or treatment scenarios.

Future research should focus on solving the H_∞ controller design on the investigated model using LPV modeling methodology, but also extended to a generalized LPV approach of Tensor Product model transformation [79], [80]. Since the scheduling parameters cannot be measured directly, accurate estimation is needed and the resulting error must be considered and incorporated into the nominal model formulation [81–85]. Furthermore, H_2 and L_1 robust controllers can be implemented and compared with the ones presented in this paper. Hybrid controllers satisfying multiple constraints or hierarchical control structure combining individualized control strategies with modern robust methods are an option as well. Practical issues, such as sensor dynamics, errors, and insulin pump failures should also be addressed together with other optimization methods e.g. [41, 64, 78]. As a final remark, it is important to mention that the aim of modern robust control is not to compete with individualized methodologies, but to efficiently extend them giving extra safety guarantees.

3. Robust Fixed Point Transformation based Control of Diabetes Mellitus and Tumor Growth

This chapter presents the examination of the applicability of the Robust Fixed-Point Transformations (RFPT) method as a viable control strategy for physiological systems. The RFPT based control idea is introduced through two examples related to the control of T1DM and tumor growth. The practical realization of the control problems and the calculations have been carried out using MATLAB^{TM}, SCILAB^{TM} and Julia^{TM} programming languages in this section.

3.1. The theoretical aspects of the RFPT methodology

In physiological control, the use of highly complex models is common, although, there are many practical disadvantages regarding this practice. The first one is obvious: complex models are more challenging to handle and it needs deep analysis of the problem to find those nonlinear or linear control design methods which work well for the certain control task. Another issue is that the widely applied techniques are model based ones which unfortunately means that one have to trust both the validity of the model structure and the parameters of it. Traditionally, the applicable control methodologies require information about the actual output or the actual states of the system. Furthermore, it is usually impossible to afford concrete information about the state variables of the system, because one do not have the necessary sensor technology or do not have access to them at all. A possible solution is the application of state observers or estimators, although, these are also affected by the different modeling uncertainties which may make their prediction imprecise or even questionable in certain cases.

These circumstances can be handled by using the methods of Lyapunov. The direct method of Lyapunov allows to determine the stability of a certain nonlinear system without solving the equations of motion. This property is the biggest advantage of the method since many real life problems do not have analytical solution and the numerical

solutions may contain significant inaccuracies. These facts make the Lyapunov methods one of the most important tools for control engineers [86]. The Lyapunov method is based on the properties of the so-called Lyapunov function $V(t,x)$. Consider a general nonlinear system $\dot{x}(t) = f(t,x)$ with $\xi = 0$ equilibrium. The system can be given as follows:

$$\dot{x}(t) = f(t,x) \qquad f(t,0) = 0 \qquad f(t,x) \in C_{t,x}^{(0,1)} \ . \tag{3.1}$$

Assume that $\exists V(t,x) \in C_{t,x}^{(1,1)}([a,\infty) \times D_x)$ positive definite Lyapunov function which has the following property $\forall x(t)$ trajectories

$$\dot{V}(t,x) = \frac{\mathrm{d}V(t,x)}{\mathrm{d}t} < 0 \qquad (x \neq 0, \dot{V} \text{ negative definite}). \tag{3.2}$$

In this case the $\xi = 0$ solution is an equilibrium of the system and $\xi = 0$ is asymptotically stable in Lyapunov sense. In general, $V(t,x) = 0$ if and only if $x = 0$, $V(t,x) > 0$ if and only if $x \neq 0$ and $\dot{V}(t,x) < 0$ if $x \neq 0$ properties must be hold for the asymptotic stability in the case of arbitrary nonlinear systems [86].

Despite the general solution which can be provided by Lyapunov's theorems, it should be noted that their practical applicability does have many drawbacks. They are able to provide controllers which guarantee the asymptotic stability of a nonlinear system, but they do not provide detailed information on how they attain it. It might happen that during operation particular transient behaviors occur, which are physically infeasible. It is hard to embed the limitations and restrictions belonging to the controlled system into the controller design. Simple rules exist only in case of a few specific nonlinear system, but each nonlinear system is different and requires unique solution and design. The practical application is hard due to it requires expert designer with good mathematical and analytical skills. Another issue is that many Lyapunov-based control design methods require internal information about the system, which is not available by default. In these cases different estimators needed to be used to approximate the internal state which could be another source of error. Altogether, these circumstances created a demand for alternative approaches, which are independent from the Lyapunov's methods and not suffering from their drawbacks, with similar effectivity and easier applicability.

The classical control approaches are based on the expected-observed scheme. Namely, there is a predefined system behavior which is expected (e.g. reference value or trajectory – which is often called nominal or desired system behavior r^d) and the system acts somehow according to its internal dynamics which is observed at the output (which is often called realized system behavior r^r). The aim of the control in these cases is to enforce the

system φ by applying the control signal u that $\varphi(u) = r^r = r^d$ when $t \to \infty$. The main problem with these approaches is that the system model φ can only be modeled approximately. Thus, the desired and realized outputs could only be equal in case of very simple systems which can exactly be modelled. This circumstance generally does not hold in case of physiological systems which stems from their complexity. The behavior of the modelled system can be described as

$$r^r = \varphi(u) \ , \tag{3.3}$$

where r^r is the actual (realized) system response obtained when u is applied on the system. The control signal calculation through the exact inverse model can be formulated as follows:

$$u = \varphi^{-1}(r^r) \ . \tag{3.4}$$

The u is the control signal to be applied to get the r^r system response. If one knows what is the beneficial response of the system, namely, the desired response r^d then one can apply u^d desired control signal on the system in order to reach it. The RFPT controller design have a number of benefits compared to the Lyapunov approaches and classical control methods. Instead of focusing on the global stability, the RFPT method focuses on the kinematics of the motion as well. In this way, not only the stability is guaranteed, but also provides details about the motion of the system as well. Global stability can also be guaranteed, but the conditions are different than other methods. It does not require exact models rather only approximate ones. Further, the uncertainties, arising from both parameter and modeling, can be handled by the RFPT-method. Finally, the realization of the controller is easier and more general compared to other nonlinear methods. The necessary design steps are the following: *(i)* realization of the approximate model by considering the essential properties of the system; *(ii)* determination of the control law to be applied by considering the goal of the control; *(iii)* realization of the control environment and tuning of the parameters of the fixed point generator function; and *(iv)* evaluation of the control environment.

The greatest advantage of the RFPT-based method is that an approximate system model is just enough for the controller design. Based on the inverse approximate model φ^{-1}_{appr}, the approximate control signal u^d_{appr} can be calculated as follows:

$$u^d_{appr} = \varphi^{-1}_{appr}(r^d) \ , \tag{3.5}$$

where r^d is the desired system response. Nevertheless, the realized and desired system

responses from the approximate system are connected to each other in the following manner:

$$r^r \equiv \varphi(\varphi^{-1}_{appr}(r^d)) \equiv f(r^d) \neq r^d \ . \tag{3.6}$$

The RFPT-based method relies on the kinematic property of the system. More precisely, the kinematically formulated trajectory tracking error relaxation is the key which can be used for the control design. The desired system response r^d can be determined as a given order time-derivative of certain variables which can be realized by the application of the control signal. The control signal is approximated by the rough system model φ^{-1}_{appr} which acts on the system φ. The output of the system φ can be described as a response function $f(r)$. Note that $f(r)$ and r have the same dimensions, however, they do not need to contain all state variables. This means that the approximate model can have much lower complexity compared to the original system.

A key idea behind RFPT is to apply an adaptive function which is able to deform the kinematically prescribed r^d value to $r_\star$, namely to reach $r^d = f(r_\star)$. In this way the inverse approximate model is not required to be tuned for different parameter configurations. The deformation can be constructed by turning the control problem into a fixed point problem so that the solution of the control task is the fixed point itself. After, an iterative sequence of the control signals can be generated in the following way: $\{r_0 \overset{def}{=} r^d, r_1 = G(r_0) \ldots, r_{n+1} = G(r_n), \ldots\}$. If the parameters of the transformation function G are well set, then this sequence converges into to the solution of the control task, that is $r_n \to r_\star$. Usually the desired response r^d depends on the lower order time-derivatives of the considered state variables and r can be arbitrary modified. The core concept of proving the stability of the RFPT-based controller relies on the utilization of the properties of Banach spaces and contractive mappings. A Banach space is a linear, normed, complete metric space in which the contractive mapping exists. Namely, it is possible to find a transformation function which can be used to make a connection between the desired, deformed and real responses of the system to be controlled through a fixed point problem:

$$r_{n+1} = G(r_n; r^d) \overset{def}{=} (r_n + K_c)\left(1 + B_c \tanh(A_c(f(r_n) - r^d))\right) - K_c \ . \tag{3.7}$$

Here K_c, A_c, and B_c ($B_c = \pm 1$) are the adaptive control parameters. The function G from (3.7) has two fixed points: $r = -K_c$, which is the trivial fixed point and cannot be utilized for control purposes and $r_\star$ for which $f(r_\star) = r^d$, which is the solution of the control task. If $\left|\mathrm{d}G/\mathrm{d}r\right| < 1$ can be ensured during all times, the iteration will converge

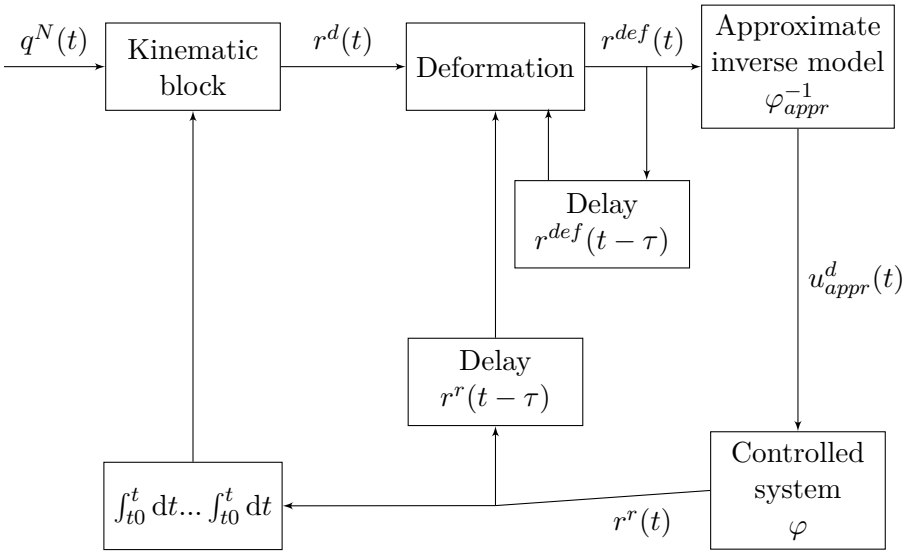


Figure 3.1.: The general RFPT controller scheme: the controller learns from the recent model inputs and observed responses ($q^N(t)$ – Nominal trajectory, $r^d(t)$ – Desired system response, $r^{def}(t)$ – Deformed system response, $r^r(t)$ – Realized system response, τ – Time shift) [89]

into the desired fixed point. Since $B_c = \pm 1$ the response values can be manipulated by tuning K_c and A_c. Additional information about the tuning of these parameters and the convergence criteria for given applications can be found in [87, 88]. The general RFPT controller structure can be seen on Fig. 3.1.

3.2. RFPT-based controller design

The goal of this section is to provide a general step-by-step overview about the RFPT controller design regarding physiological systems. Both the kinematic prescription as well as the derivation of the inverse model is introduced, on which the general design procedure can be formulated.

3.2.1. Effect chain of the control action

Assume that in case of an arbitrary nonlinear system ($f(x(t), u(t)) = y(t)$) the applied control signal and controlled output are denoted by $u(t)$ and $y(t)$, respectively. The first step of the RFPT-based controller design is to determine the connection between the control input $u(t)$ and the controlled output $y(t)$ since the controller uses only these variables and does not require internal information about the system (e.g. it does not need

to estimate internal non-measurable states). Thus, a model is needed which approximately describes this dynamics between $u(t)$ and $y(t)$. The most simple and straightforward case is to utilize the applied virtual patient model and simplify it, but approximate models can be generated in other ways as well. The three possible approaches are the following:

- Approximate model development from measurements: in this case the basis of the model is real patient data from which the approximate input-output model can be created.
- Approximate model development from simple patient model: one can derive a physiological model based on first principles to describe the input-output dynamics and making simplifications on it.
- Approximate model development from complex patient model: one can use a complex patient model and simplify it by transforming the neglected terms of the model to affine terms. Usually, the output of such model becomes a higher derivative of the measured output and the input is the considered control signal.

3.2.2. Approximate model development

As mentioned previously, there are three ways to obtain an approximate model. In the first case, one can use measurements from the patient which contain the control signal (e.g. administered insulin, injected drug, etc.) and the controlled variable (e.g. blood glucose level,tumor volume, etc.). From these measurements general mathematical models can be developed, which can serve as an approximate model. For example, nonlinear polynomial, exponential, or even the autoregressive ARIMA or ARMAX models could be appropriate for this purpose.

The next two options are connected to the utilization of a simple or complex patient model during the approximate model development. Nevertheless, these are not completely model-based solutions, because only the dynamical connection between the input and output are kept from the original model and the unnecessary dynamics and parameters are neglected. The approximate model can be generated by applying a simple patient model with only a few state variables. This model can be transformed after neglecting all of the unnecessary terms (these can be considered as affine varying or affine constant terms as well) and focusing only on the connection between the control input and the controlled output.

Usually, the patient models are described by ordinary differential equations. By mapping the input-output connection, which is the the effect chain of the control action,

an approximate model can be obtained which describe the connection between the control signal and a higher order derivative of the controlled variable (i.e. controlled measurable output). For instance, assume that the original first order non-linear system is given in the following way:

$$\dot{x}(t) = f(t, x(t), u(t)) \ , \tag{3.8}$$

where $x(t)$ and $u(t)$ denote the state variable and control input of the system, respectively. By rearranging (3.8) one get the dynamical connection between the control input and the first derivative of the state variable as follows:

$$u(t) = h(t, \dot{x}(t), x(t)) \ . \tag{3.9}$$

Thus, by using (3.9) one have to develop the control law by applying $\dot{x}(t)$. Complex patient models can also be used to develop the approximate model. In this case, the control signal effects via the effect chain, precisely, through the different state variables among the structure of the model, which are the higher order derivatives of the output. Thus, the approximate model describes the rough dynamical connection between the control input and the higher order derivates of the controlled output. The limitation in this case is that the derivative of the controlled output must exist, but this condition is true for physiological systems in general [1].

3.2.3. Control law development

The RFPT adaptive controller uses the purely kinematic prescription of the tracking error. This means that various options can be applied to generate the control law. For example, assume that the approximate model describes the connection between the third derivative of the controlled variable $\dddot{x}(t)$ and the control input $u(t)$, with a PID-type tracking error ($\Lambda > 0$ is a control parameter). Then the PID tracking can be described as:

$$\left(\frac{\mathrm{d}}{\mathrm{d}t} + \Lambda\right)^4 \int_{t_0}^{t} \left(x^N(\xi) - x(\xi)\right) \mathrm{d}\xi = 0, \tag{3.10}$$

where $x^N(t)$ is the nominal value to be tracked by the system, $x(t)$ is the realized value of the system, and $e(t) = x^N(t) - x(t)$ is the error signal, which should exponentially converge to zero, i.e. $e \to 0$, $t \to \infty$. Due to the properties of the approximate model, a third order control law must be applied in which the control signal is calculated for $\dddot{x}(t)$ and not for $x(t)$. Thus, one have to prescribe the behavior of the desired third derivative

$\dddot{x}^{Des}(t)$ in (3.10). Various control laws can be applied not just only P-, PD- and PID-kind control laws. There are examples of the application of Fuzzy and MPC control laws as well, however, their application in case of physiological systems need further examination and developments [87, 90, 91].

3.3. Control of T1DM using RFPT

In this section I introduce the controller design for T1DM by using RFPT control. In order to provide the full picture and the specificities of the task, I present all steps of the design including the related specific RFPT theoretical background as well – by focusing on the given specific control problem.

3.3.1. Diabetes model

In this section, the control is designed on a DM model which uses real patient data on the estimation of its parameters [92]. The state-space representation of the model is given as follows:

$$\dot{G}(t) = -k_{si}I(t) + k_l - k_b + D(t) \tag{3.11a}$$

$$\ddot{I}(t) = -\frac{1}{T_u^2}I(t) - \frac{2}{T_u}\dot{I}(t) + \frac{k_u}{V_i T_u^2}u(t) \tag{3.11b}$$

$$\ddot{D}(t) = -\frac{1}{T_r^2}D(t) - \frac{2}{T_r}\dot{D}(t) + \frac{k_r}{V_B T_r^2}r(t) \tag{3.11c}$$

Table 3.1 contains the description of the model parameters, and their values can be found in [92].

The model has two inputs, namely the external insulin infusion rate $u(t)$ [U/h] and the carbohydrate (CHO) intake $r(t)$ [mg/min^2], and one output, the glycemia, $G(t)$ [mg/dL]. Other states of the model are the insulinemia, $I(t)$ [U/L] and the digestion of CHO, $D(t)$ [mg/dL/min]. The first subsystem (Eq. (3.11a)) is responsible to simulate the glucose dynamics regarding the external and internal glucose appearance, the effect of insulin, and the internal insulin-independent glucose consumption. The second subsystem (Eq. (3.11b)) describes the insulin dynamics including the changing of insulinemia and external insulin intake, while the third subsystem (Eq. (3.11c)) presents the digestion dynamics and creates a connection between the CHO $r(t)$ in meal and $D(t)$. To determine the relative order of the necessary control, the order of the time-derivative of $G(t)$ has to be found. This can be immediately set by the control signal $u(t)$, which is the insulin

Table 3.1.: Parameters of the model [92]

Name	Unit	Description
k_l	$\left[\frac{\text{mg}}{\text{dL}\cdot\text{min}}\right]$	Internal glucose production by the liver
k_b	$\left[\frac{\text{mg}}{\text{dL}\cdot\text{min}}\right]$	Glucose consumption by the brain
k_{si}	$\left[\frac{\text{mg}}{\text{U}\cdot\text{min}}\right]$	Insulin dependent glucose decrease rate
k_r	[min]	Static gain constant of glucose
k_u	[min]	Static gain constant of insulin
T_u	[min]	Time constant of insulin dynamics
T_r	[min]	Time constant of glucose dynamics
V_i	[dL]	Insulin distribution volume
V_B	[dL]	Blood volume
M	[kg]	Body weight

ingress rate. For this, the effect chain of the control signal has to be expressed.

3.3.2. Effect chain of the control signal

According to (3.11b), $u(t)$ immediately influences the $\ddot{I}(t)$. Since $\ddot{I}(t)$ occurs in the 3rd time-derivative of $G(t)$, equation (3.11a) has to be differentiated two times:

$$\ddot{G}(t) = -k_{si}\dot{I}(t) + \dot{D}(t) \tag{3.12a}$$

$$\dddot{G}(t) = -k_{si}\ddot{I}(t) + \ddot{D}(t) \ . \tag{3.12b}$$

Substituting (3.11b) and (3.11c) into (3.12b) the control equation can be obtained:

$$\begin{aligned}\dddot{G}(t) = &\frac{k_{si}}{T_u^2}I(t) + \frac{2k_{si}}{T_u}\dot{I}(t) - \frac{k_u k_{si}}{V_i T_u^2}u(t) \\ &-\frac{1}{T_r^2}D(t) - \frac{2}{T_r}\dot{D}(t) + \frac{k_r}{V_B T_r^2}r(t),\end{aligned} \tag{3.13}$$

from which the necessary control signal $u(t)$ for the prescribed $\dddot{G}(t)$ can be calculated:

$$u(t) = -\frac{V_i T_u^2}{k_{si} k_u}\dddot{G}(t) + \frac{V_i}{k_u} I(t) + \frac{2V_i T_u}{k_u}\dot{I}(t) \\ -\frac{V_i T_u^2}{k_{si} k_u T_r^2} D(t) - \frac{2V_i T_u^2}{k_{si} k_u T_r}\dot{D}(t) + \frac{V_i T_u^2 k_r}{k_{si} k_u V_B T_r^2} r(t) \ . \tag{3.14}$$

Eq. (3.14) shows that the control signal $u(t)$ directly affects $\dddot{G}(t)$, which must be accounted for in the kinematic controller.

3.3.3. Determination of the relative order

In the first step the designer has to consider the physical quantity for which a reference trajectory $G^N(t)$ is defined. This step can be made on the basis of purely kinetic considerations by prescribing the appropriate order time-derivative of the controlled quantity that can be instantaneously affected by the control signal. According to the model in use, the third time-derivative of the glucose concentration of the blood $\dddot{G}\,[(\mathrm{mg})/(\mathrm{dL}\cdot\mathrm{min}^3)]$ can be directly influenced by the control input u that is the external insulin infusion rate. For instance, by considering the integrated tracking error defined as $e_{int}(t) \overset{def}{=} \int_{t_0}^{t} \left[G^N(\xi) - G(\xi)\right] \mathrm{d}\xi$, and by introducing a positive real number $0 < \Lambda\ [s^{-1}]$, one may wish to have $\left(\frac{\mathrm{d}}{\mathrm{d}t} + \Lambda\right)^4 e_{int}(t) \equiv 0$ that yields the desired system response as

$$\dddot{G}^{Desired}(t) = \dddot{G}^N(t) + 4\Lambda\left(\ddot{G}^N(t) - \ddot{G}(t)\right) \\ +6\Lambda^2\left(\dot{G}^N(t) - \dot{G}(t)\right) + 4\Lambda^3\left(G^N(t) - G(t)\right) + \Lambda^4 e_{int}(t) \ . \tag{3.15}$$

If one possess an approximate model of the system, one can use that to find u such that the output of the system is $\dddot{G}^{Desired}(t)$. Due to modeling and/or state estimation errors, when this control signal u is applied on the controlled system, the realized (and measurable) response, i.e. $\dddot{G}(t)$ will differ from $\dddot{G}^{Desired}(t)$. On this basis a response function can be defined, which for an arbitrary input $\dddot{G}^{In}$ yields the realized response as $\dddot{G} = f\left(\dddot{G}^{In}, \ldots\right)$, in which "..." refers to the zeroth, first, and the second-order derivatives of $G(t)$ and the other state-variables of the system. If $\dddot{G}$ can be instantaneously modified by u, while the other arguments in the place of the symbol "..." vary only slowly, one can use the approximation $\dddot{G} \approx f\left(\dddot{G}^{In}\right)$. In the lack of information on the exact model parameters, the analytical expression of f is not available for the controller. However, the pairs made of $\dddot{G}$ and $\dddot{G}^{In}$ are always known: the input value is determined by the controller, and $\dddot{G}$ is measurable. In the sequel, by the use of the response function, an iteration is suggested to find the appropriate value $\dddot{G}_\star$ for which $\dddot{G}^{Desired} = f\left(\dddot{G}_\star\right)$.

3.3.4. Fixed-point transformation

Assume, that one have a digital controller, and in each control step exactly only one step of iteration can be executed by the use of a function H defined as follows ([88]): $\ddot{G}_1^{In} = \ddot{G}_1^{Des}$, and

$$\begin{aligned} &\ddot{G}_{n+1}^{In} = H\left(\ddot{G}_n^{In}, \ddot{G}_{n+1}^{Des}\right) \stackrel{def}{=} \\ &\left(\ddot{G}_n^{In} + K_c\right) \cdot \left(1 + B_c \tanh\left(A_c\left[f\left(\ddot{G}_n^{In}\right) - \ddot{G}_{n+1}^{Des}\right]\right)\right) - K_c \ , \end{aligned} \tag{3.16}$$

where the real numbers K_c, A_c, and B_c are the adaptive control parameters. If $\ddot{G}_{n+1}^{Des}$ varies slowly, the $\ddot{G}^{Des} \approx$ const. assumption remains valid. Evidently, if $f\left(\ddot{G}_\star\right) = \ddot{G}^{Des}$, Eq. (3.16) provides $\ddot{G}_n^{In} = \ddot{G}_\star = \ddot{G}_{n+1}^{In}$, from which the solution of the control task is the fixed point of function H. The other trivial fixed point is $\ddot{G}_n^{In} = -K_c = \ddot{G}_{n+1}^{In}$ that cannot be used for control purposes. This construction evidently corresponds to the requirement of causality: the signal to be used in control cycle number $(n+1)$, i.e. $\ddot{G}_{n+1}^{In}$, is created by the use of the signal in cycle n, which is $\ddot{G}_n^{In}$ combined with the observed response i.e. $f\left(\ddot{G}_n^{In}\right)$. In the next subsection the convergence properties of the previously defined sequence are considered.

3.3.5. Convergence of the iteration

A Banach space (as a set, casually denoted by $\mathcal{B}$) by definition is a complete, linear, normed metric space:

- *Linearity*: $\forall \alpha, \beta \in \mathbb{C}$ and x, $y \in \mathcal{B}$, the linear combination is defined and belongs to the space: $\alpha x + \beta y \in \mathcal{B}$;
- *Existence of a norm for defining a metric*: $\forall x \in \mathcal{B}\ \exists \|x\| \geq 0$ so that from $\|a\| = 0$ it follows that $a = 0$ (i.e. the norm separates points), $\forall \alpha \in \mathbb{C}\ \|\alpha x\| = |\alpha| \cdot \|x\|$ (absolute scalability), and $\|x + y\| \leq \|x\| + \|y\|$ (norm inequality). By the use of this norm the metrics or the distance between the elements as $\rho(x, y) \stackrel{def}{=} \|x - y\|$ can be defined;
- *Completeness*: By using the norm, one can define Cauchy sequences. A sequence $\{x_n; n \in \mathbb{N}\}$ is a Cauchy sequence if $\forall L \in \mathbb{N}\ \|x_{n+L} - x_n\| \to 0$ as $n \to \infty$. Completeness means that each Cauchy sequence must be convergent in the space, i.e. for the above sequence $\exists x_\star \in \mathcal{B}$ so that $\|x_n - x_\star\| \to 0$ as $n \to \infty$;

By utilizing the norm on the space, one can introduce the concept of contractivity: $\Phi : \mathcal{B} \mapsto \mathcal{B}$ is contractive if $\forall x, y \in \mathcal{B}\ \exists K \in [0,1)$ so that $\|\Phi(x) - \Phi(y)\| \leq K\|x - y\|$. Using a contractive function, a Cauchy sequence can be generated, so that $\{x_1; x_2 \overset{def}{=} \Phi(x_1); \dots x_{n+1} \overset{def}{=} \Phi(x_n); \dots\}$. This sequence is indeed a Cauchy sequence, since:

$$\begin{aligned} &\|x_{n+L} - x_n\| = \|\Phi(x_{n-1+L}) - \Phi(x_{n-1})\| \leq \\ &\leq K\|x_{n-1+L} - x_{n-1}\| \leq \dots \\ &\qquad \leq K^{n-1}\|x_{1+L} - x_1\| \to 0 \text{ as } n \to \infty\ . \end{aligned} \tag{3.17}$$

Due to the completeness of $\mathcal{B}$, $\exists x_\star \in \mathcal{B}$ so that $\|x_n - x_\star\| \to 0$ as $n \to \infty$. It is easy to show that $x_\star$ is the fixed point of Φ, i.e. $\Phi(x_\star) = x_\star$. Using the properties of the norm one can write that:

$$\begin{aligned} &\|\Phi(x_\star) - x_\star\| = \|\Phi(x_\star) - x_n + x_n - x_\star\| \leq \\ &\|\Phi(x_\star) - x_n\| + \|x_n - x_\star\| = \\ &\|\Phi(x_\star) - \Phi(x_{n-1})\| + \|x_n - x_\star\| \leq \\ &\qquad \leq K\|x_\star - x_{n-1}\| + \|x_n - x_\star\| \to 0 \text{ as } n \to \infty\ . \end{aligned} \tag{3.18}$$

These considerations allow the application of the fixed point transformation-based approach since by properly choosing a deform function (for example (3.16)), one can ensure that it generates a Cauchy sequence by properly choosing its parameters.

3.3.6. Convergence conditions for SISO Systems

In this case the $\ddot{G} \approx f\left(\ddot{G}^{In}\right)$ response function corresponds to $f : \mathbb{R} \mapsto \mathbb{R}$, so one can use the Banach space of real numbers with the norm $\|x\| \overset{def}{=} |x|$. Since this function is differentiable, one can use a simple integral estimation for guaranteeing contractivity:

$$|f(b) - f(a)| = \left| \int_a^b \frac{\mathrm{d}f(x)}{\mathrm{d}x} \mathrm{d}x \right| \leq \int_a^b \left| \frac{\mathrm{d}f(x)}{\mathrm{d}x} \right| \mathrm{d}x, \tag{3.19}$$

which evidently means that $\exists K,\ 0 \leq K < 1$ so that $\left|\frac{\mathrm{d}f(x)}{\mathrm{d}x}\right| \leq K$, thus a contractive map can be obtained that makes the iterative sequence converge to the solution of the control task. Of course, it is enough to maintain the contractivity nearby the useful fixed point. One can see that if $|K_c| \gg |\ddot{G}|$, $B_c = \pm 1$, and A_c is a small positive number, then the fake fixed point at $-K_c$ can be made repulsive, while $\ddot{G}_\star$ can be rendered attractive. Since $|K_c|$ is very big, in this case the initial element of the iteration will be either in the

$(-K_c, \dddot{G}_\star)$ interval or it will be greater than $\dddot{G}_\star$, therefore the iteration will converge to $\dddot{G}_\star$. An advantage of this control method is that it does not require a very precise setting of its adaptive control parameters. The actual setting concerns the speed of convergence, therefore, to some extent the precision of trajectory tracking.

3.3.7. The affine model

It is evident that (3.14) corresponds to an affine structure between $u(t)$ and $\dddot{G}(t)$. It is reasonable to assume that any abrupt jump in $u(t)$ immediately affects the instant value of $\dddot{G}(t)$; hence, the additive parts of the affine model vary only slowly. Based on this observation, the value of the control sequence r_n will be the required third derivative of G. It will be referred to as $\dddot{G}(t)_{Req}$ in the sequel. According to the available model to $\dddot{G}(t)_{Req}$, the following control signal $u(t)_{Req}$can be derived:

$$\begin{aligned} u(t)_{Req} = &-\frac{V_i T_u^2}{k_{si} k_u} \ddot{G}_{req}(t) + \frac{V_i}{k_u} I(t) + \frac{2 V_i T_u}{k_u} \dot{I}(t) \\ &-\frac{V_i T_u^2}{k_{si} k_u T_r^2} D(t) - \frac{2 V_i T_u^2}{k_{si} k_u T_r} \dot{D}(t) + \frac{V_i T_u^2 k_r}{k_{si} k_u V_B T_r^2} r(t) \ . \end{aligned} \tag{3.20}$$

Practically, only $G(t)$ can be measured by the CGMS usually with 5 minutes of cycle time. No direct measurement possibilities exist for measuring $D(t)$, $I(t)$ in practice. However, in principle $r(t)$ may be known, as it depends on the action of the patient, but it cannot be expected that the patient manually provides the controller with this information. Therefore, it is assumed that the controller can detect the CHO intake by observing some increase in $G(t)$. It can be stated that in practice there is no possible way to obtain information on the actual value of the additive parts of the affine model. The main feature of the RFPT adaptive controller which is it can work with an incomplete model fits this practical problem: there is no need for the application of complicated state estimators to estimate this term. In the model this unknown contribution is denoted as an *AffineAdditive* constant term as follows:

$$u(t)_{Req} = -\frac{V_i T_u^2}{k_{si} k_u} \ddot{G}_{req} + \ \text{AffineAdditive} \ . \tag{3.21}$$

In this approach the information on the variables $D(t)$ and $I(t)$ is completely neglected in the controller.

3.3.8. Approximate model

As no real measurements can be done for the estimation of the actual $D(t)$ and $I(t)$ values of the patient, an alternative possibility is the application of some approximate model (its parameters are denoted by the symbol $\sim$) to estimate them by solving the complete equations of motion for the approximate model taking the same control signal as the actual patient $u(t)$, and producing the drift of approximate state variables $\dot{\tilde{G}}(t)$, $\dot{\tilde{I}}(t)$, $\dot{\tilde{D}}(t)$. In the estimation of $u(t)_{Req}$ the approximate quantities $\tilde{I}(t)$, $\dot{\tilde{I}}(t)$, $\tilde{D}(t)$, $\dot{\tilde{D}}(t)$ are substituted from a computer program that emulates the behavior of the approximate model, but it takes the measurable actual $G(t)$ value and – due to the lack of information on meal intake – $r(t)$ as zero:

$$\begin{aligned} u(t)_{Req} = &-\frac{\tilde{V}_i \tilde{T}_u^2}{\tilde{k}_{si}\tilde{k}_u}\dddot{\tilde{G}}_{req} + \frac{\tilde{V}_i}{\tilde{k}_u}\tilde{I}(t) + \frac{2\tilde{V}_i\tilde{T}_u}{\tilde{k}_u}\dot{\tilde{I}}(t) \\ &-\frac{\tilde{V}_i\tilde{T}_u^2}{\tilde{k}_{si}\tilde{k}_u\tilde{T}_r^2}\tilde{D}(t) - \frac{2\tilde{V}_i\tilde{T}_u^2}{\tilde{k}_{si}\tilde{k}_u\tilde{T}_r}\dot{\tilde{D}}(t) + 0 \ . \end{aligned} \tag{3.22}$$

Using this approach, the adaptive part of the controller will not contribute the same amount as in the previous case.

3.3.9. Control law

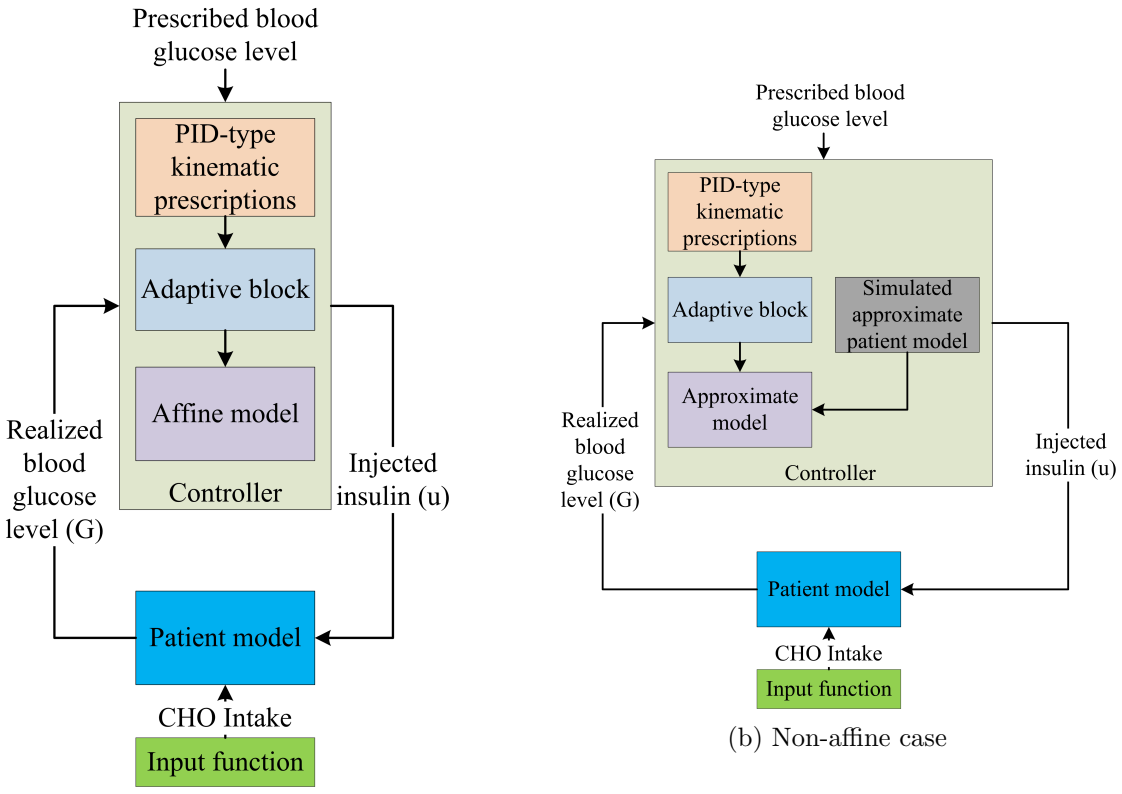
During the study, a PID-control law was used as the kinematic prescription. This is an appropriate choice if the goal of the control is trajectory tracking as it was in this case. Since the control signal acts on the third-order time derivative of the variable to be regulated, a control law of the same order has to be used:

$$\left(\frac{\mathrm{d}}{\mathrm{d}t} + \Lambda\right)^4 \int_{t_0}^{t} \Big(G^N(\xi) - G(\xi)\Big)\mathrm{d}\xi = 0 \tag{3.23}$$

which determines the following desired $\dddot{G}^{Desired}(t)$ function:

$$\begin{aligned} \dddot{G}^{Desired}(t) = &\left(\frac{\mathrm{d}}{\mathrm{d}t}\right)^3 G^N(t) + \\ &+\sum_{s=0}^{3}\binom{4}{s}\Lambda^{4-s}\left(\frac{\mathrm{d}}{\mathrm{d}t}\right)^s \int_{t_0}^{t}\Big(G^N(\xi) - G(\xi)\Big)\mathrm{d}\xi \end{aligned} \tag{3.24}$$

where the $G^N(t)$ is the reference blood glucose (BG) level, $G(t)$ is the actual BG level and the error is the $G^N(t) - G(t)$.



(a) Affine case

(b) Non-affine case

Figure 3.2.: Realization of the control structures in the affine and non-affine cases.

3.3.10. Final control environment

The final control environment consists of the PID-type kinematic prescription, the adaptive block, and the affine model as Fig. 3.2a presents it. However, in this study, another realization possibility was investigated as well, where an approximate parallel simulated model provides the non-measurable estimated states. The structure of it is presented in Fig. 3.2b. Note, that the PID-type prescription and the adaptive block were the same in both cases.

3.3.11. Results

In order to test the controller, long-term simulations were applied and a unique glucose input function was designed. In every case, the goal was that the controller should provide an appropriate control signal by which the glycemia of the patient can be stabilized if disturbances are present. The glucose input specificity of the used model required a special input function. The designed function consists of an additive mixture of an

Table 3.2.: Exact parameters of the used model [92]

Name	Unit	Value
k_l	$\left[\frac{\text{mg}}{\text{dL} \cdot \text{min}}\right]$	1.94
k_b	$\left[\frac{\text{mg}}{\text{dL} \cdot \text{min}}\right]$	$128/M$
k_{si}	$\left[\frac{\text{mg}}{\text{U} \cdot \text{min}}\right]$	197
k_r	[min]	$2.4V_B \ 10^{-3}$
k_u	[min]	$59V_i \ 10^{-3}$
T_u	[min]	122
T_r	[min]	183
V_i	[dL]	$2.5M$
V_B	[dL]	$0.65M$
M	[kg]	72

arbitrarily selected sinusoidal disturbance signal combined with an impulsive term:

$$r(t) = \sin(t) + \frac{s_h}{s_w + (t - t_i)^4}, \tag{3.25}$$

where s_h is the impulse height and s_w is the width of the impulse. The model needs the derivative of the designed function $\mathrm{d}r(t)/\mathrm{d}t$ as CHO input. The primary goal of this study was to prove the usability of the RFPT controller design in the case of the T1DM model in order to ease the inaccuracies in the identification procedures. The method relies on approximated models instead of exact patient models that allow using one of the parameter sets from the original study (Patient 1, [92] given in Table 3.2). It is also noted that the AffineAdditive elements were set to zero during the simulation.

Naturally, the parameters from Table 3.2 can only be used in the affine case. In the approximate case, the values of the state variables are non-measurable but can be roughly estimated from the parallel simulation of the model. The parameters, in this case, were half of the original values, which means that except for the body weight, every parameter in the approximate case was equal with 0.5 times its original value.

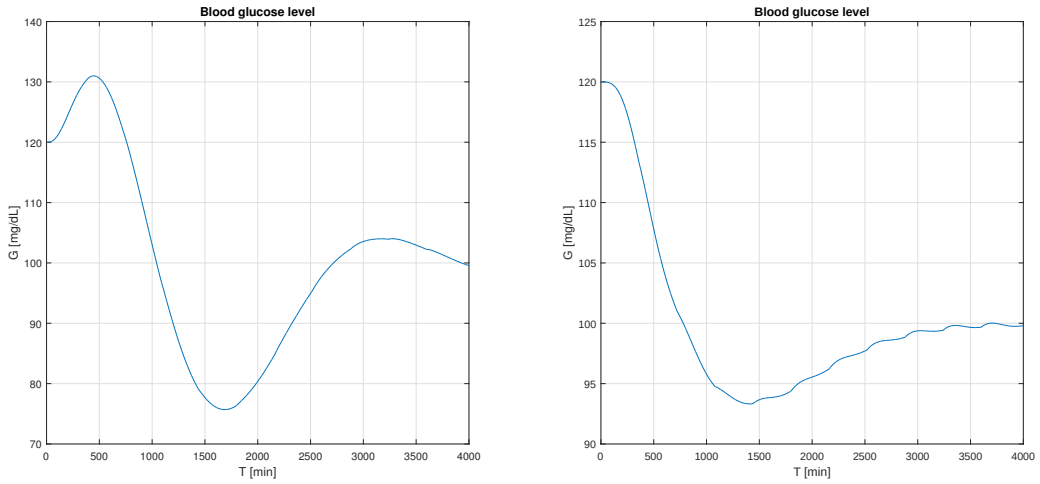
Besides the selection of the used model parameters, the appropriate selection of the control parameters is also important. The general RFPT controller parameters are

those connected to the adaptivity, namely A_c, B_c, and K_c. Moreover, depending on the applied control law, different further control parameters may occur. In this study, a kinematic control law was used with one tunable Λ gain parameter. The values of the adaptivity parameters were adjusted to the magnitudes of the controlled variable (the third derivative of $G(t)$). The last selectable variable is the reference BG level G^N which is used in the adaptivity block and the control law as well. Due to the desired goal to prove the usability of the RFPT controller, the same control parameters and reference BG level were used during the simulations, without online parameter tuning. However, in other applications these properties of the RFPT controller design were successfully tested [93], [90]. The selected control variables of the T1DM case was determined to be $K_c = -10^{-2}$, $A_c = 1/(10|K_c|)$, $B_c = 1$, and $\Lambda = 0.003$ with the reference $G^N = 100$ [mg/dL]. The simulation length was 4000 minutes (more then 66 hours, or almost 3 days) which is enough to demonstrate the benefit of the RFPT controller, because the controller adapts to the patients dynamics under this time interval.

Fig. 3.3a presents the blood glucose level over time in the affine case. It should be noted that the desired blood glucose interval is 70-120 mg/dL (the healthy human blood glucose interval). Over 120 mg/dL hyperglycaemia (high BG), under 70 mg/dL hypoglycaemia (low BG) is diagnosed. The latter is the most dangerous for a T1DM patient and should be completely avoided. Hyperglycaemia, however, could be tolerated, but the amplitude should be reduced to 140 mg/dL. The figure shows that after the first transient, the controller reacts to the increasing BG level and administers insulin in order to avoid hyperglycaemia. As a result, the BG level finally reaches the nominal BG level G^N. In the non-affine case of Fig. 3.3b, the controller acts faster since the simulated approximate model signals are available and the controller has direct, but roughly approximated information about the possible internal states.

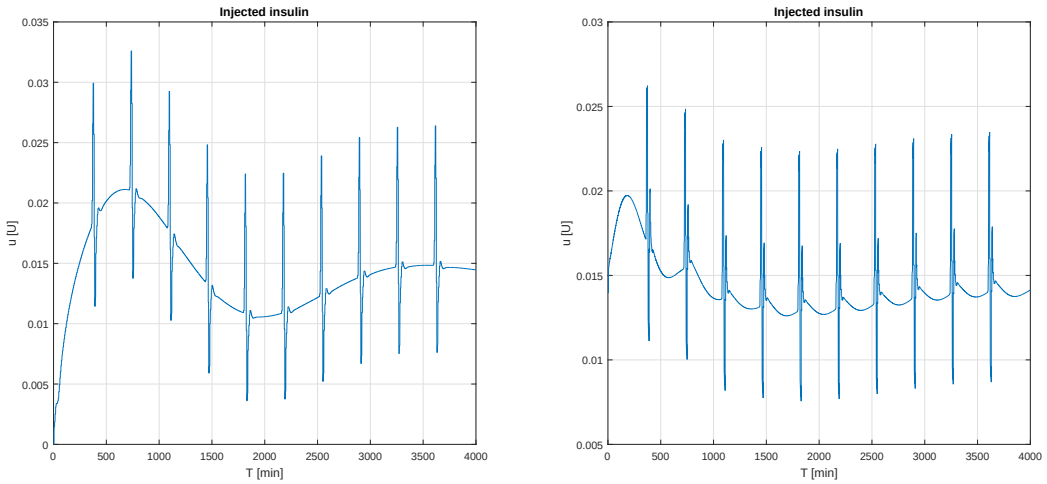
Fig. 3.4a shows the injected insulin over time in the affine case. Due to the structure of the affine model (Eq. 3.20), the insulin peaks occur over time because of the third derivative of the required $G(t)$. Originally, these effects come from the food intake signals and reflect in the $\dddot{G}(t)_{Req}$ signal, respectively. The same effects can be seen in the non-affine case (Fig. 3.4b) as well. The average magnitude of the peaks is almost the same. The main difference is that the controller has approximated internal information about the states. This knowledge about insulinemia allows us to have a nonzero initial control signal and have a non-smooth insulin signal around the peaks.

In Figs. 3.5a-3.5b one can see the output of the realized, desired, and required 3rd derivatives of the BG level $G(t)$ in both the affine and non-affine cases. In Fig. 3.5a the realized signal tends to be the desired signal after the diversion caused by the insulin



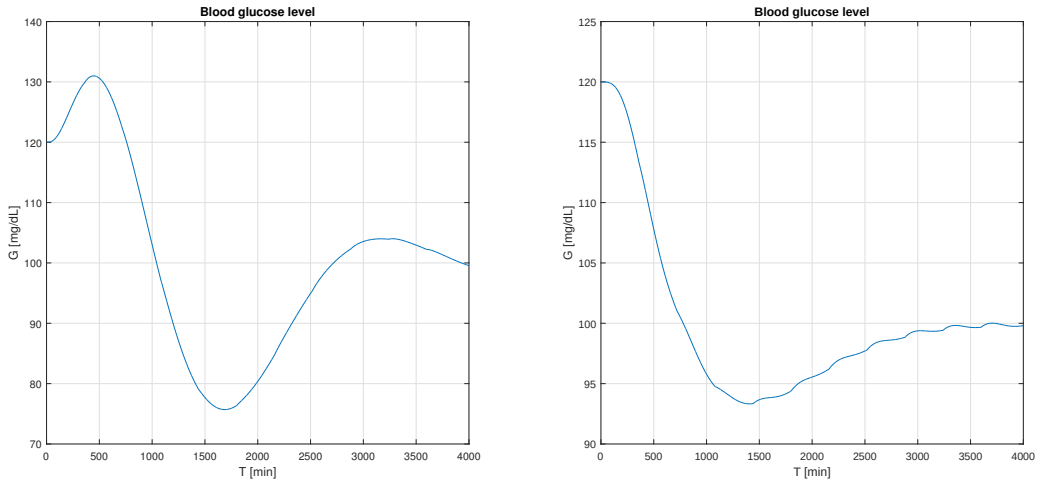
(a) Affine case (b) Non-affine case

Figure 3.3.: Simulation results of the blood glucose level in the affine and non-affine case.



(a) Affine case (b) Non-affine case

Figure 3.4.: Injected insulin in the affine and non-affine case.



(a) Affine case

(b) Non-affine case

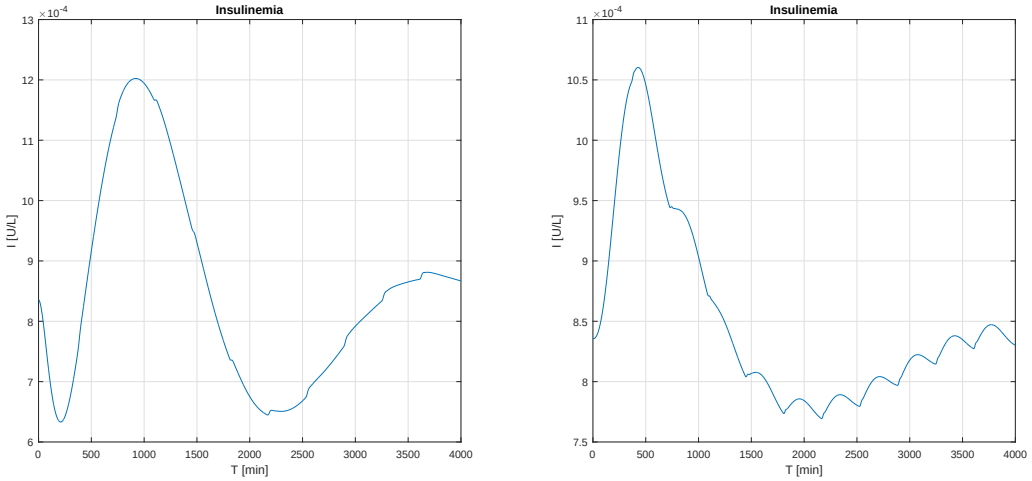
Figure 3.5.: Desired, required, and realized 3rd derivatives of $G(t)$ in the affine and non-affine case.

signals. In Fig. 3.5b the desired and required signals are almost the same. The realized $\dddot{G}(t)$ approaches the desired signal due to the fact that the desired and required signals were almost identical.

Fig. 3.6a shows insulinemia variation $I(t)$ over time. It can be seen that the control insulin signal results in a stable internal insulin level, besides the presence of the insulin peaks. Time delays of the effect due to the model structure are also visible, since despite the immediate insulin signal from the beginning the insulinemia initially decays, but stabilizes over time. However, in the non-affine case (Fig. 3.6b) the insulin peaks are more evident on $I(t)$.

3.3.12. Summary

In Sec. 3.3. the usability of RFPT controller design method was reported in the case of a T1DM nonlinear model. In line with the requirements of the T1DM model an appropriate feed intake function was designed. Using a long simulation duration the behavior of the RFPT controller were tested when disturbances are present in the system. During this study, fixed control parameters were tuned without advanced optimization techniques. On these considerations, the applicability of the novel RFPT method has been demonstrated. With online optimization techniques, a better performance can be expected which can be a bases of further research.



(a) Affine case

(b) Non-affine case

Figure 3.6.: Simulation result of insulinemia $I(t)$ in the affine and non-affine case.

3.4. Control of Tumor Growth via RFPT-based Adaptive Control Framework

In the following section, the design of the RFPT controller is shown on the famous Hahnfeldt model. In the case of T1DM model, one saw the benefits of the RFPT controller when inaccuracies are present in the model. A tumor growth model is no different, since the patient variability and the lack of precise model naturally leads to the application of robust and adaptive solutions.

3.4.1. Analysis of the tumor growth model

I used a three order model in this section which was introduced by [26], and can describe tumor growth under angiogenic therapy. The state variables of the model are the volume of the tumor $x_1(t)$ $\left[\text{mm}^3\right]$, the volume of the supporting vasculature $x_2(t)$ $\left[\text{mm}^3\right]$, and the inhibitor (Bevacizumab) serum level $x_3(t) \equiv g(t)$ $\left[\text{mg} \cdot \text{kg}^{-1}\right]$. The system is given as:

$$\begin{aligned} \dot{x}_1(t) &= -\lambda_1 x_1(t) \log\left(\frac{x_1(t)}{x_2(t)}\right) \\ \dot{x}_2(t) &= b x_1(t) - d x_1^{\alpha}(t) x_2(t) - \eta x_2(t) g(t) \\ \dot{g}(t) &= -\lambda_3 g(t) + u(t) \ , \end{aligned} \tag{3.26}$$

where the control signal is the input rate of the inhibitor $u(t)$ $\left[\mathrm{mg}\cdot\mathrm{kg}^{-1}\cdot\mathrm{h}^{-1}\right]$. The model parameters are $\lambda_1 = 0.192/24.0$ $\left[\mathrm{h}^{-1}\right]$, $b = 5.85/24.0$ $\left[\mathrm{h}^{-1}\right]$, $d = 0.0087/24.0$ $\left[\mathrm{mm}^{-2}\cdot\mathrm{h}^{-1}\right]$, $\eta = 0.66/24.0$ $\left[\mathrm{mm}^{-3}\cdot\mathrm{h}^{-1}\right]$, $\lambda_3 = 1.3/24.0$ $\left[\mathrm{h}^{-1}\right]$, and $\alpha = 2/3$. The aim is to control $x_1(t)$ by the use of the signal $u(t)$, assuming that $x_1(t)$ is directly measurable. To determine the relative order of the control task one have to observe that $\dot{x}_1(t)$ is not directly influenced by $u(t)$. It is evident that $\ddot{x}_1(t)$ depends on $\ddot{x}_2(t)$ that directly depends on $\dot{g}(t)$ which is influenced by $u(t)$. As a consequence, the relative order of this control problem is 3. To reveal the dependence of $\ddot{x}_1(t)$ on $u(t)$, by making the necessary differentiations one can arrive at the cascade of equations as follows:

$$
\begin{aligned}
\ddot{x}_1(t) &= -\lambda_1\dot{x}_1(t)\log\left(\frac{x_1(t)}{x_2(t)}\right) - \lambda_1\dot{x}_1(t) + \lambda_1\frac{x_1(t)}{x_2(t)}\dot{x}_2(t)\\
\dddot{x}_1(t) &= \ddot{x}_1(t)\left[-\lambda_1\log\left(\frac{x_1(t)}{x_2(t)}\right) - \lambda_1\right] - \lambda_1\frac{\dot{x}_1^2(t)}{x_1(t)} -\\
&-\lambda_1\frac{\dot{x}_1(t)\dot{x}_2(t)}{x_2(t)} + \lambda_1\left(\frac{\dot{x}_1(t)}{x_2(t)} - \frac{x_1\dot{x}_2(t)}{x_2^2(t)}\right)\dot{x}_2(t)\\
&\quad +\lambda_1\frac{x_1(t)}{x_2(t)}\Big(b\dot{x}_1(t) - d\alpha x_1(t)^{\alpha-1}\dot{x}_1(t)x_2(t)\\
&-dx_1^{\alpha}(t)\dot{x}_2(t) - \eta\dot{x}_2(t)g(t)\Big) + \lambda_1\eta x_1(t)\lambda_3 g(t) - \lambda_1\eta x_1(t)u(t),
\end{aligned}
\tag{3.27}
$$

whence $u(t)$ can be summarized in an affine form:

$$
\dddot{x}_1(t) = \mathcal{B}\left(x_1(t), x_2(t), g(t)\right) - \lambda_1\eta x_1(t)u(t). \tag{3.28}
$$

Equations (3.26) and (3.27) allow us to observe the following remarks:

1. The $\frac{0}{0}$ - type singularity in (3.26) does not allow this model to explain or describe the tumor formation in its early stage that precedes angiogenesis.

2. As $x_1 \to 0$, $\ddot{x}_1(t)$ becomes insensitive to $u(t)$ that anticipates, that for keeping the tumor size at a very low level it would require the use of huge Bevacizumab ingress rates. In other words, the aim cannot be the complete removal of the tumor, instead of that it should be kept at a low, but finite level.

3. During numerical simulations the physically not interpretable regions as $x_1(t)$, $x_2(t)$, $g(t) < 0$, and the physically not realizable ingress rates as $u(t) < 0$ must be evaded by appropriately completing the equations (3.26) and (3.27). The

physically clear situation corresponds to a targeted $x_{1_{final}} > 0$ state at which these phenomenological restrictions do not occur.

4. As one can only directly measure only $x_1(t)$, but no practical possibility exists for measuring $x_2(t)$ and $g(t)$, the detailed model practically is not available for developing a classical MPC. In other words, due to the lack of satisfactory information, it is not possible to construct a Kalman filter to estimate each state variable.

This situation anticipates the possible use of either some robust, or adaptive technique. Here, I concentrated on the use of an RFPT adaptive technique that could overcome the previously discussed issues.

3.4.2. Application of the RFPT technique

According to Fig. 3.1 describing the schematic structure of the RFPT-based control design, a nominal trajectory to be tracked can be designed for $x_1^N(t)$ as follows ([91]):

$$x_1^N(t) = x_{1_{final}} + x_{1_{ini}} \left(1 - \tanh(ct)\right) \quad , \tag{3.29}$$

where the initial condition corresponds to $t = 0$, $c > 0$, and $x_{1_{final}} > 0$ that guarantees the avoidance of the dynamic singularity of the model. The PD term is embedded into the control law and is responsible for the elimination of the actual tracking error denoted by $e(t) = x_1^N(t) - x_1(t)$. Since there is a direct connection between the control signal $u(t)$ and the third derivative of the first state $\dddot{x}_1(t)$ one have to use at least a third order $\left(\mathrm{d}/\mathrm{d}t + \Lambda\right)^3$ PD term. Taking into account that for a constant $\Lambda > 0$, the solution of the differential equation $\left(\mathrm{d}/\mathrm{d}t + \Lambda\right) h(t) \equiv 0$ converges to zero, since it is $h(t) = h(t_0)\, exp(-\Lambda(t - t_0))$. The tracking error can be used for the prescription of the desired $\dddot{x}_1^D$ as $\left(\mathrm{d}/\mathrm{d}t + \Lambda\right)^3 \left[x_1^N(t) - x_1(t)\right] \equiv 0$, is given as:

$$\dddot{x}_1^D = \dddot{x}_1^N(t) + \Lambda^3 e(t) + 3\Lambda^2 \dot{e}(t) + 3\Lambda \ddot{e}(t). \tag{3.30}$$

Consequently, the value $\dddot{x}_1^D$ corresponds to the desired response r^{Des}. In order to achieve this response, following adaptive deformation of the control signal used in the previous control step, the available approximate system model is used for the calculation of the control force (which in this case corresponds to $u(t)$). This force is exerted on the controlled system that produces the realized response ($\dddot{x}_1(t)$ in this particular case). If $\dddot{x}_1^D$ varies only slowly, an iterative sequence of the control signals $\{r_1 = r_1^{Des}, \ldots, r_{n+1} = G\left(r_n, f(r_n), r^{Des}\right), \ldots\}$ can be constructed, which converges to the solution of the control

task $r \equiv f(r_\star) = r^{Des}$ if the parameters of the deformation function $G\left(r_n, f(r_n), r^{Des}\right)$ are appropriately set. Practically, during one digital control step there is a possibility to make a single step of iteration. In this case $F(\xi) = \operatorname{atanh}\left(\tanh(\xi + D)/2\right)$ with the parameter $D = 0.3$ was used as a function that has an attractive fixed point at $\xi_\star \approx 0.2594$ which was combined with the fixed-point transformations:

$$r_{i+1} = \left[F(A\|f(r_i) - r^{Des}\| + \xi_\star) - \xi_\star\right] \frac{f(r_i) - r^{Des}}{\|f(r_i) - r^{Des}\|} + r_i. \tag{3.31}$$

In Eq. (3.31) A is an adaptive parameter. For $r_k = r_\star$ that provides $f(r_\star) = r^{Des}$ it yields that $r_{k+1} = r_k$, meaning that if $r_\star$ is the solution of this task, it is also the fixed point of this function. To achieve convergence, the parameter A has to be set appropriately. In the sequel, I investigate the possibilities of increasing the sampling time, i.e. the frequency of the actual tumor volume measurement.

3.4.3. Simulation Results

In the first step an ideal scenario was assumed for measuring x_1 in each hour ($\delta t = 1\,\mathrm{h}$). As a result, the time-resolution of the numerical Euler integration was $1/24\,[\mathrm{h}]$. For the tracking parameter $c = 1/200\,[\mathrm{h}^{-1}]$, and $A = -6\,[\mathrm{h}^3/\mathrm{mm}^3]$ with $x_{1_{final}} = 5^3\,[\mathrm{mm}^3]$ and $\Lambda = 0.015\,\mathrm{h}^{-1}$ a detailed model was assumed for the calculation of $\mathcal{B}\left(x_1(t), x_2(t), g(t)\right)$ in order to obtain information on these possible additive terms. In these simulations the initial values $x_1(0) = x_2(0) = 10^4\,\mathrm{mm}^3$ were chosen. All of the discrete-time steps have been selected in accordance with the model properties, measurement technology, and physiological realities. To get a full picture, I investigated four scenarios ($\delta t = [1, 24, 72, 168]\,\mathrm{h}$). The third order time-derivatives were estimated as

$$\dddot{x}_1(t) \approx \frac{x_1(t) - 3x_1(t - \delta t) + 3x_1(t - 2\delta t) - x_1(t - 3\delta t)}{\delta t^3}. \tag{3.32}$$

Figures 3.7 reveals the operation of the adaptation. The desired and the realized values are in each other's close vicinity, and they seriously differ from the deformed values. The increase in the inhibitor serum level corresponds to the expectation that decreasing $x_1(t)$ further decreases the sensitivity of the mechanism for the Bevacizumab ingress rate. Consequently, in further calculations instead of the exact model (3.28) its affine approximation (3.33) was applied that does not require the measurement of $x_2(t)$ and $x_3(t) \equiv g(t)$. The role of the adaptivity is to compensate the effects of the affine

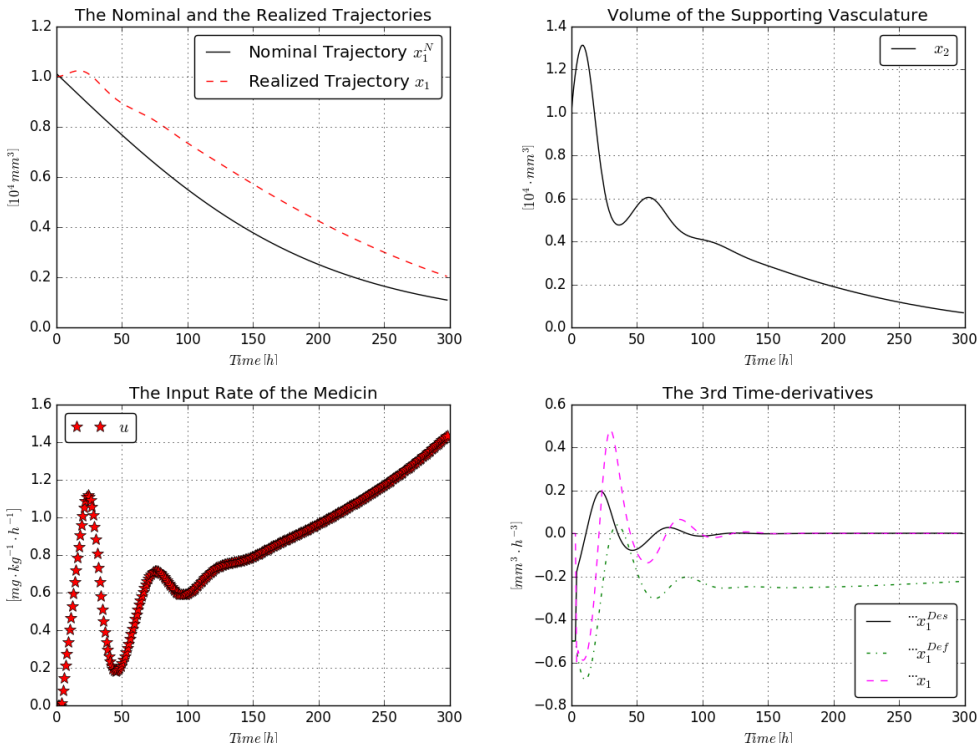


Figure 3.7.: The size of the tumor and its feeding vascular system in the ideal case, the ingress rate of the serum Bevacizumab, and the third order derivatives

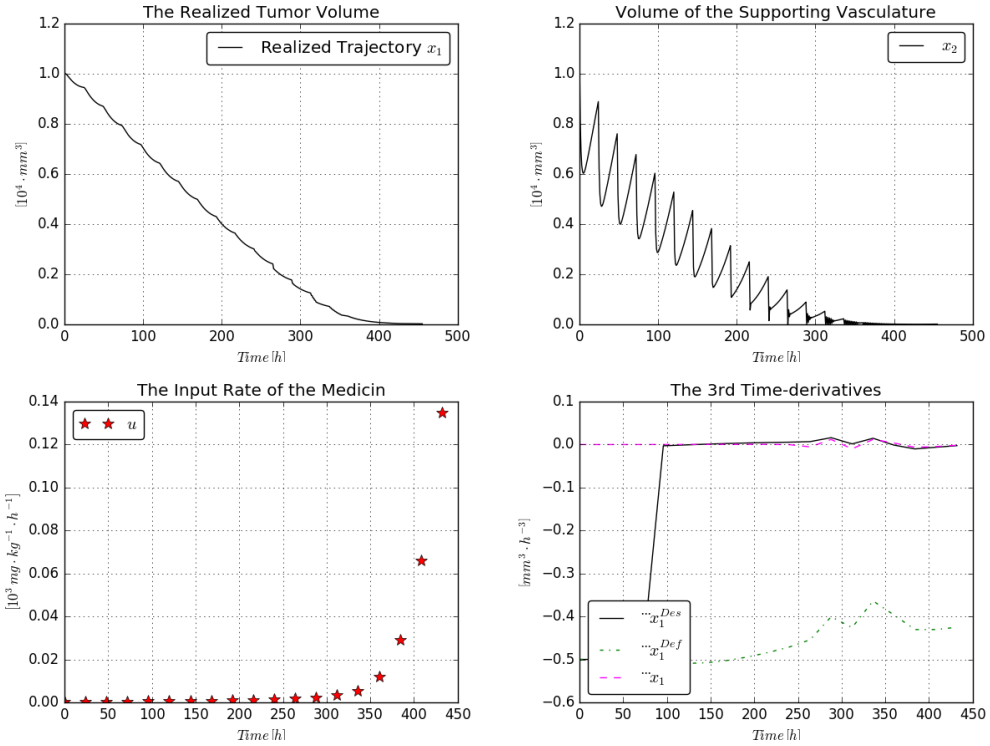


Figure 3.8.: The size of the tumor and its feeding vascular system in the $\delta t = 24$ [h] case, the ingress rate of the serum Bevacizumab, and the estimated third order derivatives.

approximation in:

$$\ddot{x}_1(t) = \hat{\mathcal{B}} - \lambda_1 \eta x_1(t) u(t) \ , \tag{3.33}$$

with a constant $\hat{\mathcal{B}} = 0.5\,[\mathrm{mm}^3 \cdot \mathrm{h}^{-3}]$. The practical usability of the theorem depends on its needed measurement frequency for variable $x_1(t)$. The worst-case corresponds to the $\delta t = 24\,h$ cycle time (i.e. to daily measurements). While fixing the times-step of the Euler integration at $\delta t_{intl} = 1\,[\mathrm{h}]$, as δt increases, (3.32) may become a more or less corrupted approximation, a substitute, and finally some surrogate of the measured third time-derivatives. In such cases, the serum is injected in the first step of the Euler integration, and $u = 0$ in the other segments of this integration. The simulation results obtained for $\delta t = 24\,[\mathrm{h}]$ are given in Fig. 3.8.

It is evident that during a day-long ($\delta t = 24$ [h]) period when the serum is injected in the first hour after the tumor size measurement, the decrease in $g(t)$ is considerable due to the decay-rate λ_3. This causes fine ripples in the tumor volume function $x_1(t)$, and an even more visible variation in the volume of the supporting vasculature. As the serum

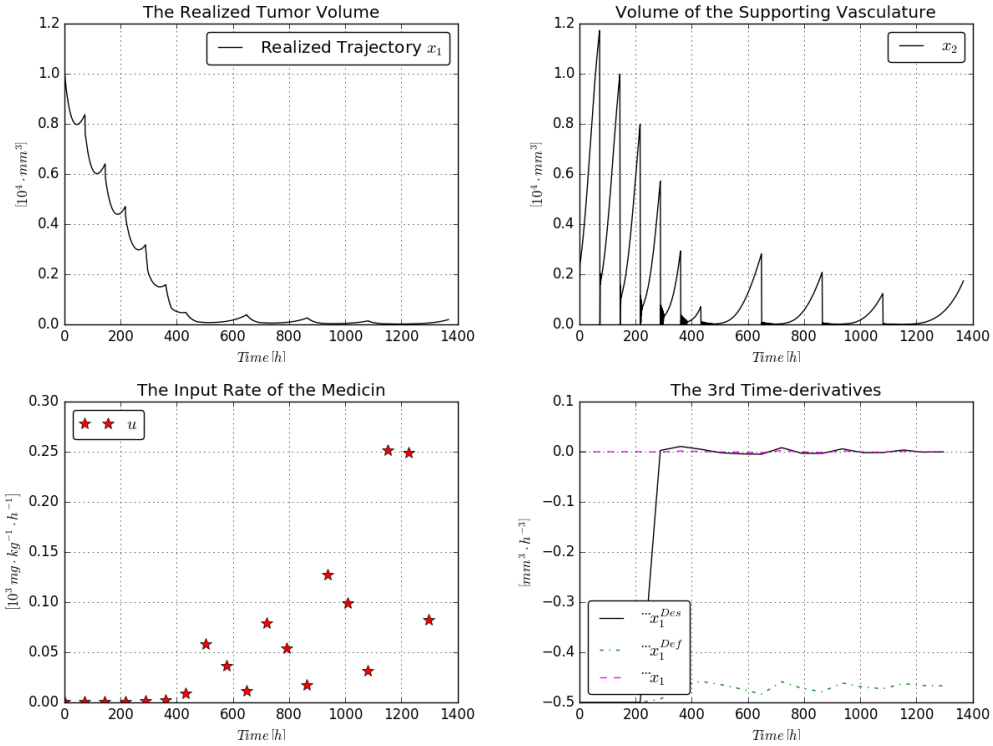


Figure 3.9.: The size of the tumor and its feeding vascular system in the $\delta t = 72$ [h] case, the ingress rate of the serum Bevacizumab, and the estimated third order derivatives.

leaves the human body, the process of angiogenesis accelerates. These effects become more visible for $\delta t = 72$ [h] cycle-time in Fig. 3.9. It is evident that the tumor has enough time to regrow before the next injection of the serum.

Finally, the physically plausible weekly measurement was investigated. For this purpose the $\delta t = 168$ [h] cycle-time must be used (Fig. 3.10).

It is evident that during the weekly treatment the supporting vasculature has enough time to grow back, and the tumor also can grow back. To evade the use of too much serum, in the next simulation I returned to the $\delta t = 72$ [h] cycle-time, but increasing the reference final tumor size to $x_{1_{final}} = 10^3$ [mm^3] (Fig. 3.11 and 3.12). According to the simulations, this parameter setting seems to be practically acceptable.

Finally, the role of the initial values $x_1(0)$ and $x_2(0)$ must be clarified. Due to the 0/0-type singularity in the dynamic model, the interdependence between these variables is not clear, as for a given $x_1(0)$ one have to make calculations for various $x_2(0)$ values. Let at first consider the pair $x_1(0) = 10^4\,\mathrm{mm}^3$, $x_2(0) = 10^6\,\mathrm{mm}^3$ (Fig. 3.13 and 3.14).

It is interesting to see that in comparison with Fig. 3.11 and 3.12, there is no

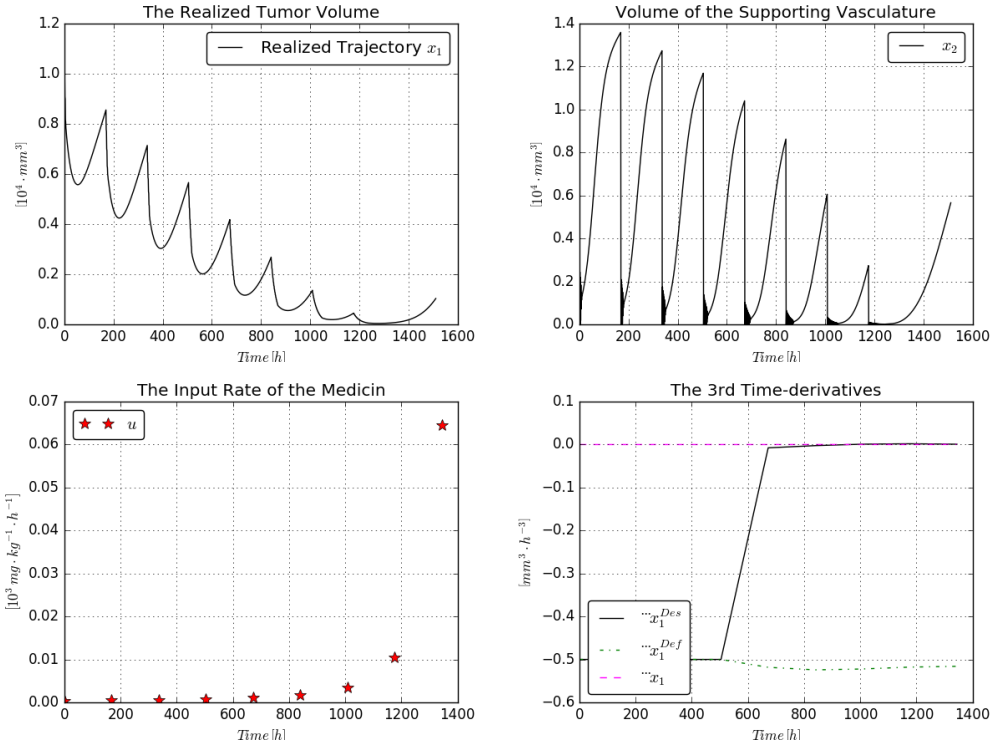


Figure 3.10.: The size of the tumor and its feeding vascular system in the $\delta t = 168$ [h] case, the ingress rate of the serum Bevacizumab, and the estimated third order derivatives.

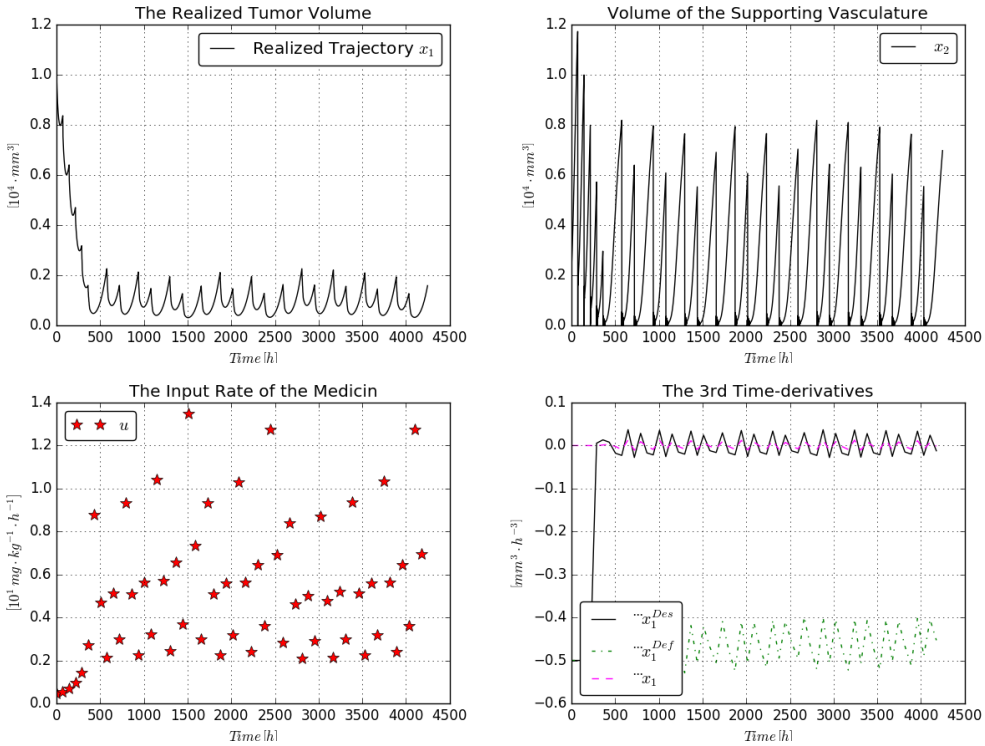


Figure 3.11.: The size of the tumor and its feeding vascular system in the $\delta t = 72$ [h], $x_{1_{final}} = 10^3$ [mm^3] case, the ingress rate of the serum Bevacizumab, and the estimated third order derivatives.

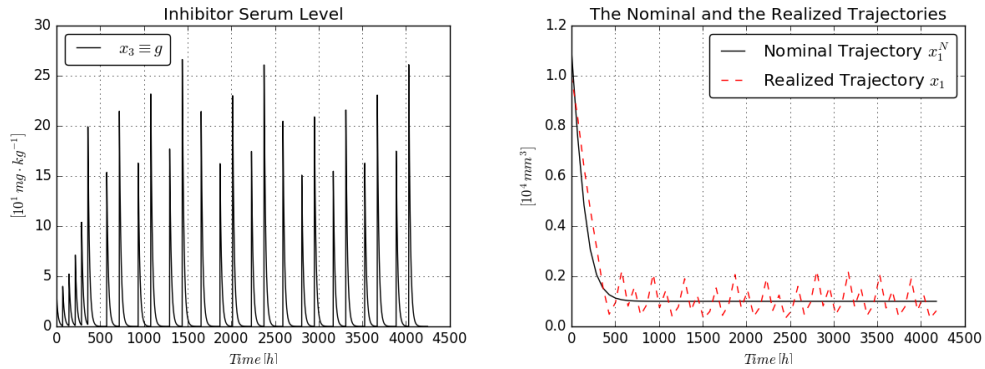


Figure 3.12.: The inhibitor serum level and the trajectory tracking in the $\delta t = 72$ [h], $x_{1_{final}} = 10^3$ [mm^3] case.

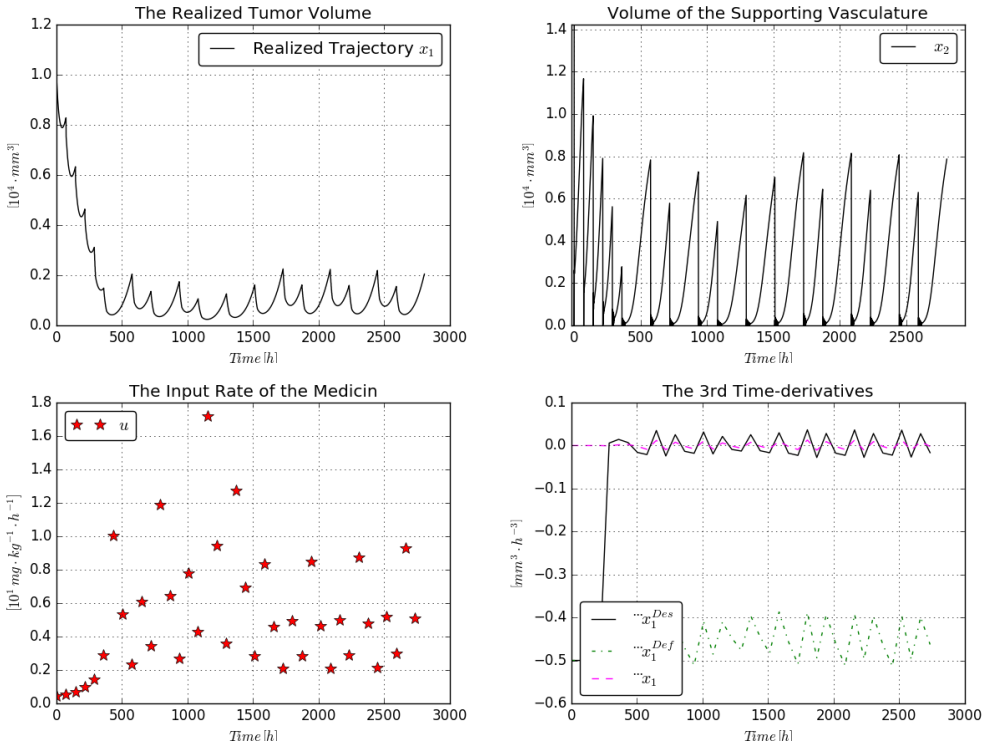


Figure 3.13.: The size of the tumor and its feeding vascular system in the $\delta t = 72$ [h], $x_{1_{final}} = 10^3$ [mm^3], $x_1(0) = 10^4$ [mm^3], $x_2(0) = 10^6$ [mm^3] case, the ingress rate of the serum Bevacizumab, and the estimated third order derivatives.

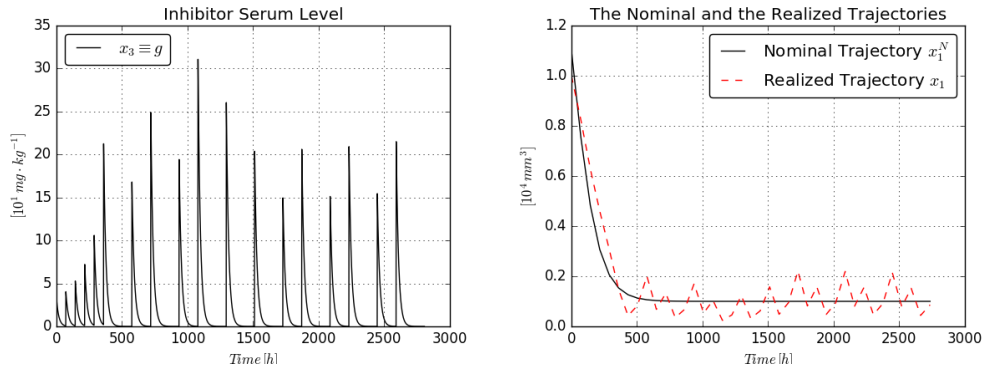


Figure 3.14.: The inhibitor serum level and the trajectory tracking in the $\delta t = 72$ [h], $x_{1_{final}} = 10^3$ [mm^3], $x_1(0) = 10^4$ [mm^3], $x_2(0) = 10^6$ [mm^3] case.

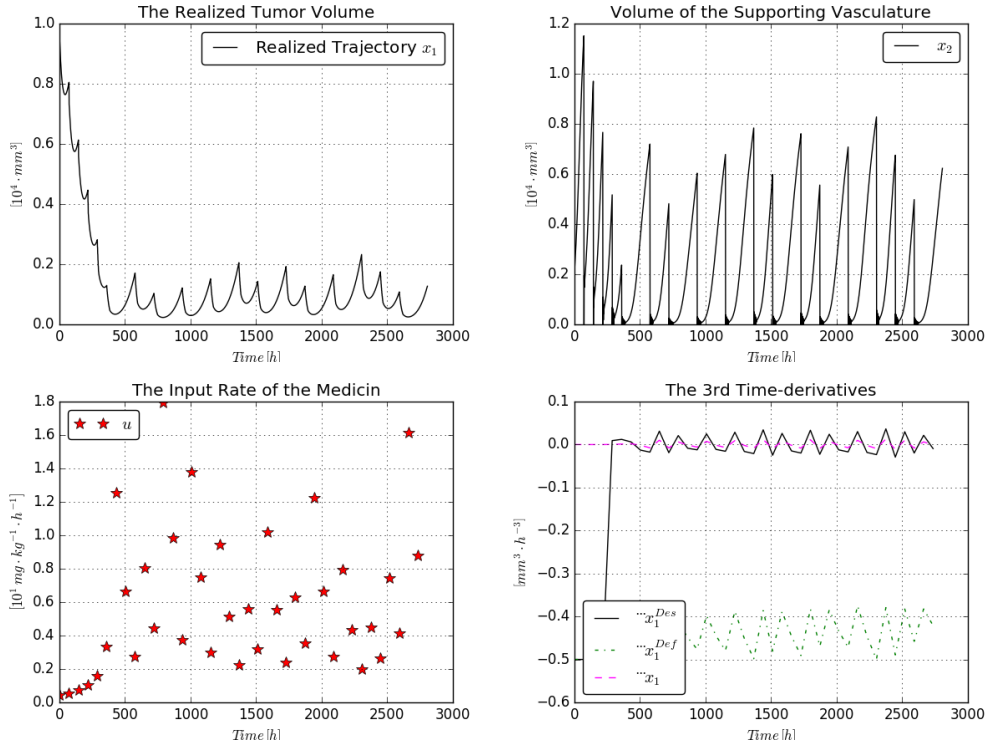


Figure 3.15.: The size of the tumor and its feeding vascular system in the $\delta t = 72$ [h], $x_{1_{final}} = 10^3$ [mm^3], $x_1(0) = 10^4$ [mm^3], $x_2(0) = 10^2$ [mm^3] case, the ingress rate of the serum Bevacizumab, and the estimated third order derivatives.

considerable difference. The huge initial vasculature quickly decreases and the injected serum rate is not increased significantly. Furthermore, consider the pair $x_1(0) = 10^4$ [mm^3], $x_2(0) = 10^2$ [mm^3] (Fig. 3.15). Again, the differences between the previously investigated cases and the present one are negligible.

3.4.4. Summary

In Section 3.4 the RFPT adaptive control approach was investigated for antiangiogenic tumor growth control using the Hahnfeldt model. The RFPT method was tuned by a single adaptive parameter. Considering the 0/0-type singularity of the model and the inefficiency of the Bevacizumab serum in inhibiting angiogenesis at very small tumor volumes, a nominal trajectory starting at $x_1(0) = 10^4$ [mm^3] and ending at $x_{1_{final}} = 10^3$ [mm^3] final tumor volume with $\delta t = 72$ [h] sampling frequency was considered. It was shown that the initial volume of the supporting vasculature $x_2(0) \in [10^2, 10^6]$ [mm^3] surprisingly does not seem to have significant effects on the results.

It should be noted that the suggested control is based only on the measurement of the tumor volume variable $x_1(t)$ at the sampling times, and does not need estimation or measurement of the state variables $x_2(t)$ and $x_3(t)$. Instead of that, it uses a simple affine model defined in (3.28), that contains a constant instead of the exact contributions that are very complicated functions of the state variables. This fact has a great practical advantage. Although the suggested control has relative order 3, it was found that it can use the very rough estimation or surrogate of $\ddot{x}_1$ on the basis of the simple estimation defined in (3.32). In further researches, the RFPT could be tested on different tumor growth models, which contain more realistic elements of the physiological process.

4. Tensor Product Model Transformation based Control of Diabetes Mellitus and Tumor Growth

This Chapter presents the results regarding the examination of the applicability of the Tensor Product (TP)-based method for physiological controls. The performance of the methodology is presented on two domains of physiological controls: control of T1DM and control of tumor growth. In the latter case, two models have been investigated which are both elementary parts of active international research.

The practical realization of the control problems and the calculations have been made by using MATLAB^{TM} and in specific cases, SIMULINK^{TM} environment. I have applied the YALMIP^{TM} framework and various numerical solvers (e.g. MOSEK^{TM}, SDPT-3^{TM}) for semidefinite numerical programming. Furthermore, the TP Toolbox^{TM} for MATLAB environment also has been applied to generate the TP model and TP controller structures.

4.1. Theoretical aspects of the Tensor Product model transformation

As I detailed in Chapter 3, one of the key questions is the effective handling of nonlinearities of the physiological systems and models. In the same Chapter, solutions were provided for this issue which does not consider the details of the nonlinearity since it handles the modeling generously by taking into account only a rough approximating model of the phenomena to be controlled.

The TP-based solutions approach the problem from an opposite direction. They consider the structures of the models and effectively utilize the model properties by transforming them into a more suitable LPV form. The TP model transformation-based modeling and control provide a general way about the handling of nonlinearities. Moreover, the combination of the methods with the LMI or Bilinear Matrix Inequality (BMI) numerical optimization can be easily solved by using the recent advancements in

LPV modeling.

The TP framework exploits the benefits of LPV modeling and LMI optimization. Thus, in the following sections, I briefly introduce these methodologies before turning on the presentation of the theoretical background of TP modeling and control. Regarding the TP control, the PDC-type controller can be effectively used as a basis (i.e. a PDC type state-feedback controller is designed which is the subject of the TP model transformation). The basis of the PDC is the switching among a network of controllers by some varying scheduling parameter. However, the PDC is a state-feedback type controller which requires pre-compensation by default. In order to avoid the drawbacks of pre-compensation, the control-oriented model description is quite beneficial because it models the difference between a certain selected model equilibrium and the actual values of the state variables. Precisely, it models the error dynamics so that by using this tool pre-compensation is not needed. This tool is also introduced concisely in the next section.

4.1.1. LPV modeling

While, LPV modeling was introduced in Sec. 2.1.3, in order to keep the integrity of this Chapter, I present the method in a more suitable way to support the idea of TP model transformation. Consider the following nonlinear time-varying system in state space form [71, 94]:

$$\begin{aligned}
\dot{\mathbf{x}}(t) &= \mathbf{A}(t)\mathbf{x}(t) + \mathbf{B}(t)\mathbf{u}(t) + \mathbf{E}(t)\mathbf{d}(t) \\
\mathbf{y}(t) &= \mathbf{C}(t)\mathbf{x}(t) + \mathbf{D}(t)\mathbf{u}(t) + \mathbf{D}_2(t)\mathbf{d}(t) \\
\begin{pmatrix} \dot{\mathbf{x}}(t) \\ \mathbf{y}(t) \end{pmatrix} &= \mathbf{S}(t) \begin{pmatrix} \mathbf{x}(t) \\ \mathbf{u}(t) \\ \mathbf{d}(t) \end{pmatrix} \\
\mathbf{S}(t) &= \begin{bmatrix} \mathbf{A}(t) & \mathbf{B}(t) & \mathbf{E}(t) \\ \mathbf{C}(t) & \mathbf{D}(t) & \mathbf{D}_2(t) \end{bmatrix},
\end{aligned} \tag{4.1}$$

where $\mathbf{x}(t) \in \mathbb{R}^n$, $\mathbf{y}(t) \in \mathbb{R}^k$, $\mathbf{u}(t) \in \mathbb{R}^m$ and $\mathbf{d}(t) \in \mathbb{R}^l$ are the state-, output-, control input- and disturbance input-vectors, respectively. The $\mathbf{A}(t) \in \mathbb{R}^{n \times n}$ is the state matrix, $\mathbf{B}(t) \in \mathbb{R}^{n \times m}$ is the control input matrix, $\mathbf{E}(t) \in \mathbb{R}^{n \times l}$ is the disturbance input matrix, $\mathbf{C}(t) \in \mathbb{R}^{k \times n}$ is the output matrix, $\mathbf{D}(t) \in \mathbb{R}^{k \times m}$ is the control feed-forward matrix, $\mathbf{D}_2(t) \in \mathbb{R}^{k \times l}$ is the disturbance feed-forward matrix. The $\mathbf{S}(t) \in \mathbb{R}^{(n+k)\times(n+m+l)}$ is the so-called system matrix.

Assume that the time varying elements of the model are selected as scheduling variables $p_i(t)$. Therefore, (4.1) can be described as an LPV system in the following way [95]:

$$\begin{aligned}
\dot{\mathbf{x}}(t) &= \mathbf{A}(\mathbf{p}(t))\mathbf{x}(t) + \mathbf{B}(\mathbf{p}(t))\mathbf{u}(t) + \mathbf{E}(\mathbf{p}(t))\mathbf{d}(t) \\
\mathbf{y}(t) &= \mathbf{C}(\mathbf{p}(t))\mathbf{x}(t) + \mathbf{D}(\mathbf{p}(t))\mathbf{u}(t) + \mathbf{D}_2(\mathbf{p}(t))\mathbf{d}(t) \\
\begin{pmatrix} \dot{\mathbf{x}}(t) \\ \mathbf{y}(t) \end{pmatrix} &= \mathbf{S}(\mathbf{p}(t)) \begin{pmatrix} \mathbf{x}(t) \\ \mathbf{u}(t) \\ \mathbf{d}(t) \end{pmatrix} \\
\mathbf{S}(\mathbf{p}(t)) &= \begin{bmatrix} \mathbf{A}(\mathbf{p}(t)) & \mathbf{B}(\mathbf{p}(t)) & \mathbf{E}(\mathbf{p}(t)) \\ \mathbf{C}(\mathbf{p}(t)) & \mathbf{D}(\mathbf{p}(t)) & \mathbf{D}_2(\mathbf{p}(t)) \end{bmatrix},
\end{aligned} \tag{4.2}$$

where $\mathbf{p}(t) = [p_1(t) \dots p_R(t)]$ is the so-called parameter vector which consists of scheduling parameters $p_i(t)$, or simply the parameters. The $\mathbf{p}(t) \in \mathbf{\Omega}^R \in \mathbb{R}^R$ is a R dimensional real vector within the $\mathbf{\Omega} = [p_{1,min}, p_{1,max}] \times [p_{2,min}, p_{2,max}] \times \dots \times [p_{N,min}, p_{N,max}] \in \mathbb{R}^R$, $\forall p$ $p_{i,min} < p_{i,max}$ hypercube inside the $\mathbb{R}^R$ real vector space. Furthermore, an LPV model is called a quasi-LPV model (qLPV) if at least one of the state variables of the system is involved in the parameter vector $\mathbf{p}(t)$ as a scheduling parameter.

4.1.2. Control oriented modeling

The use of a model form that is control-oriented is a widely used technique in control engineering if one uses state feedback-based control [96]. In this way, it can describe the deviation of the state variables from given predefined reference values which can be the model equilibrium (natural equilibrium) or prescribed values (enforced equilibrium). The usual state feedback-based control guarantees that the state variables become zero over time. Through this approach, the goal can be to reach the zero state variables over time, which means that the state variables become equal to the predefined values or equilibrium which renders the pre-compensator (i.e. reference compensator) obsolete [97, 98]. Consider the $\mathbf{x}(t) \in \mathbb{R}^n$ state vector and the $\mathbf{x}_d \in \mathbb{R}^n$ model equilibrium. One can define the error:

$$\Delta\mathbf{x}(t) = \mathbf{x}(t) - \mathbf{x}_d \ , \tag{4.3}$$

where $\Delta\mathbf{x}(t) \in \mathbb{R}^n$ is the deviation from the equilibrium and the goal of the control in this way is $\Delta\mathbf{x}(t) \to \mathbf{0}$. Substituting (4.3) into (4.2) leads to the control oriented form:

$$
\begin{aligned}
\dot{\mathbf{x}}(t) - \mathbf{0} = \Delta\dot{\mathbf{x}}(t) = \\
= \mathbf{A}(\mathbf{p}(t))\Delta\mathbf{x}(t) + \mathbf{B}(\mathbf{p}(t))\Delta\mathbf{u}(t) + \mathbf{E}(\mathbf{p}(t))\Delta\mathbf{d}(t) \\
\mathbf{y}(t) - \mathbf{y}_d = \Delta\mathbf{y}(t) = \\
= \mathbf{C}(\mathbf{p}(t))\Delta\mathbf{x}(t) + \mathbf{D}(\mathbf{p}(t))\Delta\mathbf{u}(t) + \mathbf{D}_2(\mathbf{p}(t))\Delta\mathbf{d}(t) \\
\begin{pmatrix} \Delta\dot{\mathbf{x}}(t) \\ \Delta\mathbf{y}(t) \end{pmatrix} = \mathbf{S}(\mathbf{p}(t)) \begin{pmatrix} \Delta\mathbf{x}(t) \\ \Delta\mathbf{u}(t) \\ \Delta\mathbf{d}(t) \end{pmatrix} \\
\mathbf{S}(\mathbf{p}(t)) = \begin{bmatrix} \mathbf{A}(\mathbf{p}(t)) & \mathbf{B}(\mathbf{p}(t)) & \mathbf{E}(\mathbf{p}(t)) \\ \mathbf{C}(\mathbf{p}(t)) & \mathbf{D}(\mathbf{p}(t)) & \mathbf{D}_2(\mathbf{p}(t)) \end{bmatrix},
\end{aligned}
\tag{4.4}
$$

where $\Delta\mathbf{x}(t) = \mathbf{x}(t) - \mathbf{x}_d$, $\Delta\mathbf{y}(t) = \mathbf{y}(t) - \mathbf{y}_d$, $\Delta\mathbf{u}(t) = \mathbf{u}(t) - \mathbf{u}_d$ and $\Delta\mathbf{d}(t) = \mathbf{d}(t) - \mathbf{d}_d$ are the deviations of the state-, output-, control input- and disturbance vectors, respectively. The reference signal is also transformed, where $\mathbf{r}(t)$ is the time dependent reference signal and $\mathbf{r}_d$ is the shift which belongs to the model equilibrium, therefore, $\Delta\mathbf{r}(t) = \mathbf{r}(t) - \mathbf{r}_d$. In most of the cases a constant shifted reference was applied, namely $\Delta\mathbf{r} = \mathbf{0}$. This means that the control goal becomes to eliminate the deviation of the value of the states from a given reference determined by $\mathbf{r}_d$.

The control signal provided by the controller is a shifted control signal $\Delta\mathbf{u}(t)$ and ensures that $\Delta\mathbf{x}(t) \to 0$, when $t \to \infty$. In order to apply the generated shifted control signal $\Delta\mathbf{u}(t)$ on the given LPV system (or on the original nonlinear system) a transformation is needed: $\mathbf{u}(t) = \Delta\mathbf{u}(t) + \mathbf{u}_d$, where $\mathbf{u}_d$ belongs to the given equilibrium.

4.1.3. LMI based optimization

The application of LMIs in control theory is based on the Lyapunov linearization theorem. Lyapunov showed that if a linear system $\dot{\mathbf{x}}(t) = \mathbf{A}\mathbf{x}(t)$ is stable, then all of the system trajectories converge to zero if and only if there exists a positive definite matrix $\mathbf{P}$ that is $\mathbf{A}^\top\mathbf{P} + \mathbf{P}\mathbf{A} < 0$, when $\mathbf{P} > 0$. In the cases of matrices, the $>$, $<$ inequality symbols refer to the definiteness of matrices. This LMI was the first one that has been applied successfully to analyze the stability of certain control systems [99]. In general, an LMI has the following affine form:

$$
\mathbf{F}(\mathbf{x}) \equiv \mathbf{F}_{(0)} + \sum_{k=1}^{K} x_k \mathbf{F}_{(k)} > 0 \ , \tag{4.5}
$$

where $\mathbf{x} \in \mathbb{R}^n$ are constants, $\mathbf{F}_{(k)} = \mathbf{F}_{(k)}^\top \in \mathbb{R}^{n \times n}$ $k = 0, \ldots, K$ are symmetric matrices and $\mathbf{F}(\mathbf{x})$ is positive definite, so that all of its eigenvalues $\lambda(\mathbf{F}(\mathbf{x}))$ are positive. In other words, it is a system of n polynomial inequalities related to $\mathbf{x}$ is equivalent to (4.5) where the inequality is preserved by the leading principal minors of $\mathbf{F}(\mathbf{x})$ being positive [99].

Multiple LMIs can be incorporated in one single LMI by diagonally embedding them into one equation i.e. $\mathbf{F}^{(1)}(\mathbf{x}) > 0$, $\mathbf{F}^{(2)}(\mathbf{x}) > 0$, ..., $\mathbf{F}^{(s)}(\mathbf{x}) > 0$ can be expressed as $\mathbf{F}(\mathbf{x}) \equiv \mathrm{diag}(\mathbf{F}^{(1)}(\mathbf{x}), \mathbf{F}^{(2)}(\mathbf{x}), \ldots, \mathbf{F}^{(s)}(\mathbf{x})) > 0$. Thus, $\mathbf{F}(\mathbf{x}) > 0$ means that all of the LMIs in the diagonals of $\mathbf{F}(\mathbf{x})$ must be positive definite [98].

In order to make the numerical calculations more relaxed, non-strict LMIs are also used extensively. An LMI is non-strict if $\mathbf{F}(\mathbf{x}) \geq 0$, that is the eigenvalues of $\lambda(\mathbf{F}(\mathbf{x}))$ must be positive or zero. Another approach is for relaxation is replacing $\mathbf{F} > 0$ with $\mathbf{F} > \mathbf{U}$, where $\mathbf{U}$ is diagonal containing small negative numbers. If an LMI is represented as $\mathbf{F} > \mathbf{T}$, then by rearranging it as $\mathbf{F} - \mathbf{T} > 0$ lead to a relaxed representation which makes the numerical procedures also more reliable [100]. Equation 4.5 is a convex constraint interpreted for $\mathbf{x}$ if the set $\{\mathbf{x} | \mathbf{F}(\mathbf{x}) > 0\}$ is convex. One can say that the LMI conditions are feasible if there exists $\mathbf{x} \in \mathbf{X}$, where $\mathbf{X}$ is called the feasible set. The feasible set of LMI conditions are always convex [101].

Convex numerical optimization is the most important tool regarding LMI based optimization related to control engineering [102]. For example, an often employed approach is the minimization of convex scalar functions via semidefinite programming, which is the essence of many control-related LMIs. For example, a typical semi-definite programming task is the following: assume that there exists a convex scalar function be $f(\mathbf{x})$, and let $f(\mathbf{x})$ be the subject of an LMI condition as

$$\begin{aligned} &\min_{\mathbf{x}} f(\mathbf{x}) \\ &\text{subject to} \quad \mathbf{F}(\mathbf{x}) > 0\,, \mathbf{G}(\mathbf{x}) > 0. \end{aligned} \tag{4.6}$$

Equation 4.6 is a convex optimization problem due to the given constraints on $\mathbf{x}$ which enforce it to be a convex set and the convex function is optimized on it [102]. In the next section, I show the mathematical foundations connected to the TP model transformation as the last necessary piece of the theoretical background before I show its application on the physiological problems.

In accordance with Lyapunov's direct method, $\dot{\mathbf{x}}(t) = \mathbf{A}\mathbf{x}(t)$ is stable if there exists a $V(\mathbf{x}) = \mathbf{x}^\top \mathbf{P}\mathbf{x}$ positive definite quadratic Lyapunov function and $\dot{V}(\mathbf{x}) = \mathbf{x}^\top(\mathbf{A}^\top\mathbf{P} + \mathbf{P}\mathbf{A})\mathbf{x}$ is negative definite which is:

$$\mathbf{A}^\top\mathbf{P} + \mathbf{P}\mathbf{A} < \mathbf{0}, \qquad \mathbf{P} = \mathbf{P}^\top > \mathbf{0}\ . \tag{4.7}$$

The LPV model $\dot{\mathbf{x}}(t) = \mathbf{A}(\mathbf{p}(t))\mathbf{x}(t) + \mathbf{B}(\mathbf{p}(t))\mathbf{u}(t)$ is the equation of a general, polytopic system, where the $[\mathbf{A}(\mathbf{p}(t)) \ \mathbf{B}(\mathbf{p}(t))] = \sum_{r=1}^{R} w_r(\mathbf{p})[\mathbf{A}_r \ \mathbf{B}_r]$ are the polytopic vertices and $w_r(\mathbf{p})$ is a convex weighting function. By using the Lyapunov function $V(\mathbf{x}(t)) = \mathbf{x}^\top \mathbf{P}\mathbf{x} = \mathbf{x}^\top \mathbf{X}^{-1}\mathbf{x}$ a possible controller structure can be defined as [103]:

$$\mathbf{u}(t) = \mathbf{M}(\mathbf{p}(t))\mathbf{X}^{-1}\mathbf{x}(t) = \sum_{j=1}^{J} w_j(\mathbf{p})\mathbf{M}_j\mathbf{X}^{-1}\mathbf{x}(t) \ . \tag{4.8}$$

By computing the derivative of the Lyapunov function, the following term appears, where the "Sym" abbreviates symmetric:

$$\dot{V}(\mathbf{x}(t)) = \mathbf{x}^\top(t)\mathbf{X}^{-1} \cdot Sym\Big(\mathbf{A}(\mathbf{p})\mathbf{X} + \mathbf{B}(\mathbf{p})\mathbf{M}(\mathbf{p})\Big) \cdot \mathbf{X}^{-1}\mathbf{x}^\top(t) \ , \tag{4.9}$$

The symmetric term can be described by using the polytopic weighting functions as follows:

$$Sym\Big(\mathbf{A}(\mathbf{p})\mathbf{X} + \mathbf{B}(\mathbf{p})\mathbf{M}(\mathbf{p})\Big) = \sum_{i=1}^{R}\sum_{j=1}^{R} w_i(\mathbf{p})w_j(\mathbf{p}) \Big(\mathbf{A}_i\mathbf{X} + \mathbf{B}_i\mathbf{M}_j\Big) < \mathbf{0} \ . \tag{4.10}$$

The $\mathbf{S}(\mathbf{p}(t)) = Co(\mathbf{S}_1, \mathbf{S}_2, \ldots, \mathbf{S}_R)$ and $\mathbf{G}(\mathbf{p}(t)) = Co(\mathbf{G}_1, \mathbf{G}_2, \ldots, \mathbf{G}_R)$ are polytopic structures and the "Co" acronym means convex combination. The use of the same weighting functions $\mathbf{w}(\mathbf{p}(t))$ to describe the polytopic qLPV system and controller as well as to use them in the design of a PDC type controller is possible [98].

4.1.4. TP model transformation

TP model transformation originates from parameter dependent fuzzy system techniques [97]. The foundations of the TP methodology was presented first in [104] and was later extended in [98, 100, 105–107] for qLPV based TP modeling and controller design. TP model transformation is possible in the case of multi-variable functions, neural networks, or even fuzzy constructs. Due to its flexibility, it is possible to use the TP model transformation to transform a given model described by its LPV (or qLPV) representation into polytopic TP model form as well [98]. In practice, the TP model transforms a given model into multiplications consisting of orthonormal weighting function systems depending on one variable, namely, the $p(t)$ scheduling variable. The resulting TP model can approximate the original LPV model within the desired accuracy. The TP model transformation can be combined with LMI-based controller design because the

developed sub-controllers can be connected by the occurring weighting functions and the resulting controller becomes equal to the convex combination of them [98, 100, 105].

To realize the TP model transformation, (4.2) can be considered where the bounded $\mathbf{\Omega}$ hypercube – interpreted inside the $\mathbb{R}^R$ vector space – is the transformational space. In the following part, I introduce the main terms and structures which are needed to execute the TP model transformation on a given class of LPV models.

Definition 4.1.1. The finite element convex polytopic model describes the $\mathbf{S}(\mathbf{p}(t))$ actual model as a convex combination of the $\mathbf{S}_r \in \mathbb{R}^{(n+k)\times(n+m+l)}$ LTI sub-models – LTI vertices – inside the $\mathbf{\Omega}$ hypercube in the following way:

$$\mathbf{S}(\mathbf{p}(t)) = \sum_{r=1}^{R} w_r(\mathbf{p}(t))\mathbf{S}_r \ , \tag{4.11}$$

where $w_r(\mathbf{p}(t)) \in [0,1]$ is continuous convex weighting function.

Definition 4.1.2. The finite element TP type convex polytopic model describes the $\mathbf{S}(\mathbf{p}(t))$ actual model as a convex combination of the $\mathbf{S}_r \in \mathbb{R}^{(n+k)\times(n+m+l)}$ LTI vertex system inside the $\mathbf{\Omega}$ hypercube in the following way:

$$\begin{aligned}\mathbf{S}(\mathbf{p}(t)) = \sum_{i_1=1}^{I_1}\sum_{i_2=1}^{I_2}\dots\sum_{i_R=1}^{I_R}\prod_{r=1}^{R} w_{r,i_r}(p_r(t))\mathbf{S}_{i_1,i_2,\dots,i_R} = \\ = \mathcal{S}\prod_{\mathrm{r=1}}^{\mathrm{R}}\boxtimes \mathbf{w}_r(p_r(t)),\end{aligned} \tag{4.12}$$

where $\mathcal{S} \in \mathbb{R}^{I_1\times I_2\times\dots\times I_R\times(n+k)\times(n+m+l)}$ coefficient tensor can be derived from the $\mathbf{S}_{i_1,i_2,\dots,i_R}$ LTI vertex system and the $\mathbf{w}_r(p_r(t))$ weighting function vector consisting of the $w_{r,i_r}(p_r(t))$ $(i_r = 1\dots I_R)$ univariate continuous weighting functions.

The High Order Singular Value Decomposition (HOSVD) method [98, 108, 109] allows the construction of a tensor product structure according to the significance of each component. The result of the TP model transformation is the numerical reconstruction of the HOSVD of the given LPV model without the consideration of complexity reduction and convex hull manipulation. The resulting HOSVD canonical form consists of singular functions in orthonormal structure and a core tensor consists of LTI system vertices assigned to the higher-order singular values.

Definition 4.1.3. A general convex hull can be defined in the following way:

$$\mathrm{Conv}(\mathbf{\Omega}) = \left\{ \sum_{i=1}^{|\mathbf{\Omega}|} w_i q_i | (\forall i : w_i \geq 0) \wedge \sum_{i=1}^{|\mathbf{\Omega}|} w_i = 1 \right\} \ , \tag{4.13}$$

where $\mathbf{\Omega}$ is the convex set, w_i are the weighting parameters and q_i are the points inside $\mathbf{\Omega}$. Namely, the $\mathbf{\Omega}$ can be defined with a convex combination of w_i and q_i, if $q_i \in \mathbf{\Omega}$ [110].

One can obtain a convex TP model if the weighting functions satisfy the following criteria:

$$\begin{aligned} \forall r, i, p_r(t) : w_{r,i_r}(p_r(t)) \in [0,1] \\ \forall r, p_r(t) : \sum_{i=1}^{I_R} w_{r,i_r}(p_r(t)) = 1. \end{aligned} \tag{4.14}$$

The minimal volume simplex (MVS) is a convex hull which has the smallest convex region to be defined inside the parameter space [100]. In this case $(\mathcal{S})_{j_r=j}$ r-mode sub-tensors evolve a minimal volume bounding simplex for $\mathcal{S} \times_r \mathbf{w}_{jr}^{(r)}(p_r)$ trajectory over $r = 1...R$ for the $\mathcal{S} \in \mathbb{S}^{I_1 \times ... \times I_R}$ core tensor, which is realized from the $\mathbf{S}_{i_1,...,i_R}$ matrices as follows:

$$\mathbf{S}(\mathbf{p}) = \mathcal{S} \overset{\mathrm{R}}{\underset{\mathrm{r=1}}{\boxtimes}} \mathbf{w}^{(r)}(p_r) \ . \tag{4.15}$$

The control input in the case of a general state-feedback controller can be described as

$$\mathbf{u}(t) = \mathbf{K}(\mathbf{p}(t))\mathbf{x}(t), \tag{4.16}$$

where $\mathbf{K}(\mathbf{p}(t)) \in \mathbb{R}^{m \times n}$ is the parameter dependent controller gain. A parallel distributed controller (PDC) kind state-feedback controller in polytopic structure can be described in the following way:

$$\mathbf{K}(\mathbf{p}(t)) = \mathcal{K} \overset{\mathrm{R}}{\underset{\mathrm{r=1}}{\boxtimes}} \mathbf{w}_r(p_r(t)) = \mathcal{K} \times_r \mathbf{w}(\mathbf{p}(t)) \ . \tag{4.17}$$

Additional context on the use of TP transformations for control can be found in [98, 100, 105–107, 111–113]. I have used the TP Toolbox [114] in this study in order to execute the TP model transformation and get the appropriate weighting functions belonging to the given TP model form.

4.2. TP-based control of T1DM

4.2.1. Model description

The controlled model consists of three different submodels: a core model which describes the glucose-insulin dynamics [15]; CHO absorption submodel; and insulin absorption submodel [39]. The CHO submodel describes how the orally ingested CHO affects the

rate of appearance of glucose in the blood. The insulin absorption submodel describes the rate of appearance of insulin in the blood injected subcutaneously. The submodels are represented by (4.18a) - (4.18d). The core model is responsible for describing the glucose-insulin dynamics (4.18e) - (4.18g):

$$\dot{D}_1(t) = -\frac{1}{\tau_D} D_1(t) + \frac{1000 A_g}{M_{wG} V_G} C \cdot d(t) \tag{4.18a}$$

$$\dot{D}_2(t) = -\frac{1}{\tau_D} D_2(t) + \frac{1}{\tau_D} D_1(t) \tag{4.18b}$$

$$\dot{S}_1(t) = -\frac{1}{\tau_S} S_1(t) + \frac{1}{V_I} u(t) \tag{4.18c}$$

$$\dot{S}_2(t) = -\frac{1}{\tau_S} S_2(t) + \frac{1}{\tau_S} S_1(t) \tag{4.18d}$$

$$\dot{G}(t) = -(p_1 + X(t))G(t) + p_1 G_B + \frac{1}{\tau_D} D_2(t) \tag{4.18e}$$

$$\dot{X}(t) = -p_2 X(t) + p_3 (I(t) - I_B) \tag{4.18f}$$

$$\dot{I}(t) = -n(I(t) - I_B) + \frac{1}{\tau_S} S_2(t). \tag{4.18g}$$

The core model has three state variables, $G(t)$ [mg/dL] the blood glucose (BG) concentration, $X(t)$ [1/min] insulin-excitable tissue glucose uptake activity, and $I(t)$ [mU/L] the blood insulin concentration. The glucose and insulin absorption submodels consist of the $D_1(t)$ [mg/dL], $D_2(t)$ [mg/dL], $S_1(t)$ [mU/L], and $S_2(t)$ [mU/L] state variables respectively. The disturbance input $d(t)$ [g/min] represents the glucose intake which is transformed by the $\Big((1000 A_g)/(M_{wG} V_G)\Big) C$ complex into the appropriate dimension to fit to the $D_1(t)$. The control input $u(t)$ [mU/L/min] is directly connected to the $S_1(t)$. The detailed description of the used model parameters can be found in Table 4.1.

4.2.2. CGMS model description

Modeling the sensor noise in CGMS applications is a crucial question. CGMS devices measure the BG level from the subcutaneous space of the abdomen or arm. However, the measured values can be different from a given average BG level in the body. Undesirable

Table 4.1.: Parameters of the model [15, 39].

Notation	Value	Unit	Description
G_B	110	[mg/dL]	Basal glucose level
I_b	1.5	[mU/L]	Basal insulin level
p_1	0.028	[1/min]	Transfer rate
p_2	0.025	[1/min]	Transfer rate
p_3	0.00013	[L/mU · min]	Transfer rate
n	0.23	[1/min]	Time constant for insulin disappearance
BW	74	[kg]	Body weight
V_I	0.12 BW	[L]	Insulin distribution volume
V_G	0.16 BW	[L]	Glucose distribution volume
M_{wG}	180.1558	[g/mol]	Molecular weight of glucose
A_g	0.8	-	Glucose utilization
C	18.018	[mmol/L]	Convert rate between [mg/dL] and [mmol/L]
τ_D	40	[min]	CHO to glucose absorption constant
τ_S	55	[min]	Insulin absorption constant

effects also appear in the CGMS model, for example, time delay, heat effects, which can affect the obtained measurements. To model these phenomena I have applied the CGMS model of [115]. The developed model can be directly connected to the introduced model described by (4.18e) - (4.18g). The CGMS model consists of the following equations:

$$e_k = 0.7(e_{k-1} + v_k), \quad k \geq 1, \tag{4.19}$$

$$v_k \sim N_{iid}(0, 1), \tag{4.20}$$

$$\eta_k = \xi + \lambda \sinh\left(\frac{e_k - \gamma}{\delta}\right), \tag{4.21}$$

$$\dot{G}_{sub}(t) = \frac{1}{\tau_{sub}}(G(t) - G_{sub}(t)), \tag{4.22}$$

$$G_{CGM}(kT) = G_{sub}(kT) + \eta_k. \tag{4.23}$$

I used the parameters given by [115]: τ_{sub}=15 [min], ξ=-5.471 [mg/dL], λ=15.96 [mg/dL], γ=-0.5444 and δ=1.6898. The stochastic term can be initialized with $e_0 \sim N_{iid}(0, 1)$. The noisy measurement data can be calculated by using the sampled output of the virtual patient system $G(t)$. The model includes a first order process in order to approximate the delay between the different glucose compartments and a noise term. The control goal is

to hold the blood glucose level $G(t)$ within a safe region. Due to physiological limitations, the primary goal is to avoid hypoglycemia and allow only short hyperglycemic periods. The selected constraint here was 60 [mg/dL] (3.33 [mmol/L]) $\leq G(t) \leq$ 320 [mg/dL] (17.76 [mmol/L]) which must not exceeded by the blood glucose level at all.

4.2.3. LPV model representation

The model, described by (4.18a) - (4.18g) can be transformed into the form of (4.4). Considering the measurable state $G(t)$ from (4.18e):

$$\begin{aligned} \dot{G}(t) - 0 = -(p_1 + X(t))G(t) + p_1 G_B + \frac{1}{\tau_D} D_2(t) - \\ \Big[-(p_1 + X_d)G_d + p_1 G_B + \frac{1}{\tau_D} D_{2,d} \Big] = \\ = -(p_1 + X_d)\Delta G(t) - G(t)\Delta X(t) + \frac{1}{\tau_D}\Delta D_2(t), \end{aligned} \tag{4.24}$$

the LPV model can be represented by the matrix in 4.26. By applying the same transformation on the remaining state equations, the deviation-based control oriented state-space description can be represented by its system matrix $\mathbf{S}(\mathbf{p}(t))$ that the aim of the control is to keep $G(t)$ within 60 [mg/dL] and 320 [mg/dL]. This leads to the $\mathbf{\Omega}^1 = [G_{min}, G_{max}] = [60, \ldots, 320]$ one dimensional parameter space where the $p(t)$ can be changed. Furthermore, only $\mathbf{A}(\mathbf{p}(t))$ is affected by $p(t)$. In 4.3 the equilibrium point was chosen as $\mathbf{x}_d = [D_{1,d}, D_{2,d}, S_{1,d}, S_{2,d}, G_d, X_d, I_d]^\top = [0, 0, 0, 0, G_B, 0, I_B]^\top$, $u_d = 0$ and $d_d = 0$.

4.2.4. The realized TP model form

Using the TP model transformation on (4.18), the general TP model structure becomes $\mathbf{S}(G(t)) = \mathcal{S} \times_1 \mathbf{w}(G(t))$. The weighting functions are linear due to the properties of the model described by (4.18). The resulting specific TP model form in this case becomes

$$\mathbf{S}(G(t)) = \mathcal{S} \times_1 \mathbf{w}_1(G(t)) \ , \tag{4.25}$$

whence $\mathcal{S} = [\mathbf{S}(G_{min}), \mathbf{S}(G_{max})]$.

4.3. LMI based controller design

Several LMI based methods are available for controller design to get the $\mathcal{K}$ feedback gain tensor [101, 116]. Due to the disturbance input, I have selected the robust pole

$$\mathbf{S}(\mathbf{p}(t)) = \begin{bmatrix} \mathbf{A}(\mathbf{p}(t)) & \mathbf{B} & \mathbf{E} \\ \mathbf{C} & \mathbf{D} & \mathbf{D}_2 \end{bmatrix} =$$

$$= \begin{bmatrix} -\frac{1}{\tau_D} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & \frac{1000A_g}{M_{wG}V_G}C \\ \frac{1}{\tau_D} & -\frac{1}{\tau_D} & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & -\frac{1}{\tau_S} & 0 & 0 & 0 & 0 & \frac{1}{V_I} & 0 \\ 0 & 0 & \frac{1}{\tau_S} & -\frac{1}{\tau_S} & 0 & 0 & 0 & 0 & 0 \\ 0 & \frac{1}{\tau_D} & 0 & 0 & -(p_1 + X_d) & -G(t) & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & -p_2 & p_3 & 0 & 0 \\ 0 & 0 & 0 & \frac{1}{\tau_S} & 0 & 0 & -n & 0 & 0 \\ 0 & 0 & 0 & 0 & 10 & 0 & 0 & 0 & \end{bmatrix}. \tag{4.26}$$

clustering method for the controller design via LMI optimization [117, 118]. By applying this method, the poles of the closed-loop system lie inside the so-called LMI-region on the complex plane which is defined as:

Definition 4.3.1. [94]: A given subset $\mathcal{D}$ inside the complex plane is an LMI region if there exists a $\alpha = [\alpha_{kl}] \in \mathbb{R}^{m\times m}$ symmetric matrix and a $\beta = [\beta_{kl}] \in \mathbb{R}^{m\times m}$ matrix such that

$$\begin{gathered} \mathcal{D} = \{s \in \mathbb{C} : \ \ f_{\mathcal{D}}(s)\} < 0 \\ f_{\mathcal{D}}(s) := \alpha + s\beta + \bar{s}\beta^{\top} = [\alpha_{kl} + \beta_{kl}s + \beta_{lk}\bar{s}]_{1\le k,l\le m} \end{gathered}, \tag{4.27}$$

where the characteristic function $f_{\mathcal{D}}(s)$ takes values in the space of $m \times m$ Hermitian matrices and < 0 means negative definite.

Theorem 4.3.1. *The matrix* $\mathbf{A}$ *is* $\mathcal{D}$ *stable if and only if there exists a positive definite symmetric matrix* $\mathbf{X}$ *such that*

$$\begin{gathered}\mathbf{X}>0\\ M_{\mathcal{D}}(\mathbf{A},\mathbf{X})<0\\ M_{\mathcal{D}}(\mathbf{A},\mathbf{X})=\alpha\otimes\mathbf{X}+\beta\otimes(\mathbf{AX})+\beta^{\top}\otimes(\mathbf{AX})^{\top}=\\ =[\alpha_{ab}\mathbf{X}+\beta_{ab}(\mathbf{AX})+\beta_{ba}(\mathbf{AX})^{\top}]_{ab}\end{gathered}\quad , \tag{4.28}$$

where $M_{\mathcal{D}}$ is an $m\times m$ block matrix characterizes the pole location in a given LMI region. The proof of the theorem can be found in [94, 118, 119].

Next, I introduce the design method and the stability on the intersection of LMI regions. If i pieces of given $\mathcal{D}_i$ LMI regions are specified then the $\mathbf{A}$ matrix is $\mathcal{D}$ stable if and only if there exists a positive definite, symmetric matrix $\mathbf{X}$ such that

$$\begin{gathered}\mathbf{X}>0\\ M_{\mathcal{D}}(\mathbf{A},\mathbf{X})_i<0,\ \ \forall i\in\mathbb{N}\end{gathered}\quad . \tag{4.29}$$

The following substitution can be applied regarding to $f_{\mathcal{D}}(s)$ (4.27) and $M_{\mathcal{D}}(\mathbf{A},\mathbf{X})$ (4.28):

$$(\mathbf{X},(\mathbf{AX}),(\mathbf{AX})^{\top})\leftrightarrow(1,s,\bar{s})\ . \tag{4.30}$$

Note that in case of the closed loop, the results is slightly different because of the introduction of the $\mathbf{L}\in\mathbb{R}^{m\times n}$ term as follows:

$$(\mathbf{X},(\mathbf{AX}+\mathbf{BL}),(\mathbf{AX}+\mathbf{BL})^{\top})\leftrightarrow(1,s,\bar{s})\ , \tag{4.31}$$

whence the controller gain $\mathbf{K}$ can be calculated as

$$\mathbf{K}:=\mathbf{LX}^{-1}\ . \tag{4.32}$$

By considering the general $\mathcal{D}$ stability determined by (4.28) – (4.31), the so-called α-stability and disk of LMI regions can be defined in the presence of disturbances:

$$2\alpha\mathbf{X}+(\mathbf{AX}+\mathbf{BL})+(\mathbf{AX}+\mathbf{BL})^{\top}+\mathbf{EE}^{\top}<0\ , \tag{4.33a}$$

$$\begin{bmatrix}-r\mathbf{X} & q\mathbf{X}+(\mathbf{AX}+\mathbf{BL})\\ q\mathbf{X}+(\mathbf{AX}+\mathbf{BL})^{\top} & -r\mathbf{X}\end{bmatrix}<0\ , \tag{4.33b}$$

where the $\mathbf{K}=\mathbf{LX}^{-1}$ is in accordance with (4.32).

The α-stability region is described by (4.33a) which determines a half-plane on the negative left-hand side and ensures that all of the closed-loop poles lie on this plane. In this case, the α tuning parameter can be interpreted as the distance between the imaginary axis and the half-plane. Moreover, the disk region described by (4.33b) determines a disk plane in the complex domain and ensures that all of the poles of the closed system lie inside this plane. The tuning parameters are the q and r variables, which can be interpreted as the center and the radius of the disk plane, respectively. Figure 4.1 provides a graphical interpretation of the detailed inequalities. The resulting feedback gain guarantee that the poles of the closed-loop system lie in the shaded region.

In the case of LPV systems, the use of the previous LMI techniques from (4.33a) – (4.33b) are still possible. In accordance with [118, 120, 121] the following feasibility LMI optimization problem needed to be solved in order to get the $\mathbf{K}_i$ subcontrollers belong to the $\mathbf{S}_i$ LTI vertices of the system which ensures the stability and prompt control action. For notational brevity, $\mathbf{K}_i$ and $\mathbf{S}_i$ are introduced instead of $\mathbf{K}(p_i)$ and $\mathbf{S}(p_i)$ where $p_i = [G_{min}, G_{max}]$. In order to get the $\mathbf{K}_i$ controller gains, one have to solve the following optimization problem:

$$\mathbf{X} > 0 \ , \tag{4.34a}$$

$$2\alpha\mathbf{X} + (\mathbf{A}_i\mathbf{X} + \mathbf{B}\mathbf{L}_i) + (\mathbf{A}_i\mathbf{X} + \mathbf{B}\mathbf{L}_i)^\top + \mathbf{E}\mathbf{E}^\top < 0 \ , \tag{4.34b}$$

$$\begin{bmatrix} -r\mathbf{X} & q\mathbf{X} + (\mathbf{A}_i\mathbf{X} + \mathbf{B}\mathbf{L}_i) \\ q\mathbf{X} + (\mathbf{A}_i\mathbf{X} + \mathbf{B}\mathbf{L}_i)^\top & -r\mathbf{X} \end{bmatrix} < 0 \ , \tag{4.34c}$$

$$i < j \ \text{ s.t. } \ w_i \cap w_j \neq \phi \ ,$$

which provides stable controller gains in the Lyapunov sense which satisfy the predefined criteria against the poles of the closed loop. To evaluate the inequalities MOSEK Apps. solver [122] and the YALMIP toolbox [123] to solve the LMI optimization problem described by (4.34a) – (4.34c).

Remark 4.3.1.1. *The proposed difference based LPV system in* (4.26) *is not fully controllable, because* $\text{rank}(\mathcal{C}(\mathbf{A}, \mathbf{B})) = 5$*, where* $\mathcal{C}$ *is the controllability matrix, and the state dimension is* $n = 7$*. Hence, two uncontrollable modes appear in the system. Both uncontrollable modes are stable, namely, both of them decay to zero asymptotically (the eigenvalues do have negative real parts) and all of the unstable modes are controllable.*

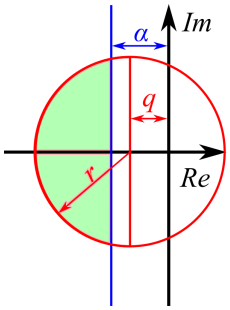


Figure 4.1.: The $\mathcal{D}$ regions method allows that the poles of the closed loop system will lie within the shaded region.

Therefore, the system is stabilizable [124].

The two uncontrollable, but stable modes are $\lambda_{uc1,uc2} = -0.025$ which requires the selection of α and q to cover them in order to satisfy (4.34a) – (4.34b). In accordance with this requirement, $\alpha = 0.02$ and $q = -0.02$ were selected, which guarantees that all of the closed-loop poles are placed beyond -0.02 at the negative half-plane. In order to reach satisfactory oscillations, I have chosen $r = 10$ which means that all of the real parts of the poles are between -10.02 and -0.02. Based on (4.32) the controller gains can be calculated as $\mathbf{K}_i = \mathbf{L}_i\mathbf{X}^{-1}$. Numerically, the following $\mathbf{K}_i$ gains were obtained:

$$\begin{aligned} \mathbf{K}_1 = \mathbf{K}(G_{min}) = \\ = \begin{bmatrix} -1.0414 & 11.4231 & -28.5733 & -58.1709 \\ 10.5541 & -1.537 \cdot 10^5 & -90.5105 \end{bmatrix}, \end{aligned} \tag{4.35}$$

and

$$\begin{aligned} \mathbf{K}_2 = \mathbf{K}(G_{max}) = \\ = \begin{bmatrix} -1.0308 & 11.396 & -28.5111 & -58.0372 \\ 10.5171 & -1.5346 \cdot 10^5 & -90.2944 \end{bmatrix}, \end{aligned} \tag{4.36}$$

which leads to $\mathcal{K} = [\mathbf{K}(G_{min}), \mathbf{K}(G_{max})]^\top$. Members of $\mathbf{K}_i$ that has the highest magnitudes are caused by the small p_3 model parameter. Due to the gains being close to each other, a soft control action can be expected. Figure 4.2 shows the calculated poles of the closed-loop system at the extremes of the parameter domain ($\lambda(\mathbf{A}_i + \mathbf{B}\mathbf{K}_i)_i$) in the simulation environment. As it can be seen, the poles lie in the determined LMI region,

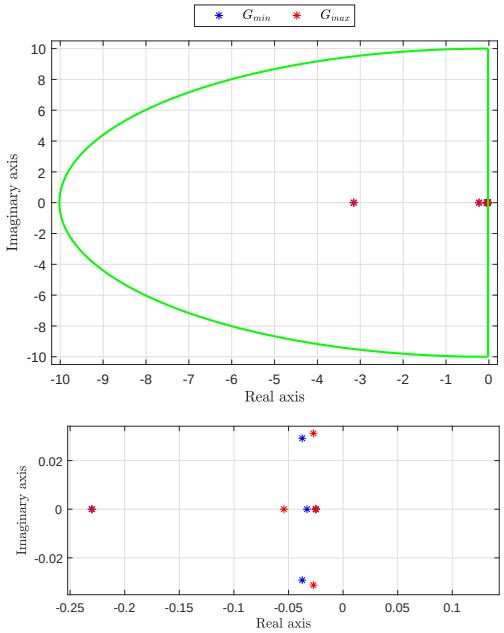


Figure 4.2.: Closed loop poles $(\lambda(\mathbf{A}_i + \mathbf{B}\mathbf{K}_i)_i)$ belong to the vertices of the LPV systems. The upper diagram is an overview about the whole complex plane with the selected LMI region. It can be seen that all of the closed loop poles lie inside the determined LMI region. The region close to the imaginary axis is shown in the bottom figure. It can be seen that the poles lie in the LMI region, namely, $\mathrm{Re}(\lambda)_i < -0.02$ in accordance with the selected α and q.

which is parametrized by the α, q, and r parameters.

4.4. Design of mixed additive/non-additive EKF

As only the blood glucose level $G(t)$ can be directly measured one need to estimate the remaining states as well. I designed a specific Extended Kalman Filter (EKF) to estimate the values of the states. Since the carbohydrate intake in the glucose metabolism model and the measurement noise is also an additive term, the overall system can be given in the following form:

$$\begin{aligned} \dot{\mathbf{x}} &= f(\mathbf{x}(t), \mathbf{u}(t)) + \mathbf{d}(t) \\ \mathbf{z}_k &= \mathbf{C}\mathbf{x}_k + \mathbf{v}_k \end{aligned}, \tag{4.37}$$

where $\mathbf{x}(t)$ is the actual state, $\mathbf{u}(t)$ is the actual control signal, $\mathbf{w}(t)$ is the actual disturbance, $\mathbf{v}_k$ is the actual sensor noise, $\mathbf{C}$ is the output matrix, and the output of the system $\mathbf{z}$ is linearly dependent on the BG level and on the sensor noise. The $\mathbf{d}(t)$ impulse

like disturbance affects the corresponding states. The values of the $n \times n$ semidefinite $\mathbf{Q}(t)$ covariance matrix had to be selected according to the effect of the disturbance on each state. In this given case the sensor noise was described in 4.2.2, with the $\mathbf{v}_k$ being approximated with zero mean and 10 [mg/dL] variance $\mathbf{v}_k \sim \mathcal{N}(0, \mathbf{R}_k)$ in conjunction with the $\mathbf{R}_k$ covariance matrix. In the light of the aforementioned considerations, the prediction and update algorithm of the EKF will be described next.

Predict phase The predicted state estimate is given by:

$$\dot{\hat{\mathbf{x}}}(t) = f(\hat{\mathbf{x}}(t), \mathbf{u}(t)) \ , \tag{4.38}$$

with predicated covariance estimate:

$$\dot{\mathbf{P}}(t) = \mathbf{F}(t)\mathbf{P}(t) + \mathbf{P}(t)\mathbf{F}(t)^\top + \mathbf{Q}(t), \tag{4.39}$$

where $\mathbf{F}(t) = \left.\dfrac{\partial f}{\partial \mathbf{x}}\right|_{\hat{\mathbf{x}}(t),\mathbf{u}(t)}$, $\hat{\mathbf{x}}_{k+1,k} = \hat{\mathbf{x}}(t_k)$, and $\mathbf{P}_{k+1,k} = \mathbf{P}(t_k)$ by applying appropriate sampling.

Update phase The innovation residual is

$$\tilde{\mathbf{y}}_{k+1} = \mathbf{z}_{k+1} - \mathbf{C}\hat{\mathbf{x}}_{k+1|k} \ , \tag{4.40}$$

with innovation covariance

$$\mathbf{S}_{k+1} = \mathbf{C}\mathbf{P}_{k+1|k}\mathbf{C}^\top + \mathbf{R}_{k+1} \ , \tag{4.41}$$

Kalman gain

$$\mathbf{K}_{k+1} = \mathbf{P}_{k+1|k}\mathbf{C}^\top\mathbf{S}_{k+1}^{-1} \ , \tag{4.42}$$

updated state estimate:

$$\hat{\mathbf{x}}_{k+1|k+1} = \hat{\mathbf{x}}_{k+1|k} + \mathbf{K}_{k+1}\tilde{\mathbf{y}}_{k+1} \ , \tag{4.43}$$

and updated covariance estimate

$$\mathbf{P}_{k+1|k+1} = (\mathbf{I} - \mathbf{K}_{k+1}\mathbf{C})\mathbf{P}_{k+1|k} \ , \tag{4.44}$$

where $\mathbf{I}$ is the unit matrix and $\mathbf{C}$ is the output matrix, respectively [125, 126]. Due to the model specificities, the applied sampling time for the EKF was 1 [min] because the

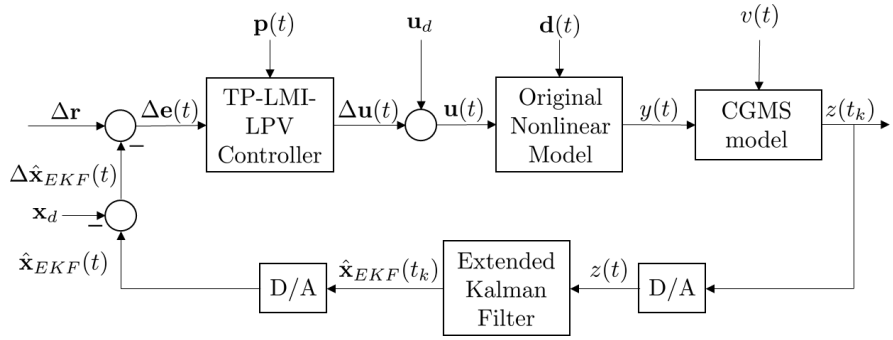


Figure 4.3.: Final control structure with the designed TP-LMI-LPV controller and mixed EKF. The D/A converter is added to provide the continuous signal to the continuous process model used by the EKF in the predict phase.

primary goal was to demonstrate the usability of the TP-LMI-LPV controller.

4.5. Final Control Structure

Figure 4.3 presents the developed control structure. The original nonlinear model is described by (4.18a) - (4.18g). The output of the model is the blood glucose level $y(t) = G(t)$ which is affected by the $v(t)$ additive random sensor noise. The measured output is the $z(t) = y(t) + v(t)$. The EKF provides the $\hat{\mathbf{x}}_{EKF}(t)$ estimated states from which the deviation based estimated states are generated as $\Delta\hat{\mathbf{x}}_{EKF}(t) = \hat{\mathbf{x}}_{EKF}(t) - \mathbf{x}_d$. The deviation error $\Delta e(t)$ is based on a comparison between the reference and estimated states, namely, $\Delta\mathbf{e}(t) = \Delta\mathbf{r} - \Delta\hat{\mathbf{x}}_{EKF}(t)$. The applied $\Delta\mathbf{r} = \mathbf{0}_{7\times1}$ reference was constant zero, which basically means the zero deviation of $\mathbf{x}(t)$ through $\hat{\mathbf{x}}_{EKF}(t)$ from the desired states $\mathbf{x}_d$. The controller directly get information about the scheduling parameter $\mathbf{p}(t) = p(t) = G(t)$, which was in this case the measured parameter and provides the appropriate difference based control signal $\Delta\mathbf{u}(t)$. The applied control signal can be calculated as $\mathbf{u}(t) = \Delta\mathbf{u}(t) + \mathbf{u}_d$. It should be noted that I applied the filtered BG level instead of the measured one ($p(t) = G_{EKF}(t) \neq z(t)$), since it is accessible and in this way I was able to reduce the high noise on it.

4.6. Numerical simulations

4.6.1. Initial conditions and setup

The simulations were performed using the following initial state variables: $\mathbf{x}(t_0) = [0, 0, 0, 0, 110, 0, 5]^\top$. It was assumed that no food and insulin intakes have been done

Table 4.2.: Applied meal intakes on daily basis.

Meal	Time instance [min]	Amount of intake [g]
First meal	$30 + 5 \cdot randn$	$90 + 10 \cdot randn$
Second meal	$220 + 5 \cdot randn$	$15 + 10 \cdot randn$
Third meal	$400 + 5 \cdot randn$	$100 + 10 \cdot randn$
Fourth meal	$720 + 5 \cdot randn$	$15 + 10 \cdot randn$
Fifth meal	$980 + 5 \cdot randn$	$80 + 10 \cdot randn$

before t_0, thus the belonging state variables have been taken as zero $\mathbf{x}_{1-4}(t_0) = 0$. The initial state values belonging to $G(t_0), X(t_0)$ and $I(t_0)$ have been arbitrarily selected. The initial states of the cross-validation system $\mathbf{x}_{cv}(t_0) = [0, 0, 0, 0, 110, 0, 5]^\top$ have been considered as the same as $\mathbf{x}(t_0)$ in order to facilitate the comparability. The initial condition of the EKF was set to $\hat{\mathbf{x}}_{EKF}(t_0) = [0, 0, 0, 0, 130, 0, 11]^\top$. The same assumptions hold for $\hat{\mathbf{x}}_{EKF,1-4}(t_0)$ as in case of $\mathbf{x}_{1-4}(t_0)$, namely that, neither food nor insulin have not been taken before the beginning of the simulation. The $\hat{\mathbf{x}}_{EKF,5-7}(t_0)$ have been arbitrarily selected, but comparable to $\mathbf{x}_{5-7}(t_0)$ to simulate the uncertainty of the EKF at the beginning of the simulation. The reference was set to $\Delta\mathbf{r} = \mathbf{0}_{7\times1}$ throughout the control period.

During the investigations a multiple randomized disturbance signal has been applied, where both the time instances and the amounts of food intake were randomized within a given range. The glucose absorption submodel uses the CHO intake and the given utilization rate (A_g). During the CHO intake design, the dietary recommendations for diabetic patients was considered as a primary intake model [127–130]. The amount of 300 ± 50 g was taken daily (which is higher than the recommended 300 g CHO/day) and split into 5 meals to simulate a high glucose load. To model a realistic eating schedule, the consumption of 20 g of CHO at given time instances was assumed. For example, if the total amount of CHO was 108 g in a meal then the developed algorithm realized five portions of 20 g of CHO and one portion of 8 g of CHO at consecutive time instances. Furthermore, a saturation was added to avoid negative intakes which may appear due to the applied randomization method. In this way, I were able to test the control solution under unfavorable conditions to investigate its performance. A standard normal distribution ($randn = \mathcal{N}(0, 1)$) was used for the randomization, with the exact details of the meal protocol that can be found in Table 4.2.

The time grid of the simulation was chosen to be 1440 minutes (24 hours) during each day, with a total simulation duration of 30 days.

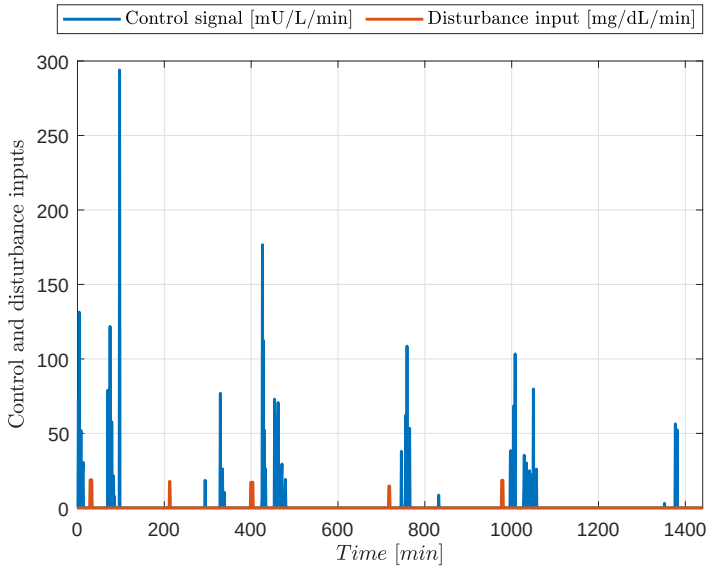


Figure 4.4.: The applied control and disturbance signals. The upper figure shows the $\mathbf{d}(t)$ disturbance signal in accordance with the applied glucose intake protocol. The lower figure shows the $\mathbf{u}(t)$ control signal provided by the controller.

4.6.2. Results

Figure 4.4–4.7 shows the first day of the evolution of the system. Through these diagrams, I graphically demonstrate the operation of the control framework in detail. It should be noted that the BG levels are either given in [mmol/L] or [mg/dL]. The model uses [mg/dL], thus I considered this unit during the control design and calculations. The exchange rate of 18.018 [mg/dl] = 1 [mmol/L] was applied here.

Figure 4.4 shows the $d(t)$ disturbance and $u(t)$ control inputs, respectively. It can be seen that the controller became active right after the disturbance intake to act and decrease the error. Figure 4.5 shows the absorbed glucose ($D_2(t)/\tau_D$) and insulin ($S_2(t)/\tau_S$) over time. Due to the model specificities (insulin distribution volume and time constants), the rate of absorption of insulin is delayed and shrank compared to the effect of glucose.

Figure 4.6 represents the blood glucose levels, namely the blood glucose concentration measured by the sensor, estimated by the EKF, and the real blood glucose level. The goal was to use the EKF to demonstrate the usability of the proposed control solution.

Figure 4.7 shows the variation of the BG level with and without control. It is visible that the controller provided better performance with lower peaks and the total time of hyperglycemia was also much lower by applying the developed controller. As usual in state

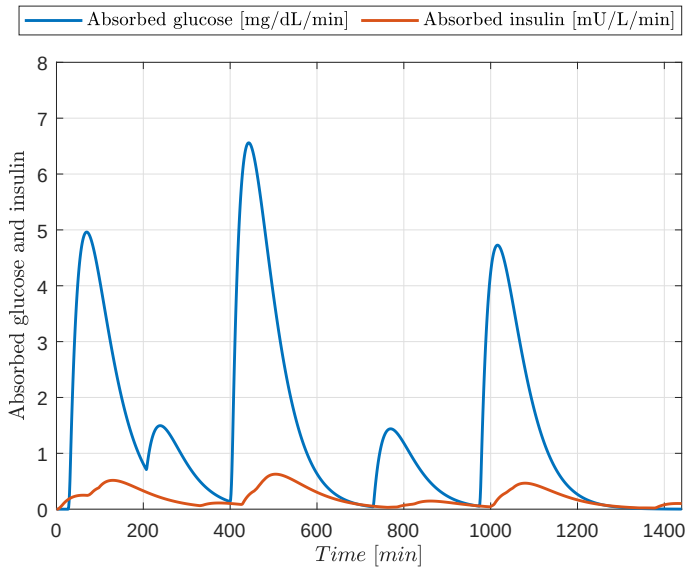


Figure 4.5.: Appearance of the absorbed insulin ($S_2(t)$) and carbohydrate ($D_2(t)$) in the blood.

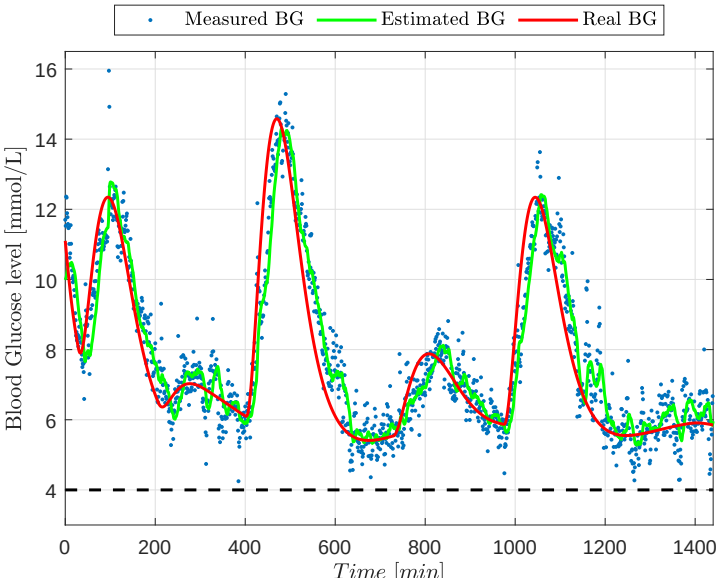


Figure 4.6.: Measured, estimated and real blood glucose level during a 24 hours long simulation under the surveillance of the developed control scheme.

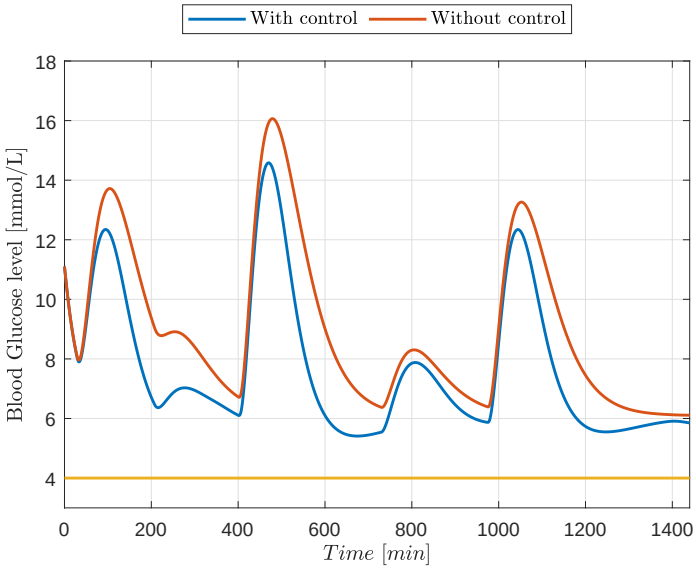


Figure 4.7.: Numerical simulation of a 24 hours period. The controller was able to avoid the hypoglycemia despite the high glucose load.

feedback controllers, the control goal was to reach the zero error over time $\Delta\mathbf{e}(t) \leftarrow \mathbf{0}$. Due to the control framework, this is equivalent to reaching the zero deviation-based states, since the deviation-based reference signal was zero ($\Delta\mathbf{r} = \mathbf{0}$). In other words, when the state variables approach the zero value then the real state variables and the desired equilibrium are approaching each other. It can be seen in the figure that the controller can enforce the deviation-based state variables to approach zero over time. Hence, without disturbance, the error signal of the deviated state variables is evolving towards zero. The fluctuation in the signal is coming from the simple fact that the states to be used for the comparison are provided by the EKF ($\Delta\mathbf{x}_{EKF}(t)$). Figure 4.8 shows the control variability grid analysis (CVGA) diagram. The diagram points out the lowest (horizontal axis) and the highest (vertical axis) BG levels daily. Namely, each point belongs to the given minimum and maximum BG levels occurring on the same simulated day. The black dots belong to the measured values (the model output loaded by the simulated sensor noise), the white dots belong to the estimated values (produced by the EKF) and the blue dots belong to the real values (the model output without any noise), respectively. It is clearly visible that the controller performed well, since, it kept the mean BG level in a narrow $132 < G(t) < 145$ [mg/dL] range.

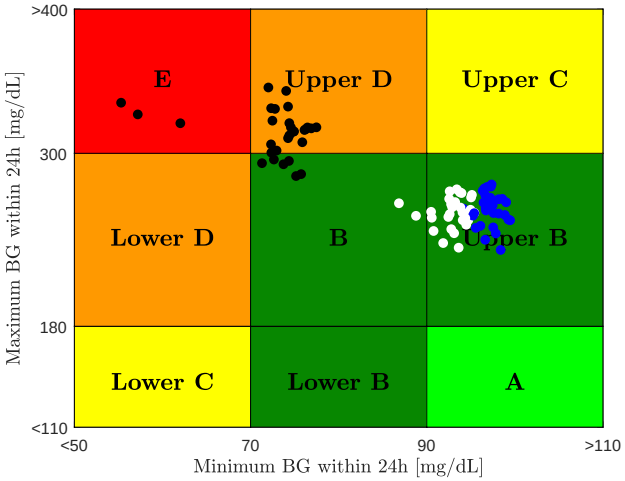


Figure 4.8.: CVGA plot of the blood glucose levels within 24 hours during 30 days long simulation. Black dots: measured BG level with sensor noise; White dots: Estimated BG by EKF; Blue dots: real BG levels.

4.7. Discussion

Upon evaluating the results, one has to analyze the specificities of the model first. Neither the control signal nor the disturbance signal does not have an immediate action because of the time coefficients of the applied absorption submodels. Therefore, during the controller design only soft control actions, which can be translated as applying slower poles in the closed-loop, should be used in the given framework to avoid overcompensation, i.e. overdosing the insulin. This can be improved by limiting the input and output signals by using appropriate LMIs. Results on the daily treatment can be seen in Figure 4.6 and 4.7.

The model has its specific equilibrium belonging to G_B and I_B. Without any external excitation, the states move into the origin, except $G(t)$ and $I(t)$ which are closing to G_B and I_B, respectively, which can also be seen in Figure 4.6. Without any control input, the BG level provided by the model does not steer away. Instead, after the exhaustion of the glucose, when the effect of the food intake is over, the BG level approaches G_B. The definition of hypoglycemia and hyperglycemia according to [3, 131, 132] can be found in Table 4.3.

As it can be seen in Figure 4.8 the sensor noise has an apparent effect on the control, even if one knows that the real BG level can be very different. A higher additive random noise was used in this research to simulate the sensor uncertainty. Without applying filtering, it would be difficult to use the noisy output for control purposes. Thus, by

Table 4.3.: Definition of hypoglycemia and hyperglycemia in the utilized model.

Hypoglycemia	$G(t) \leq 3.9$ mmol/L (70 [mg/dL])
Hyperglycemia (fasting)	$7 \leq G(t)$ mmol/L (126.126 [mg/dL])
Hyperglycemia (2 hours after meal)	$11.1 \leq G(t)$ mmol/L (200 [mg/dL])

accounting for the errors caused by the sensor, the control solution can be more stable. It should be noted that the controller did not allow to decrease under 75 [mg/dL] (4, 16 mmol/L) with the BG level, but it allowed to reach higher glucose values as a consequence of the determined "soft" control action via the settings of the LMIs. Nevertheless, by the applied soft control action the control solution can intervene effectively. Besides the controller fully avoids hypoglycemia, it decreases the duration of the hyperglycemic periods and the BG level reached by the model. The duration of the hyperglycemic periods is half as long with treatment as without it and the maximum BG levels are significantly lower both in peaks and averages as well. As it is reflected in the blue dots (Figure 4.8) the realized BG levels are fairly acceptable, in accordance with the definitions summarized by Table 4.3.

4.7.1. Summary

In this Section, I investigated the applicability of TP model transformation in the case of a well-known Intensive Care Unit (ICU) diabetes model to realize different TP models. I have examined two cases: the TP model when the "operating equilibrium of glycemia (G_d)" of the model was considered equal to the model equilibrium of glycemia (G_E) and where it was not. Based on numerical validation I found that in the case of realistic simulations I can reach better performance, namely, a smaller difference between the realized TP model and the original model, when the operating equilibrium is not equal to the model equilibrium.

4.8. Model based TP-LPV-LMI control of tumor growth

4.8.1. Tumor growth model transformation

In the case of controlling a tumor using TP-based control, I have used the Hahnfeldt model here as well as in Chapter 3, with the same parameters. The system of differential equations describing the process were already introduced in equation 3.26. Consider denoting the state variables by $z_1(t)$, $z_2(t)$, and $z_3(t)$. It was already mentioned that the

system has a singularity in $z_1 = z_2 = 0$, which makes it difficult to control in that region. Consider the following coordinate transform [55, 133]: $x_1(t) = \ln(z_1(t))$, $x_2(t) = \ln(z_2(t))$, and $x_3(t) = z_3(t)$. By choosing these variables as the new states of the system, the Hahnfeldt model can be alternatively written as:

$$\dot{x}_1(t) = -\lambda_1 x_1(t) + \lambda_1 x_2(t) \ , \tag{4.45}$$

$$\dot{x}_2(t) = be^{x_1(t)-x_2(t)} - de^{2x_1(t)/3} - \eta x_3(t) \ , \tag{4.46}$$

$$\dot{x}_3(t) = -\lambda_3 x_3(t) + u(t) \ . \tag{4.47}$$

One can see that the original state variables $z_{1,2}(t)$ are limited, and a nontrivial equilibrium of the model can be calculated based on equation 3.26 beside permanent inhibitor level ($z_3(t) \equiv z_{3,\infty}$, $z_{1,\infty}$ and $z_{2,\infty}$) in the following manner [54, 134]:

$$\begin{aligned} z_{1,\infty} = z_{2,\infty} &= \left(\frac{b - \eta z_{3,\infty}}{d}\right)^{3/2}, \\ z_{1,max} = z_{2,max} &= \left(\frac{b}{d}\right)^{3/2} \leftrightarrow z_{3,\infty} = \frac{1}{\lambda_3} u_\infty \equiv 0. \end{aligned} \tag{4.48}$$

Equation (4.48) shows that the operating domain of the $z_{1,2}(t)$ original state variables are $z_{1,2}(t) = \left(0, (b/d)^{3/2}\right]$. For the transformed state variables, the region $x_{1,2}(t) = \left(\ln(1), \ln((b/d)^{3/2})\right]$ is valid. In accordance with [55], the goal of the control can be determined as the $x_{1,2}(t)$ to be equal to $\ln(1) = 0$ [mm^3].

4.8.2. qLPV model development

An error dynamics-based control-oriented qLPV model was developed for the design of the TP controller. The model can describe the deviation between the state variables of the system to be controlled and a prescribed equilibrium or a reference trajectory. The

transformation of the first and third states can be expressed as:

$$\begin{aligned}
&\Delta\dot{x}_1(t) = \dot{x}_1(t) - \dot{x}_{1,ref}(t) = \\
&-\lambda_1 x_1(t) + \lambda_1 x_2(t) - \\
&\Big(- \lambda_1 x_{1,ref}(t) + \lambda_1 x_{2,ref}(t)\Big) = \\
&-\lambda_1(x_1(t) - x_{1,ref}(t)) + \lambda_1(x_2(t) - x_{2,ref}(t)) = \\
&-\lambda_1 \Delta x_1(t) + \lambda_1 \Delta x_2(t)
\end{aligned} \quad . \tag{4.49}$$

$$\begin{aligned}
&\Delta\dot{x}_3(t) = \dot{x}_3(t) - \dot{x}_{3,ref}(t) = \\
&-\lambda_3 x_3(t) + u(t) - \Big(- \lambda_3 x_{3,ref}(t) + u_{ref}(t)\Big) = \\
&-\lambda_3 \Delta x_3(t) + \Delta u(t)
\end{aligned} \quad . \tag{4.50}$$

The derivation of the second state is more subtle. Consider

$$\begin{aligned}
&\Delta\dot{x}_2(t) = \dot{x}_2(t) - \dot{x}_{2,ref}(t) = \\
&be^{x_1(t)-x_2(t)} - de^{2x_1(t)/3} - \eta x_3(t) \\
&-\Big(be^{x_{1,ref}(t)-x_{2,ref}(t)} - de^{2x_{1,ref}(t)/3} - \eta x_{3,ref}(t)\Big).
\end{aligned} \quad . \tag{4.51}$$

Combining the equation with (4.50), the following manipulations can be asserted:

$$\begin{aligned}
&be^{x_1(t)}e^{-x_2(t)} - be^{x_{1,ref}(t)}e^{-x_{2,ref}(t)} - 0 = \\
&be^{x_1(t)}e^{-x_2(t)} - be^{x_{1,ref}(t)}e^{-x_{2,ref}(t)} - be^{x_{1,ref}(t)}e^{-x_2(t)} \\
&\qquad + be^{x_{1,ref}(t)}e^{-x_2(t)} = \\
&be^{-x_2(t)}(e^{x_1(t)} - e^{x_{1,ref}(t)}) \cdot 1 \\
&\qquad - be^{-x_{1,ref}(t)}(e^{x_2(t)} - e^{x_{2,ref}(t)}) \cdot 1 = \\
&be^{-x_2(t)}\frac{(e^{x_1(t)} - e^{x_{1,ref}(t)})}{\Delta x_1(t)}\Delta x_1(t) \\
&\qquad - be^{-x_{1,ref}(t)}\frac{(e^{x_2(t)} - e^{x_{2,ref}(t)})}{\Delta x_2(t)}\Delta x_2(t)
\end{aligned} \tag{4.52}$$

$$\begin{aligned}
&-de^{2x_1(t)/3} + de^{2x_{1,ref}(t)/3} = \\
&-d\Big(e^{2x_1(t)/3} - e^{2x_{1,ref}(t)/3}\Big) \cdot 1 = \\
&-d\frac{\Big(e^{2x_1(t)/3} - e^{2x_{1,ref}(t)/3}\Big)}{\Delta x_1(t)}\Delta x_1(t).
\end{aligned}$$

From (4.52), two scheduling variables can be selected:

$$p_1(t) = be^{-x_2(t)} \frac{\left(e^{x_1(t)} - e^{x_{1,ref}(t)}\right)}{\Delta x_1(t)} - d\frac{\left(e^{2x_1(t)/3} - e^{2x_{1,ref}(t)/3}\right)}{\Delta x_1(t)} \tag{4.53}$$

$$p_2(t) = -be^{-x_{1,ref}(t)} \frac{(e^{x_2(t)} - e^{x_{2,ref}(t)})}{\Delta x_2(t)} \tag{4.54}$$

In this manner, the transformed $\Delta x_2(t)$ state becomes as follows:

$$\Delta \dot{x}_2(t) = p_1(t)\Delta x_1(t) + p_2(t)\Delta x_2(t) - \eta \Delta x_3(t) \ . \tag{4.55}$$

It should be noted that the $p_{1,2}(t)$ may cause numerical instability, when $\Delta x_{1,2}(t) \to 0$ and singularity, when $\Delta x_{1,2}(t) = 0$. By applying the L'Hospital's rule [135] it can be seen that both terms have finite final values which allow the application of them in practice without any numerical problem:

$$\begin{aligned} &\lim_{\Delta x_1(t)\to 0} \quad b\, e^{-x_2(t)} \frac{\left(e^{x_1(t)} - e^{x_{1,ref}(t)}\right)}{\Delta x_1(t)} \\ &\qquad\qquad -d\, \frac{\left(e^{2x_1(t)/3} - e^{2x_{1,ref}(t)/3}\right)}{\Delta x_1(t)} = \\ &b\, e^{-x_2(t)} e^{x_{ref,1}(t)} - d\, \frac{2}{3} e^{2x_{ref,1}(t)/3}, \text{and} \\ &\lim_{\Delta x_2(t)\to 0} \quad be^{-x_{1,ref}(t)} \frac{(e^{x_2(t)} - e^{x_{2,ref}(t)})}{\Delta x_2(t)} = \\ &\qquad\qquad -be^{x_{ref,1}(t)} - e^{-x_{ref,2}(t)}. \end{aligned} \tag{4.56}$$

The variables $p_{1,2}(t)$ can be defined for practical use as:

$$\begin{aligned} p_1(t) = &\begin{cases} b\, e^{-x_2(t)} e^{x_{ref,1}(t)} - d\, \frac{2}{3} e^{2x_{ref,1}(t)/3}, & \text{if } \Delta x_1(t) = 0 \\ b\, e^{-x_2(t)} \frac{\left(e^{x_1(t)} - e^{x_{1,ref}(t)}\right)}{\Delta x_1(t)} & \\ \qquad -d\, \frac{\left(e^{2x_1(t)/3} - e^{2x_{1,ref}(t)/3}\right)}{\Delta x_1(t)}, & \text{otherwise} \end{cases} \\ p_2(t) = &\begin{cases} -be^{x_{ref,1}(t)} - e^{-x_{ref,2}(t)}, & \text{if } \Delta x_2(t) = 0 \\ -be^{-x_{1,ref}(t)} \frac{(e^{x_2(t)} - e^{x_{2,ref}(t)})}{\Delta x_2(t)}, & \text{otherwise} \end{cases} \end{aligned} \tag{4.57}$$

The domains of $p_{1,2}(t)$ are $p_1(t) = [0, \ldots, 13]$ and $p_2(t) = [4, \ldots, 15]$. These domains originate from the operating region of $x_{1,2}(t)$ and from physiological considerations [54], which allows to change $p_{1,2}(t)$ within these boundaries. As a consequence, the following LPV form is obtained by considering (4.49), (4.50) and (4.55):

$$\begin{aligned} \dot{\mathbf{x}}(t) &= \mathbf{A}(\mathbf{p}(t))\mathbf{x}(t) + \mathbf{B}\mathbf{u}(t) \\ \mathbf{y}(t) &= \mathbf{C}\mathbf{x}(t) \\ \mathbf{S}(\mathbf{p}(t)) = \begin{bmatrix} \mathbf{A}(\mathbf{p}(t)) & \mathbf{B} \\ \mathbf{C} & 0 \end{bmatrix} &= \begin{bmatrix} -\lambda_1 & \lambda_1 & 0 & 0 \\ p_1(t) & p_2(t) & -\eta & 0 \\ 0 & 0 & -\lambda_3 & 1 \\ 1 & 0 & 0 & 0 \end{bmatrix}. \end{aligned} \tag{4.58}$$

4.8.3. LMI based controller design

We have applied the PDC framework through which a quadratically stabilizing state-feedback controller can be designed for continuous polytopic systems by using LMI optimization. A possible solution to develop PDC type controllers via LMI optimization is the design of LMI regions through pole clustering. Pole clustering allows us to determine the place of the poles of the closed system in the complex plane. The same half-disk type of LMI constraint was used here, which was also employed in the previous section in equations 4.34a–4.34c. The $\mathbf{K}_i$ gains here were obtained by solving the LMI optimization problem with $\alpha = 0$, $q = 0$ and $r = 12$ for which the YALMIP framework [123] and the SeDuMi 1.3 solver was applied [136], with respect to the difference based qLPV model from equation 4.58. The obtained $\mathbf{K}_{1,\ldots,4}$ gains have been the following: $\mathbf{K}_1 = [225.025 \;\; 292.6693 \;\; -22.0255]$, $\mathbf{K}_2 = [585.19 \;\; 283.3383 \;\; -21.6512]$, $\mathbf{K}_3 = [222.2539 \;\; 529.3 \;\; -20.7009]$, $\mathbf{K}_4 = [525.7506 \;\; 535.8547 \;\; -21.0306]$. As a result, the poles of the closed-loop at the vertices became $\lambda(\mathbf{A}_1 + \mathbf{B}\mathbf{K}_1) = [-0.5082 \;\; -9.5097 + 1.8531i \;\; -9.5097 - 1.8531i]^\top$, $\lambda(\mathbf{A}_2 + \mathbf{B}\mathbf{K}_2) = [-0.3952 \;\; -9.3790 + 0.9612i \;\; -9.3790 - 0.9612i]^\top$, $\lambda(\mathbf{A}_3 + \mathbf{B}\mathbf{K}_3) = [-1.5562 + 2.3167i \;\; -1.5562 - 2.3167i \;\; -4.0906]^\top$, $\lambda(\mathbf{A}_4 + \mathbf{B}\mathbf{K}_4) = [-1.6765 + 0.8012i \;\; -1.6765 - 0.8012i \;\; -4.1797]^\top$.

4.8.4. Final control structure

The original model was considered as reference model during the controller design by assuming that it is an exactly model with known parameters and dynamics. A constant $u_{ref}(t) = u_{ref} = 14$ [mg/kg/min] reference was used which guaranteed that $x_{1,2}(t) = 1$

[mm^3] at the end of the therapy. Because the $x_{2,3}(t)$ state variables of the controlled system cannot be measured, an Extended Kalman Filter (EKF) estimated them. The EKF was a mixed continuous/discrete EKF with $T = 1$ [day] sampling time in its measurement part [126, 137]. Through the control action, the controller enforces the original model to behave as the given reference model, i.e. $\mathbf{x}(t) = \mathbf{x}_{ref}(t)$, $t \to \infty$. This is equivalent to $\Delta\mathbf{r} = \mathbf{x} - \mathbf{x}_{ref} = \mathbf{0}$, where $\Delta\mathbf{r} = \mathbf{0}$. As a consequence, the controller eliminates the deviation between $\mathbf{x}$ and $\mathbf{x}_{ref}$ over time.

4.8.5. Results

The designed control framework was implemented in Simulink. The applied initial conditions were $\mathbf{x}(t_0) = [\ln(14900),\ \ln(14900),\ 0]^\top$, $\mathbf{x}_{ref}(t_0) = [\ln(17000),\ \ln(17000),\ 0]^\top$, $\hat{\mathbf{x}}(t_0) = [\ln(17000),\ \ln(17000),\ 0]^\top$, respectively. The initial conditions were arbitrarily selected, however, I assumed the lack of therapeutic agents before the beginning of the therapy ($x_3(t_0) = \hat{x}_3(t_0) = x_{ref,3}(t_0) = 0$) and $\mathbf{x}_{ref}(t_0) = \hat{\mathbf{x}}(t_0)$, thus the reference and EKF state variables are adjusted by us at the beginning of the therapy. The selected values were reasonable from the viewpoint of the domain of $\mathbf{x}_i$. Figure 4.9 presents the state trajectories of the original system ($\mathbf{x}(t)$), the EKF ($\hat{\mathbf{x}}(t)$) and the reference system $\mathbf{x}_{ref}(t)$, respectively. It can be seen that both of them behaves similarly. The controlled system and the EKF approaches the reference model with high accuracy. The final values for $x_{1,2}(t)$ in case of all models are 1 mm^3, which is the lower boundary of the domain as it was expected.

Figure 4.10 shows the deviation between the state variables of the parts of the controller. The upper subfigure is the difference between the original system and the EKF, namely, $\mathbf{x}(t) - \hat{\mathbf{x}}(t)$. It can be seen that this approximation is loaded with a small error in the case of $x_{1,2}(t)$ compared to the magnitudes of the states. The higher, but a quickly decaying error in $x_3(t)$ comes from the discretization error. The middle subfigure is the difference between the reference system and the EKF, that is $\mathbf{x}_{ref}(t) - \hat{\mathbf{x}}(t)$. From the controller's point of view, this is the important measure, since this is the error signal which is used by the controller. The lower subfigure represents the difference between the reference system and the original system, $\mathbf{x}_{ref}(t) - \mathbf{x}(t)$. It is visible that the deviations are small, and decay rapidly. The final Root Mean Square Error (RMSE) for all state variables are the following over the whole simulation interval:

- $\mathrm{RMSE}_{\mathbf{x}(t)-\hat{\mathbf{x}}(t)} = [2.2290, 3.8269, 3.5293]$;
- $\mathrm{RMSE}_{\mathbf{x}_{ref}(t)-\hat{\mathbf{x}}(t)} = [2.2116, 3.8149, 5.4068]$;
- $\mathrm{RMSE}_{\mathbf{x}_{ref}(t)-\mathbf{x}(t)} = [0.1843, 0.0565, 2.0559]$.

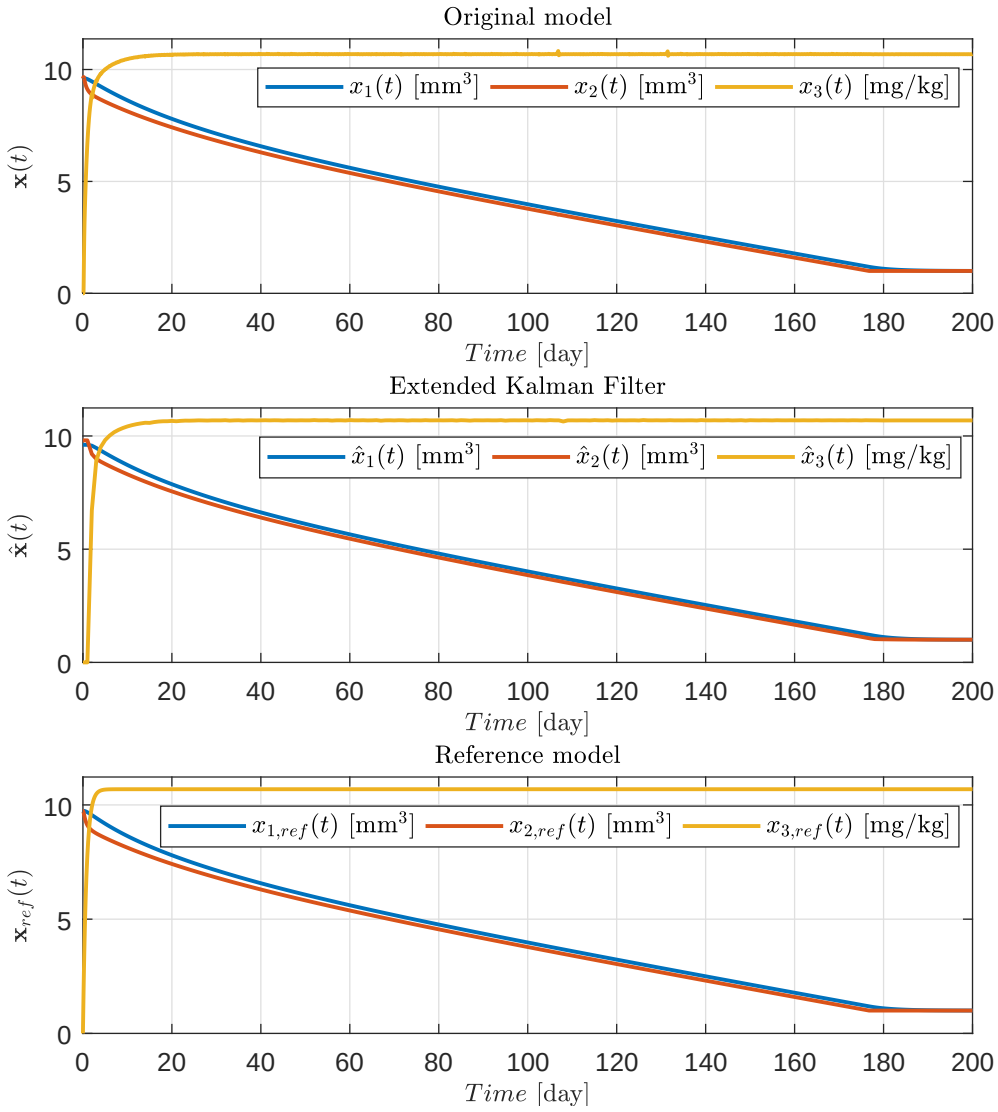


Figure 4.9.: Trajectories of the state variables: $\mathbf{x}(t)$ original system, $\hat{\mathbf{x}}(t)$ EKF, $\mathbf{x}_{ref}(t)$ reference system.

Consequently, the controller led to satisfying and enforced the controlled original nonlinear system to behave as the reference system.

4.8.6. Summary

The study reflected the benefits of applying a TP-LPV-LMI control solution on the Hahnfeldt model. The original model was transformed into a form that has no singularities within. An LPV model was then introduced which was only dependent on the scheduling parameter, thus enabling the use of a TP transformation. After defining the transformation, the optimal controller gains were computed. In the simulation, an assumption was made on the observability of the model states. An EKF was then applied which was able to estimate two of the state variables which was directly inaccessible. In silico results showed that the controller was able to perform the desired task, that is to tame cancer and keep the tumor volume at a low region. The LMI based design procedure also ensured that the closed-loop poles of the system result in a closed-loop action that is robust to the parametric uncertainties of the reference model and reality. A next step in the development of a true TP solution on the Hahnfeldt model could be the investigation of the controller in the presence of sensor noise and unknown model behavior.

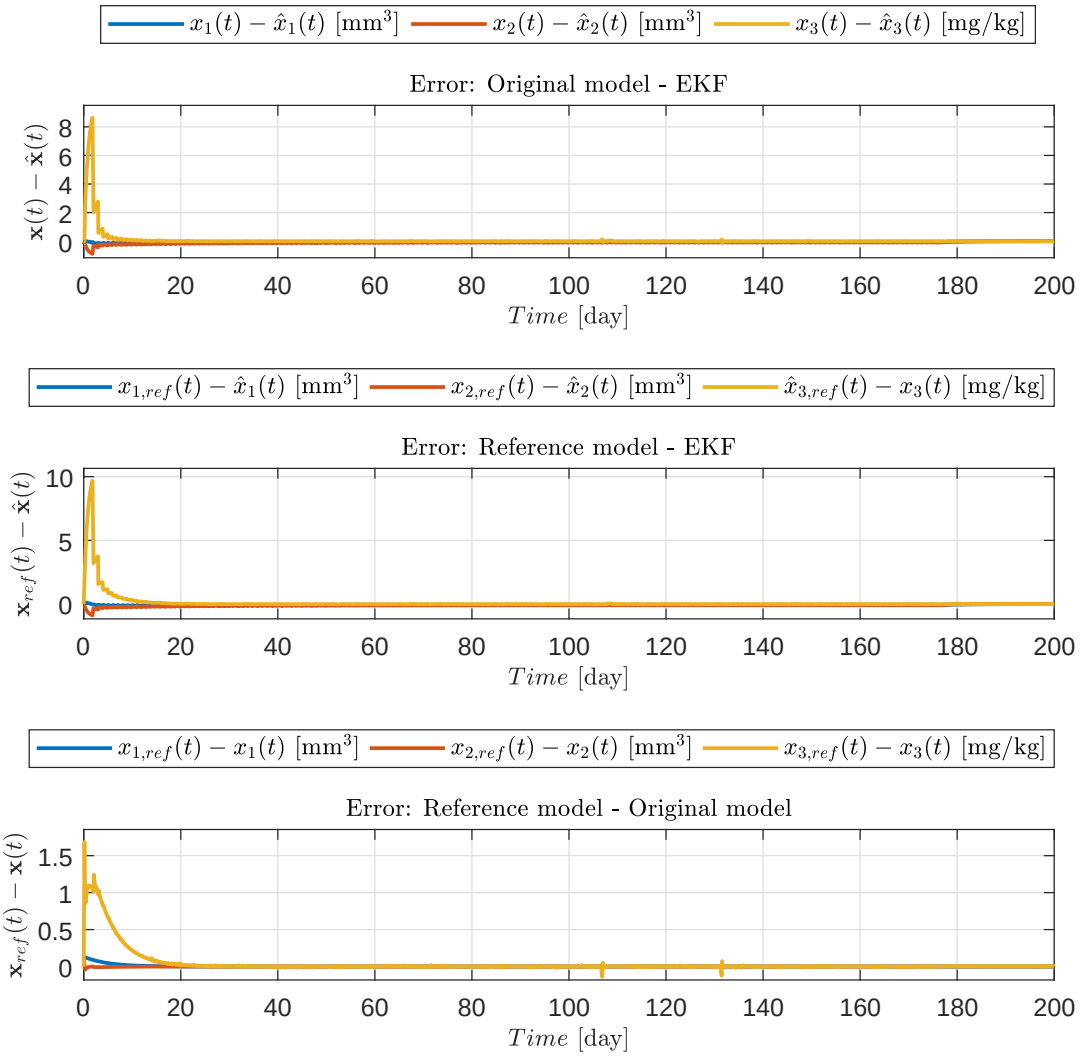


Figure 4.10.: Deviations between the states of the models.

5. Conclusions

5.1. New scientific results

The new scientific results shown in the work are summarized in the following theses with my corresponding publications.

1. thesis - I have developed a robust LPV control for artificial pancreas.

I have applied LPV methodologies on DM problems first in the literature, from which it could be seen that safer operation could be obtained using these methods.

1.1. I created an LPV model of the DM problem

I have developed an affine-qLPV model for the Cambridge DM model, in order to handle it more efficiently.

1.2. I developed robust control structures for the AP concept

I developed and showed the applicability of various H_∞ based controller structure in the context of AP. I discussed the design procedure and the guarantees on robustness which can be used to evade hypoglycaemic episodes. These results provide a basis for ongoing research concerning AP. Moreover, I have showed with realistic time series that the order of the controller can be lowered significantly by using a parallel architecture, where each controller is operating on a specific glucose region which leads to better regulation.

Relevant publications pertaining to the thesis: [431, 432, 433, 434, 435, 436]

2. thesis - Robust fixed-point transformations based control for physiological systems

I showed first the applicability of the RFPT method in the context of T1DM and tumor control. The advantage of the method is that is can use only an approximate model of the process and does not require any state estimation techniques. Elements of the design were introduced and the application was demonstrated thoroughly.

Relevant publications pertaining to the thesis: [56, 138, 437, 438, 439, 440, 441].

3. thesis - New scientific results corresponding to TP transformation based control on physiological systems

I have used LPV based TP transformation control in the context of DM and tumor control, first in the literature. The developed framework has the advantage that it can give general design procedure for nonlinear physiological systems. It allows one to use linear design technique by transforming the original nonlinear problem in a domain where their effects can not be seen. Another practical advantage of the method is that LMI based optimization can be used during the design procedure, which makes it uniformly applicable in other biological problems as well.

3.1. Development of an LPV-TP framework in the case of T1DM and tumor control

I have developed a solution based on LPV modeling, which is easily generalizable for physiological problems, and proved its applicability using T1DM and tumor control problems.

3.2. I have developed a TP transformation based LPV framework on the AP and tumor control problems

I have developed a solution based on LPV modeling and TP transformation, which is easily generalizable for physiological problems, and showed its operation using on the T1DM, and the tumor regulation problem.

Relevant publications pertaining to the thesis: [442, 443, 444, 445, 446, 447, 448, 449, 450, 451, 452, 453, 454, 455].

5.2. Further research directions

The presented ideas in the thesis has strong applicability in the domain of physiological control. These methods can be employed not just in the case of DM and tumor control due to their robust properties. Because H_∞ control has become a standard technique in robust control, there is a vast knowledge corresponding to the design procedure for a number of systems. Combining this knowledge with current research in LPV and qLPV systems, there is a number of possibility to further improve their conjoined variant. Generalizing the technique to particular types of nonlinear systems could be beneficiary for a much broader application. A possible extension could be the replacement of the H_∞ controller to different linear robust methods on LPV systems. I have also investigated

situations, where not only the parametric uncertainties posed issues, but unknown dynamics were also present. The RFPT method shown to be very useful in such cases, as it can adaptively discover the internal dynamics of a system using only a limited number of measurement. Since the control technique is quite novel, a large number of possible research directions can be formulated. Investigating the connection of different deform functions and nonlinear systems is crucial in the future for the successful application of the method. Convergence properties could also be further elaborated by connecting the method with feedback linearization and showing its potential in general systems. The question of using a rough inverse model must also be investigated. Possible general affine models could be tested, where there is no need for the discovery of a concrete inverse model, but rather create it from a data-driven perspective. Since the kinematic block is also just a matter of choice, other linear controllers can be utilized as well, state feedback for example. In terms of the TP-LPV approach, there is also an endless number of possible way to enhance its effectiveness. Identification of the scheduling parameters and building a qLPV model could be automated in the future by using soft-computing methods which can represent these models. Because modelling physiological systems can be extremely difficult in many cases, the data-driven viewpoint is particularly attractive in this case as well. Nevertheless, the problem of limited measurements must be taken into account when using neural networks for example, but the development of sophisticated biosensors can mitigate this issue in the near future. In conclusion the fast evolving field of physiological control can provide more effective approaches in treating diseases. Combining the presented approaches with the discovery of new medicine will be a major milestone in healthcare and hopefully will provide the means to save more lives in the future.

Bibliography

References

[1] J.D. Bronzino and D.R. Peterson, eds. *The Biomedical Engineering Handbook*. 4th. Boca Raton, USA: CRC Press, 2016.

[2] L.A. Segel and L. Edelstein-Keshet. *A Primer on Mathematical Models in Biology*. 1st. Philadelphia, USA: Society for Industrial and Applied Mathematics, 2013.

[3] World Health Organization. *Global Report on Diabetes*. Geneva, Switzerland: WHO Press, 2016.

[4] V. Adam. *Medical Biochemistry (in Hungarian)*. 4th. Budapest, Hungary: Medicina Press, 2006.

[5] International Diabetes Federation. *IDF Diabetes Atlas*. 8th. London, UK: International Diabetes Federation, 2017.

[6] R. Bilous and R. Donnelly. *Handbook of Diabetes*. 4th. Chichester, UK: Wiley-Blackwell, 2010.

[7] M. Pisano. "Overview of Insulin and Non-Insulin Delivery Devices In the Treatment of Diabetes". In: *Pharma Therap* 39.12 (2014), pp. 866–873.

[8] G. Scheiner. "Product Guide - Insulin Pumps". In: (2016). URL: http://www.diabetesforecast.org/2016/mar-apr/product-guide-insulin-pumps.html (visited on 08/08/2016).

[9] D.M. Maahs, L.A. Horton, and H.P. Chase. "The Use of Insulin Pumps in Youth with Type 1 Diabetes". In: *Diab Techn Therap* Suppl1 (2010), S59–S65.

[10] Y. Reznik and O. Cohen. "Insulin Pump for Type 2 Diabetes". In: *Diab Care* 36 (Suppl2 2013), S219–S225.

[11] B.H. McAdams and A. Ali. "An Overview of Insulin Pumps and Glucose Sensors for the Generalist". In: *J Clin Med* 5.1 (2016), p. 5.

[12] J.L. Selam. "Evolution of Diabetes Insulin Delivery Devices". In: *J Diab Sci Techn* 4.3 (2010), pp. 505–513.

[13] F.J. Doyle, L.M. Huyett, J.B. Lee, H.C. Zisser, and E. Dassau. “Closed-Loop Artificial Pancreas Systems: Engineering the Algorithms”. In: *Diab Care* 37.5 (2014), pp. 1191–1197.

[14] V.N. Shah, A. Shoskes, B. Tawfik, and S.K. Garg. “Closed-Loop System in the Management of Diabetes: Past, Present, and Future”. In: *Diab Techn Therap* 16.8 (2014), pp. 477–490.

[15] F. Chee and T. Fernando. *Closed-Loop Control of Blood Glucose*. Springer Berlin Heidelberg, 2007.

[16] C. Cobelli, E. Renard, and B. Kovatchev. “Artificial Pancreas: Past, present and future”. In: *Diabetes* 60.11 (2011), pp. 2672–2682.

[17] S. Trevitt, S. Simpson, and A. Wood. “Artificial Pancreas Device Systems for the Closed-Loop Control of Type 1 Diabetes: What Systems Are in Development?” In: *J Diab Sci Techn* Preprint version, 2015 (2015), pp. 1–10.

[18] T. Peyser, E. Dassau, and J.S. Skyler. “The artificial pancreas: current status and future prospects in the management of diabetes”. In: *Ann N Y Acad Sci* 1311 (2014), pp. 102–123.

[19] L. Kovács and Gy. Eigner. “System Engineering Approach of Diabetes Treatment”. In: *Int J Diab Clin Diagn* 3.116 (2016), pp. 1–6.

[20] Gy. Eigner and L. Kovács. “Realization methods of continuous glucose monitoring systems”. In: *Scientific Bulletin of Politechnica University of Timisoara Transactions on Automatic Control and Computer Science* 59.2 (2014), pp. 175–183.

[21] S. Glynn. “Artificial Pancreas Set To Transform Treatment Of Diabetes”. In: (2016). URL: http://www.medicalnewstoday.com/articles/262354.php (visited on 08/08/2016).

[22] G. Carioli, M. Malvezzi, P. Bertuccio, P. Boffetta, F. Levi, C. La Vecchia, and E. Negri. “European cancer mortality predictions for the year 2021 with focus on pancreatic and female lung cancer”. In: 32.4 (Apr. 2021), pp. 478–487.

[23] D.E. Gerber. “Targeted therapies: a new generation of cancer treatments”. In: 77.3 (2008), pp. 311–319.

[24] G.J. Kelloff, C.W. Boone, V.E. Steele, J.R. Fay, R.A. Lubet, J.A. Crowell, and C.C. Sigman. “Mechanistic considerations in chemopreventive drug development”. In: *J Cell Biochem Suppl* 20 (1994), pp. 1–24.

[25] J.M. Pluda. “Tumor-associated angiogenesis: mechanisms, clinical implications, and therapeutic strategies”. In: *Semin Oncol* 24.2 (1997), pp. 203–218.

[26] P. Hahnfeldt, D. Panigrahy, J. Folkman, and L. Hlatky. “Tumor development under angiogenic signaling: A dynamical theory of tumor growth, treatment response, and postvascular dormancy”. In: *Cancer Res* 59 (1999), pp. 4770–4775.

[27] M.S. O’Reilly, T. Boehm, Y. Shing, N. Fukai, G. Vasios, W. S. Lane, E. Flynn, J. R. Birkhead, B. R. Olsen, and J. Folkman. “Endostatin: An endogenous inhibitor of angiogenesis and tumor growth”. In: *Cell* 88 (1997), pp. 277–285.

[28] I. Petersen. “Antiangiogenesis, anti-VEGF(R) and outlook”. In: *Recent Results In Cancer Research, Targeted Therapies in Cancer*. Ed. by M. Dietel. Springer–Verlag, 2007.

[29] *Tamed Cancer*. URL: https://cordis.europa.eu/project/id/679681.

[30] H. Thabit and R. Hovorka. “Coming of age: the artificial pancreas for type 1 diabetes”. In: *Diabetologia* 59.9 (2016), pp. 1795–1805.

[31] S. Kamath. “Model based simulation for Type 1 Diabetes Patients”. In: *Asian Am J Chem* 1.1 (2013), pp. 11–19.

[32] G. Marchetti, M. Barolo, L. Jovanovic, H. Zisser, and D.E. Seborg. “An Improved PID Switching Control Strategy for Type 1 Diabetes”. In: *IEEE T Bio-Med Eng* 55.3 (2004), pp. 857–865.

[33] Y. Ramprasad, G.P. Rangaiah, and S. Lakshminarayanan. “Robust PID Controller for Blood Glucose Regulation in Type I Diabetics”. In: *Ind Eng Chem Res* 43 (2004). bibtex*[supply=], pp. 8257–8268.

[34] M. Goharimanesh, A. Lashkaripour, and A. Abouei Mehrizi. “Fractional Order PID Controller for Diabetes Patients”. In: *J Comp Appl Mech* 46.1 (2015), pp. 69–76.

[35] A. Gentilini, C. Frei, A.H. Glattfelder, M. Morari, T.J. Sieber, R. Wymann, T. Schnider, and A.M. Zbinden. *Closed loop control in Anesthesia*. July 2000.

[36] N. Cardoso and J. M. Lemos. “Model Predictive control of Depth of Anaesthesia: Guidelines for controller configuration”. In: *2008 30th Annual International Conference of the IEEE Engineering in Medicine and Biology Society*. bibtex*[venue=Vancouver;eventdate=2008-08-20/2008-08-25] event-place: Vancouver, BC, Canada. ACM, 2008, pp. 5822–5825.

[37] I. Nascu, A. Krieger, C.M. Ionescu, and E.N. Pistikopoulos. “Advanced model-based control studies for the induction and maintenance of intravenous anaesthesia”. In: *IEEE Tran Biomed Eng* 62.3 (2015), pp. 832–841.

[38] H. Kirchsteiger and L. del Re. “Nonlinear model predictive control with moving horizon state and disturbance estimation - Application to the normalization of blood glucose in the critically ill”. In: *Proceedings of the 17th World Congress The International Federation of Automatic Control*. bibtex*[eventdate=2013-07-06/2013-07-11;venue=Seoul, Korea] event-place: Seoul. IFAC, 2013, pp. 9069–9074.

[39] R. Hovorka, V. Canonico, L.J. Chassin, U. Haueter, M. Massi-Benedetti, M. Orsini-Federici, T.R. Pieber, H.C. Schaller, L. Schaupp, T. Vering, and Wilinska M.E. “Nonlinear model predictive control of glucose concentration in subjects with type 1 diabetes”. In: *Physiol Meas* 25.4 (2004). bibtex*[supply=], pp. 905–920.

[40] G. Schlotthauer, L.G. Gamero, M.E. Torres, and G.A. Nicolini. “Modeling, identification and nonlinear model predictive control of type I diabetic patient”. In: *Med Eng Phys* 28.3 (2006), pp. 240–250.

[41] P. Maxime, H. Gueguen, and A. Belmiloudi. “A Robust Receding Horizon Control Approach to Artificial Glucose Control for Type 1 Diabetes”. In: *Nonlin Contr Sys* 9.1 (2013), pp. 833–838.

[42] Y. Ho, B.P. Nguyen, and C-K. Chui. “Ant Colony Optimization for Model Predictive Control for Blood Glucose Regulation”. In: *Proceedings of the Third Symposium on Information and Communication Technology*. SoICT ’12. bibtex*[venue=Ha Long] event-place: Ha Long, Vietnam. ACM, 2012, pp. 214–217.

[43] K.G. Osgouie and A. Azizi. “Optimizing fuzzy logic controller for diabetes type I by genetic algorithm”. In: *2010 The 2nd International Conference on Computer and Automation Engineering (ICCAE)*. bibtex*[eventdate=2010-02-26/2010-02-28;venue=Singapore, Singapore] event-place: Singapore. ICCAE, 2010, pp. 4–8.

[44] P. Herrero, P. Georgiou, N. Oliver, D.G. Johnston, and C. Toumazou. “A Bio-Inspired Glucose Controller Based on Pancreatic β-Cell Physiology”. In: *J Diabetes Scien Technol* 6.3 (2012), pp. 606–616.

[45] E. Atlas, R. Nimri, S. Miller, E.A. Grunberg, and M. Phillip. “MD-Logic Anrtificial Pancreas System. A pilot study in adults with type 1 diabetes”. In: *Diab Care* 33 (2010), pp. 1072–1076.

[46] L. Kovács, P. Szalay, Zs. Almássy, and L. Barkai. "Applicability Results of a Nonlinear Model-Based Robust Blood Glucose Control Algorithm". In: *J Diabetes Scien Technol* 7.3 (2013), pp. 708–716.

[47] L. Kovács, B. Benyó, J. Bokor, and Z. Benyó. "Induced L_2-norm Minimization of Glucose-Insulin System for Type I Diabetic Patients". In: *Comp Meth Prog Biomed* 102.2 (2011). bibtex*[supply=], pp. 105–118.

[48] L. Kovács, P. Szalay, B. Benyó, and G.J. Chase. "Applicability Results of a Nonlinear Model-Based Robust Blood Glucose Control Algorithm". In: *IFAC WC - 18th World Congress of the International Federation of Automatic Control*. bibtex*[booksubtitle=;booktitleaddon=;eventdate=2011-08-29/2011-09-02;venue=Milano, Italy] event-place: Milano. 2011, pp. 4995–5000.

[49] P. Szalay, Gy. Eigner, and L. Kovács. "Linear Matrix Inequality-based Robust Controller design for Type-1 Diabetes Model". In: *Proceedings of the 19th IFAC World Congress, 2014*. Ed. by E. Boje and X. Xia. bibtex*[eventdate=2014-08-24/2014-08-29;venue=Cape Town, South Africa]. IFAC, 2014, pp. 9247–9252.

[50] P. Latafat, P. Palumbo, P. Pepe, L. Kovács, S. Panunzi, and A. De Gaetano. "An LMI-based Controller for the Glucose-Insulin System". In: *2015 European Control Conference (ECC)*. bibtex*[booksubtitle=;booktitleaddon=;eventdate=2015-07-15/2015-07-17;venue=Linz, Austria] event-place: Linz. IFAC, 2015, pp. 7–12.

[51] P. Szalay, Gy. Eigner, M. Kozlovszky, I. Rudas, and L. Kovács. "The significance of LPV modeling of a widely used T1DM model". In: *EMBC 2013 – 35th Annual International Conference of the IEEE Engineering in Medicine and Biology Society*. bibtex*[eventdate=2013-07-03/2013-07-07;venue=Osaka, Japan] event-place: Osaka. IEEE EMBS, 2013, pp. 3531–3534.

[52] S ZIETZ and C NICOLINI. "Mathematical approaches to optimization of cancer chemotherapy". In: *Bulletin of Mathematical Biology* 41.3 (1979), pp. 305–324. DOI: 10.1016/s0092-8240(79)90014-4.

[53] J. Aroesty, T. Lincoln, N. Shapiro, and G. Boccia. "Tumor growth and chemotherapy: Mathematical methods, computer simulations, and experimental foundations". In: *Mathematical Biosciences* 17.3-4 (Aug. 1973), pp. 243–300. DOI: 10.1016/0025-5564(73)90072-2.

[54] J. Sájevicsé Sápi. "Controller-managed automated therapy and tumor growth model identification in the case of antiangiogenic therapy for most effective,

individualized treatment". PhD thesis. Budapest, Hungary: Applied Informatics and Applied Mathemathics Doctoral School, Óbuda University, 2015.

[55] D.A. Drexler, J. Sápi, and L. Kovács. "Positive nonlinear control of tumor growth using angiogenic inhibition". In: *IFAC-PapersOnLine* 50.1 (2017). bibtex*[publisher=Elsevier], pp. 15068–15073.

[57] Bence Geza Czako, Daniel Andras Drexler, and Levente Kovacs. "Impulsive Control of Tumor Growth via Nonlinear Model Predictive Control Using Direct Multiple Shooting". In: *2020 European Control Conference (ECC)*. IEEE, May 2020. DOI: 10.23919/ecc51009.2020.9143755.

[58] Dániel András Drexler, Tamás Ferenci, András Füredi, Gergely Szakács, and Levente Kovács. "Experimental data-driven tumor modeling for chemotherapy". In: *IFAC-PapersOnLine* 53.2 (2020), pp. 16245–16250. DOI: 10.1016/j.ifacol.2020.12.619.

[59] Levente Kovács. "Linear parameter varying (LPV) based robust control of type-I diabetes driven for real patient data". In: *Knowl-Based Syst* 122 (2017). bibtex*[publisher=Elsevier], pp. 199–213.

[60] K. Zhou, J.C. Doyle, and K. Glover. *Robust and Optimal Control*. Upper Saddle River, NJ, USA: Prentice-Hall, Inc., 1996.

[61] P. Colmegna, R.S. Sanchez-Pena, R. Gondhalekar, E. Dassau, and F.J. Doyle. "Reducing Risks in Type 1 Diabetes Using H_∞ Control". In: *IEEE Trans Biomed Eng* 61.12 (2014). bibtex*[publisher=Institute of Electrical and Electronics Engineers (IEEE)], pp. 2939–2947.

[62] L. Kovács, B. Benyó, J. Bokor, and Z. Benyó. "Induced L_2-norm minimization of glucose–insulin system for Type I diabetic patients". In: *Comp Meth Progr Biomed* 102.2 (2011). bibtex*[publisher=Elsevier BV], pp. 105–118.

[63] R.S. Parker, F.J. Doyle, J.H. Ward, and N.A. Peppas. "Robust H_∞ glucose control in diabetes using a physiological model". In: *AIChE Journal* 46.12 (2000). bibtex*[publisher=Wiley], pp. 2537–2549.

[64] P.H. Colmegna, R.S. Sanchez-Pena, R. Gondhalekar, E. Dassau, and F.J. Doyle. "Switched LPV Glucose Control in Type 1 Diabetes". In: *IEEE Tran Biomed Eng* 63.6 (). bibtex*[publisher=Institute of Electrical and Electronics Engineers (IEEE)], pp. 1192–1200.

[65] B. Khan, G. Valencia-Palomo, J.A. Rossiter, C.N. Jones, and R. Gondhalekar. "Long horizon input parameterisations to enlarge the region of attraction of MPC". In: *Optim Contr Appl Meth* 37.1 (2014). bibtex*[publisher=Wiley], pp. 139–153.

[66] P.r Szalay, Gy. Eigner, and L.A. Kovács. "Linear Matrix Inequality-based Robust Controller design for Type-1 Diabetes Model". In: *IFAC Proc Vol* 47.3 (2014). bibtex*[publisher=Elsevier BV], pp. 9247–9252.

[67] M.E. Wilinska, L.J. Chassin, C.L. Acerini, J.M. Allen, D.B. Dunger, and R. Hovorka. "Simulation Environment to Evaluate Closed-Loop Insulin Delivery Systems in Type 1 Diabetes". In: *J Diab Scien Techn* 4.1 (2010). bibtex*[publisher=SAGE Publications], pp. 132–144.

[68] R. Hovorka, D. Elleri, H. Thabit, J.M. Allen, L. Leelarathna, R. El-Khairi, K. Kumareswaran, K. Caldwell, P. Calhoun, C. Kollman, H.R. Murphy, C.L. Acerini, M.E. Wilinska, M. Nodale, and D.B. Dunger. "Overnight Closed-Loop Insulin Delivery in Young People With Type 1 Diabetes: A Free-Living, Randomized Clinical Trial". In: *Diab Care* 37.5 (2014). bibtex*[publisher=American Diabetes Association], pp. 1204–1211.

[69] L. Kovács, P. Szalay, A. György, Z. Benyó, J.G. Chase, B. Benyó, and C.E. Hann. "Investigating the Applicability of qALPV Modeling to ICU Models for Glycaemic Control". In: *UKACC International Conference on CONTROL 2010*. Institution of Engineering and Technology, 2010.

[70] L.H. Lee. "Identification and Robust Control of Linear Parameter-Varying Systems". In: (1997).

[71] Andrew P. White, Guoming Zhu, and Jongeun Choi. *Linear Parameter-Varying Control for Engineering Applications*. Springer London, 2013.

[72] L. Kovács, P. Szalay, I. Sas, Gy. Eigner, Zs. Almássy, E. Felszeghy, Gy. Kocsis, J. Fövényi, A. Korner, L. Kautzky, H. Soós, A. Orbán, T. Niederland, A. Juhászné Tuifel, T. Tóthné Sebestyén, A. Soós, A. Török, and L Barkai. "Preliminary model-free results of a Hungarian robust artificial pancreas algorithm". In: 15 (2013). bibtex*[booktitle=Diab Techn Ther], A–96.

[73] R. Gondhalekar, E. Dassau, H.C. Zisser, and .J. Doyle. "Periodic-Zone Model Predictive Control for Diurnal Closed-Loop Operation of an Artificial Pancreas". In: *J Diab Scien Techn* 7.6 (2013). bibtex*[publisher=SAGE Publications], pp. 1446–1460.

[74] L. Kovács, B. Kulcsár, A. György, and Z. Benyó. “Robust servo control of a novel type 1 diabetic model”. In: *Optim Cont Appl Meth* 32.2 (2010). bibtex*[publisher=Wiley], pp. 215–238.

[75] C.C. Palerm. “Physiologic insulin delivery with insulin feedback: A control systems perspective”. In: *Compu Meth Progr Biomed* 102.2 (2011). bibtex*[publisher=Elsevier BV], pp. 130–137.

[76] L. Magni, D.M. Raimondo, C. Dalla Man, M. Breton, S. Patek, G. De Nicolao, C. Cobelli, and B.P. Kovatchev. “Evaluating the Efficacy of Closed-Loop Glucose Regulation via Control-Variability Grid Analysis”. In: *J Diab Scien Techn* 2.4 (2008). bibtex*[publisher=SAGE Publications], pp. 630–635.

[77] P. Szalay, Z. Benyo, and L. Kovács. “Long-term prediction for T1DM model during state-feedback control”. In: *2016 12th IEEE International Conference on Control and Automation (ICCA)*. IEEE, 2016.

[78] L. Kovács and P. Szalay. “Uncertainties and Modeling Errors of Type 1 Diabetes Models”. In: *Lect N Bioeng*. Springer International Publishing, 2015, pp. 211–225.

[79] Gy. Eigner, J.K. Tar, I. Rudas, and L. Kovács. “LPV-based quality interpretations on modeling and control of diabetes”. In: *Acta Pol Hung* 13.1 (2016). bibtex*[publisher=Obuda University].

[80] R.E. Precup, C. Dragos, S. Preitl, M. Radac, and E.M. Petriu. “Novel Tensor Product Models for Automatic Transmission System Control”. In: *IEEE Syst J* 6.3 (2012). bibtex*[publisher=Institute of Electrical and Electronics Engineers (IEEE)], pp. 488–498.

[81] U.R. Acharya, K.S. Vidya, D.N. Ghista, W.J.E. Lim, F. Molinari, and M. Sankaranarayanan. “Computer-aided diagnosis of diabetic subjects by heart rate variability signals using discrete wavelet transform method”. In: *Knowl-Based Syst* 81 (2015). bibtex*[publisher=Elsevier BV], pp. 56–64.

[82] Ö. Türkşen and M. Tez. “An application of Nelder-Mead heuristic-based hybrid algorithms: Estimation of compartment model parameters”. In: 14 (2016). bibtex*[booktitle=Int J Artif Int], pp. 112–129.

[83] H. Fujita, U.R. Acharya, V.K. Sudarshan, D.N. Ghista, S.V. Sree, W.J.E. Lim, and J.E.W. Koh. “Sudden cardiac death (SCD) prediction based on nonlinear heart rate variability features and SCD index”. In: *Appl Soft Comp* 43 (2016). bibtex*[publisher=Elsevier BV], pp. 510–519.

[84] N. Tomin, A. Zhukov, D. Sidorov, V. Kurbatsky, D.A. Panasetsky, and V. Spiryaev. "Random forest based model for preventing large-scale emergencies in power systems". In: 13 (2015). bibtex*[booktitle=Int J Artif Int], pp. 211–228.

[85] U.R. Acharya, H. Fujita, M. Adam, O.S. Lih, V.K. Sudarshan, T.J. Hong, J.E.W. Koh, Y. Hagiwara, C.K. Chua, C.K. Poo, and T.R. San. "Automated characterization and classification of coronary artery disease and myocardial infarction by decomposition of ECG signals: A comparative study". In: *Inf Scienc* 377 (2017). bibtex*[publisher=Elsevier BV], pp. 17–29.

[86] D. Cheng, X. Hu, and T. Shen. *Analysis and Design of Nonlinear Control Systems*. Springer, 2010.

[87] J.K. Tar, L. Nadai, and I.J. Rudas, eds. *System and Control Theory with Especial Emphasis on Nonlinear Systems*. 1st. Budapest, Hungary: Typotex, 2012.

[88] J.K. Tar, J.F. Bitó, L. Nádai, and J.A.T. Machado. "Robust Fixed Point Transformations in Adaptive Control Using Local Basin of Attraction". In: *ACTA Pol Hung* 6.1 (2009), pp. 21–37.

[89] Gy. Eigner. "Closed-Loop Control of Physiological Systems". PhD thesis. Budapest, Hungary: Applied Informatics and Applied Mathemathics Doctoral School, Óbuda University, 2017.

[90] T. Varkonyi. "New adaptive methods for Robust Fixed Point Transformations-based control of nonlinear systems". PhD thesis. Budapest, Hungary: Applied Informatics Doctoral School, Óbuda University, 2013.

[91] B.G. Czakó, J. Sápi, and L. Kovács. "Model-based Optimal Control Method for Cancer Treatment Using Model Predictive Control and Robust Fixed Point Method". In: *In Proc. of the 21st International Conference on Intelligent Engineering Systems (INES 2017), Larnaca, Cyprus* (2017), pp. 271–276.

[92] N. Magdelaine, L. Chaillous, I. Guilhem, J-Y. Poirier, M. Krempf, C.H. Moog, and E. Le Carpentier. "A Long-Term Model of the Glucose–Insulin Dynamics of Type 1 Diabetes". In: *IEEE T. Bio-Med. Eng.* 62.6 (2015), pp. 1546–1552.

[93] J.K. Tar, L. Nádai, I.J. Rudas, and T.A. Várkonyi. "RFPT-based Adaptive Control Stabilized by Fuzzy Parameter Tuning". In: *9th European Workshop on Advanced Control and Diagnosis (ACD 2011)*. 2011, pp. 1–8.

[94] Mahmoud Chilali and Pascal Gahinet. "H_∞ Design with Pole Placement Constraints: An LMI approach". In: *IEEE T Aut Contr* 41.3 (1996). bibtex*[publisher=IEEE], pp. 358–367.

[95] O. Sename, P. Gáspár, and J. Bokor. "Robust Control and Linear Parameter Varying Approaches, Application to Vehicle Dynamics". In: vol. 437. Lecture Notes in Control and Information Sciences. Berlin: Springer-Verlag, 2013.

[96] W.S. Levine. *The Control Engineering Handbook*. 2nd. Boca Raton: CRC Press, Taylor and Francis Group, 2011.

[97] K. Tanaka and H.O. Wang. *Fuzzy Control Systems Design and Analysis: A Linear Matrix Inequality Approach*. 1st. Chichester, UK: John Wiley and Sons, 2001.

[98] P. Baranyi, Y. Yam, and P. Várlaki. *Tensor Product Model Transformation in Polytopic Model-Based Control*. 1st. Series: Automation and Control Engineering. Boca Raton, USA: CRC Press, 2013.

[99] S. Boyd, L. El Ghaoui, E. Feron, and V. Balakrishnan. *Linear Matrix Inequalities in System and Control Theory*. 1st. SIAM Studies in Applied Mathematics. Philadelphia: SIAM, 1994.

[100] J. Kuti. "Generalization of Tensor Product Model Based Control Analysis and Synthesis". PhD thesis. Budapest, Hungary: Applied Informatics and Applied Mathemathics Doctoral School, Óbuda University, 2018.

[101] C. Scherer and S. Weiland. *Lecture Notes DISC Course on Linear Matrix Inequalities in Control*. 2nd. Delft University, The Netherlands: Delft University, 1999.

[102] Stephen Boyd and Lieven Vandenberghe. *Convex optimization*. Cambridge, UK: Cambridge University Press, 2004.

[103] J. Kuti, P. Galambos, and P. Baranyi. "Control Analysis and Synthesis through Polytopic Tensor Product Model: a General Concept". In: *IFAC-PapersOnLine* 50.1 (2017). bibtex*[publisher=Elsevier], pp. 6558–6563.

[104] P. Baranyi. "TP model transformation as a way to LMI-based controller design". In: *IEEE T Ind Electr* 51.2 (2004), pp. 387–400.

[105] P. Baranyi. *TP-model Transformation-based-control Design Frameworks*. Springer, 2016.

[106] P. Baranyi. "The generalized TP model transformation for T–S fuzzy model manipulation and generalized stability verification". In: *IEEE T Fuzzy Syst* 22.4 (2014). bibtex*[publisher=IEEE], pp. 934–948.

[107] P. Baranyi. "Extension of the Multi-TP Model Transformation to Functions with Different Numbers of Variables". In: *Complexity* 2018 (2018). bibtex*[publisher=Hindawi].

[108] József Kuti, Péter Galambos, Péter Baranyi, and Péter Várlaki. “A hands-on demonstration of control performance optimization using tensor product model transformation and convex hull manipulation”. In: *2015 IEEE International Conference on Systems, Man, and Cybernetics (SMC)*. bibtex*[organization=IEEE]. 2015, pp. 2609–2614.

[109] J. Kuti, P. Galambos, and P. Baranyi. “Minimal volume simplex (MVS) convex hull generation and manipulation methodology for TP model transformation”. In: *Asian J Contr* 19.1 (2017), pp. 289–301.

[110] M. de Berg, Ch. Otfried, M. van Kreveld, and M. Overmars. *Computational Geometry: Algorithms and Applications*. 3rd. Heidelberg, Germany: Springer, 2008.

[111] Lorena-Elena Hedrea, Claudia-Adina Bojan-Dragos, Radu-Emil Precup, Raul-Cristian Roman, Emil M Petriu, and Ciprian Hedrea. “Tensor product-based model transformation for position control of magnetic levitation systems”. In: *2017 IEEE 26th International Symposium onIndustrial Electronics (ISIE)*. bibtex*[organization=IEEE]. 2017, pp. 1141–1146.

[112] B. Takarics and P. Baranyi. “Friction Compensation in TP Model Form - Aeroelastic Wing as an Example System”. In: *ACTA Pol Hung* 12.4 (2015), pp. 127–145.

[113] P. Galambos and P. Baranyi. “TP Model Transformation: A Systematic Modelling Framework to handle Internal Time Delays in Control Systems”. In: *Asian J Contr* 17.2 (2015), pp. 1–11.

[114] MTA SZTAKI. “TPtool - Tensor Product MATLAB Toolbox”. In: (2016). URL: http://tptool.sztaki.hu (visited on 03/01/2016).

[115] Dimitri Boiroux, Vladimir Batora, Morten Hagdrup, Sabrina Lyngbye Wendt, Niels Kjolstad Poulsen, Henrik Madsen, and John Bagterp Jorgensen. “Adaptive model predictive control for a dual-hormone artificial pancreas”. In: *Journal of Process Control* 68 (2018), pp. 105–117.

[116] G-R. Duan and H-H. Yu. *LMIs in Control Systems: Analysis, Design and Applications*. 1th. Boca Raton, USA: CRC Press, 2013.

[117] Wissam El Messoussi, Olivier Pagès, and Ahmed El Hajjaji. “Robust Pole Placement for Fuzzy Models with Parametric Uncertainties: An LMI Approach”. In: *EUSFLAT Conf.* 2005, pp. 810–815.

[118] Mahmoud Chilali, Pascal Gahinet, and Pierre Apkarian. “Robust pole placement in LMI regions”. In: *IEEE T Aut Contr* 44.12 (1999). bibtex*[publisher=IEEE], pp. 2257–2270.

[119] G. Balas, R. Chiang, A. Packard, and M. Safonov. *Rontrol Control Toolbox Getting Started Guide*. bibtex*[version=Version 2017b;organization=The MathWorks, Inc]. Mathworks. 282 pp.

[120] MH Bouazizi, A Kochbati, and M Ksouri. “LPV control with observed state feedback and dynamic output feedback”. In: *American Control Conference, 2001. Proceedings of the 2001*. Vol. 5. bibtex*[organization=IEEE]. 2001, pp. 3908–3913.

[121] MH Bouazizi, A Kochbati, and M Ksouri. “LPV control with observer and dynamic compensator”. In: *Control Conference (ECC), 2001 European*. bibtex*[organization=IEEE]. 2001, pp. 444–450.

[122] MOSEK ApS. *The MOSEK optimization toolbox for MATLAB manual. Version 7.1 (Revision 28)*. 2015. URL: http://docs.mosek.com/7.1/toolbox/index.html.

[123] J. Löfberg. “YALMIP : A Toolbox for Modeling and Optimization in MATLAB”. In: *In Proceedings of the CACSD Conference*. event-place: Taipei, Taiwan. 2004.

[124] Katsuhiko Ogata and Yanjuan Yang. *Modern control engineering*. Vol. 4. Prentice hall India, 2002.

[125] J. Hartikainen, A. Solin, and S. Särkkä. *Optimal Filtering with Kalman Filters and Smoothers a Manual for the Matlab toolbox EKF/UKF*. V1.3. Aalto University, 2011.

[126] M.S. Grewal and A.P. Andrews. *Kalman Filtering: Theory and Practice Using MATLAB*. 3rd. Chichester, UK: John Wiley and Sons, 2008.

[127] Alison B Evert, Jackie L Boucher, Marjorie Cypress, Stephanie A Dunbar, Marion J Franz, Elizabeth J Mayer-Davis, Joshua J Neumiller, Robin Nwankwo, Cassandra L Verdi, Patti Urbanski, et al. “Nutrition therapy recommendations for the management of adults with diabetes”. In: *Diab Care* 37 (Supplement 1 2014). bibtex*[publisher=Am Diabetes Assoc], S120–S143.

[128] Thomas MS Wolever, Safa Hamad, Jean-Louis Chiasson, Robert G Josse, Lawrence A Leiter, N Wilson Rodger, Stuart A Ross, and Edmond A Ryan. “Day-to-day consistency in amount and source of carbohydrate intake associated with improved blood glucose control in type 1 diabetes”. In: *J American Col Nutr* 18.3 (1999). bibtex*[publisher=Taylor & Francis], pp. 242–247.

[129] John P Bantle, Judith Wylie-Rosett, Ann L Albright, Caroline M Apovian, Nathaniel G Clark, Marion J Franz, Byron J Hoogwerf, Alice H Lichtenstein, Elizabeth Mayer-Davis, Arshag D Mooradian, et al. "Nutrition recommendations and interventions for diabetes: a position statement of the American Diabetes Association". In: *Diab Care* 31 (2008), S61–S78.

[130] U.S. Department of Health and Human Services and U.S. Department of Agriculture. *2015 – 2020 Dietary Guidelines for Americans*. bibtex*[edition=8th]. 2015. URL: https://health.gov/dietaryguidelines/2015/guidelines/.

[131] World Health Organization and others. "Definition and diagnosis of diabetes mellitus and intermediate hyperglycemia: report of a WHO/IDF consultation". In: *World Health Org* (2006).

[132] American Diabetes Association et al. "Diagnosis and classification of diabetes mellitus". In: *Diab Care* 37 (Supplement 1 2014). bibtex*[publisher=Am Diabetes Assoc], S81–S90.

[133] J. Klamka, H. Maurer, and A. Swierniak. "Local controllability and optimal control for amodel of combined anticancer therapy with control delays". In: *Math Biosci Eng* 14.1 (2017), pp. 195–216.

[134] Johanna Sápi, Dániel András Drexler, and Levente Kovács. "Potential Benefits of Discrete-Time Controllerbased Treatments over Protocol-based Cancer Therapies". In: *Acta Pol Hung* 14.1 (2017). bibtex*[publisher=Óbuda University], pp. 11–23.

[135] George Brinton Thomas, Ross L Finney, Maurice D Weir, and Frank R Giordano. *Thomas' calculus*. Addison-Wesley Reading, 2003.

[136] Imre Polik, Tamas Terlaky, and Yuriy Zinchenko. "SeDuMi: a package for conic optimization". In: *IMA workshop on Optimization and Control, Univ. Minnesota, Minneapolis*. bibtex*[organization=Citeseer]. 2007.

[137] H. Musoff and P. Zarchan. *Fundamentals of Kalman Filtering: A Practical Approach*. 3rd. American Institute of Aeronautics and Astronautics, 2009.

[139] A. Fonyó and E. Ligeti. *Physiology (in Hungarian)*. 4rd. Budapest, Hungary: Medicina, 2011.

[140] G. Williams and J.C. Pickup. *Handbook of Diabetes*. 3rd. Oxford, UK: Blackwell Publishing, 2004.

[141] Denise R. Ferrier. *Biochemistry*. 6th. Amsterdam, The Netherlands: Lippincott Williams and Wilkins, 2014.

[142] dream10f. “Digestion of glucose”. In: (2016). URL: http://www.slideshare.net/dream10f/4-digestion-pdf (visited on 07/09/2018).

[143] Austin Community College. “Glucose Regulation”. In: (2016). URL: http://www.austincc.edu/apreview/EmphasisItems/Glucose_regulation.html (visited on 07/09/2018).

[144] Darekk2. “Stoichiometry of aerobic respiration and most known fermentation types in eucaryotic cell”. In: (2016). URL: https://en.wikipedia.org/wiki/Cellular_respiration#/media/File:Cellular_respiration.gif (visited on 07/09/2018).

[145] Benjamin Cummings. “Regulation of the utilization of glucose”. In: (2001). URL: http://weightlossfrogs.blogspot.hu/2010/11/glucose-glucagon-and-insulin.html (visited on 07/09/2018).

[146] W.F. Boron and E.L. Boulpaep. *Medical Physiology*. 3rd. Heidelberg, Germany: Elsevier, 2016.

[147] V. Adam. *Medical Biochemistry (in Hungarian)*. 5th. Budapest, Hungary: Medicina Press, 2016.

[148] S. Schaefer. “Insulin secreation mechanism”. In: (2011). URL: http://stephanieschaefer.ca%20/2011/03/longtime-mystery-solved-the-mechanism-of-insulin-secretion/ (visited on 07/09/2018).

[149] B. Hellman, E. Gylfe, E. Grapengiesser, H. Dansk, and A. Salehi. “Insulin oscillations – clinically important rhythm. Antidiabetics should increase the pulsative component of the insulin release”. In: *Lakartidningen* 104 (2007), pp. 32–33.

[150] B. Hellman. “Pulsatility of insulin release – a clinically important phenomenon”. In: *Upsala J Med Sci* 114.4 (2009), pp. 193–205.

[151] M. Häggström. “Insulin oscillations, Medical gallery of Mikael Häggström 2014”. In: (2014). URL: https://en.wikiversity.org/wiki/Wikiversity_Journal_of_Medicine/Medical_gallery_of_Mikael_H%C3%A4ggstr%C3%B6m_2014#/media/File:Insulin_oscillations.svg (visited on 07/09/2018).

[152] XcepticZP. “Insulin oscillations, Medical gallery of Mikael Häggström 2014”. In: (2014). URL: https://upload.wikimedia.org/wikipedia/en/thumb/4/45/Citric_acid_cycle_noi.JPG/754px-Citric_acid_cycle_noi.JPG (visited on 07/09/2018).

[153] R.A. DeFronzo, E. Ferrannini, P. Zimmet, and K.G.M.M. Alberti. *International textbook of diabetes mellitus*. 4th. Chichester, UK: John Wiley & Sons, 2015.

[154] K. Cherney and S.J. Bliss. “A Complete List of Diabetes Medications”. In: (2016). URL: http://www.healthline.com/health/diabetes/medications-list#Overview1 (visited on 07/09/2018).

[155] UPMC Life Changing Medicine. “Insulin Pens: How to Give a Shot”. In: (2013). URL: http://www.upmc.com/patients-visitors/education/diabetes/Pages/insulin-pens-how-to-give-a-shot.aspx (visited on 07/09/2018).

[156] Mayo Clinic. “Artificial Pancreas”. In: (2016). URL: http://www.mayo.edu/research/labs/artificial-pancreas/overview (visited on 07/09/2018).

[157] R. Weinberg. *The biology of cancer*. 2nd. New York, USA: Garland Science, a Taylor & Francis Group, 2013.

[158] D. Hanahan and R.A. Weinberg. “The Hallmarks of Cancer”. In: *Cell* 100.1 (2000). bibtex*[publisher=Elsevier BV], pp. 57–70.

[159] P. Anand, A.B. Kunnumakara, C. Sundaram, K.B. Harikumar, S.T. Tharakan, O.S. Lai, B. Sung, and B.B. Aggarwal. “Cancer is a Preventable Disease that Requires Major Lifestyle Changes”. In: *Pharm Res* 25.9 (2008). bibtex*[publisher=Springer Nature], pp. 2097–2116.

[160] Kerr, D.J. and Haller, D.G. and van de Velde, C.J.H. and Baumann, M. *Oxford Textbook of Oncology*. 3rd. Oxford, UK: Oxford University Press, 2016.

[161] S. McGuire. “World cancer report 2014. Geneva, Switzerland: World Health Organization, international agency for research on cancer, WHO Press, 2015”. In: (2016). bibtex*[location=Oxford, UK;publisher=Oxford University Press].

[162] B.W. Feig and C.D. Ching, eds. *The M.D. Anderson surgical oncology handbook*. 4th. Philadelphia, USA: Lippincott Williams & Wilkins, 2006.

[163] R.G. Holzheimer and J.A. Mannick, eds. *Surgical treatment: evidence-based and problem-oriented*. 1st. Germering, Germany: W. Zuckschwerdt Verlag GmbH., 2001.

[164] P. Price and K. Sikora, eds. *Treatment of Cancer*. 6th. Boca Raton, USA: CRC Press, 2014.

[165] P.P. Connell and S. Hellman. “Advances in radiotherapy and implications for the next century: a historical perspective”. In: *Cancer Res* 69.2 (2009). bibtex*[publisher=AACR], pp. 383–392.

[166] Gazda, M.J. and Lawrence, R.C. “Principles of radiation therapy, Cancer management: a multidisciplinary approach”. In: (2001). URL: http://www.thymic.org/uploads/reference_sub/02radtherapy.pdf (visited on 07/09/2018).

[167] R. Page and C. Takimoto. “Principles of chemotherapy, Cancer management: a multidisciplinary approach”. In: (2013).

[168] D.E. Gerber. “Targeted therapies: a new generation of cancer treatments”. In: *Am Fam Physician* 77.3 (2008), pp. 311–319.

[169] D. O’Mahony and M.R. Bishop. “Monoclonal antibody therapy”. In: *Front Biosci* 11 (2006), pp. 1620–1635.

[170] D.A. Frank. *Signaling Pathways in Cancer Pathogenesis and Therapy*. 1th. New York, USA: Springer-Verlag New York, 2012.

[171] N.S. Vasudev and A.R. Reynolds. “Anti-angiogenic therapy for cancer: current progress, unresolved questions and future directions”. In: *Angiogenesis* 17.3 (2014), pp. 471–494.

[172] K. Xing and S. Lisong. “Molecular targeted therapy of cancer: The progress and future prospect”. In: *Front Lab Med* 1.2 (2017). bibtex*[publisher=Elsevier], pp. 69–75.

[173] S.W. Lowe and A.W. Lin. “Apoptosis in cancer”. In: *Carcinogenesis* 21.3 (2000), pp. 485–195.

[174] S. Dinda. “Anti-hormones: mechanism and use in treatment of breast cancer”. In: *Clin Lab Sci* 25.1 (2012), pp. 45–49.

[175] C. Rossig. “Immune modulation by molecular cancer targets and targeted therapies”. In: *OncoImmunology* 1.3 (2012). bibtex*[publisher=Informa UK Limited], pp. 358–360.

[176] T.A. Waldmann. “Immunotherapy: past, present and future”. In: *Nat Med* 9.3 (2003), pp. 269–277.

[177] G. Kaur, C.R. Long, and J.M. Dufour. “Genetically engineered immune privileged Sertoli cells: A new road to cell based gene therapy”. In: *Spermatogenesis* 2(1) (2012), pp. 23–31.

[178] P. Charlton and J. Spicer. “Targeted therapy in cancer”. In: *Medicine* 44.1 (2016). bibtex*[publisher=Elsevier], pp. 34–38.

[179] A. Hoeben, B. Landuyt, M.S. Highley, H. Wildiers, A.T. Van Oosterom, and E.A. De Bruijn. “Vascular Endothelial Growth Factor and Angiogenesis”. In: *Pharmacol Rev* 56 (2004), pp. 549–580.

[180] Letellier, C. and Viger, L. and Denis, F. and Draghi, C. "Modeling Tumor Growth and Cancer Dynamics". In: (2015). URL: http://www.atomosyd.net/spip.php?article150 (visited on 07/09/2018).

[181] S.P. Kalva, S. Namasivayam, and D.V. Sahani. "Imaging Angiogenesis". In: *Antiangiogenic Agents in Cancer Therapy*. Ed. by B.A. Teicher and L.M. Ellis. 2nd. Humana Press, Springer, 2008.

[182] C. Srinivas. "Anti-Angiogenic Drugs: A Chemotherapy?" In: *Journal of Young Investigators* 17 (2010). http://www.jyi.org/features/ft.php?id=1117.

[183] A.M.E. Abdalla, L. Xiao, M. Wajid Ullah, M. Yu, C. Ouyang, and G. Yang. "Current Challenges of Cancer Anti-angiogenic Therapy and the Promise of Nanotherapeutics". In: *Theranostics* 8.2 (2018). bibtex*[publisher=Ivyspring International Publisher], pp. 533–548.

[184] R. Kerbel. "A cancer therapy resistant to resistance". In: *Nature* 390 (1997), pp. 335–336.

[185] T. Boehm, J. Folkman, T. Browder, and M.S. O'Reilly. "Antiangiogenic therapy of experimental cancer does not induce acquired drug resistance". In: *Nature* 390 (1997), pp. 404–407.

[186] D. Zhang, E.M. Hedlund, S. Lim, F. Chen, Y. Zhang, B. Sun, and Y. Cao. "Antiangiogenic agents significantly improve survival in tumor-bearing mice by increasing tolerance to chemotherapy-induced toxicity". In: *Proc Natl Acad Sci USA* 108.10 (2011), pp. 4117–4122.

[187] F.G. Banting, C.H. Best, J.B. Collip, W.R. Campbell, and A.A. Fletcher. "Pancreatic extracts in the treatment of diabetes mellitus". In: *Can Med Assoc J* 12.3 (1922), pp. 141–146.

[188] A.M. Ahmed. "History of diabetes mellitus". In: *Saudi Med J* 23.4 (2002), pp. 373–378.

[189] Narayanese. "Cytric Acid Cycle". In: (2008). URL: https://commons.wikimedia.org/wiki/File:Citric_acid_cycle_with_aconitate_2.svg (visited on 07/09/2018).

[190] Blair, E. and Joslin Diabetes Center. "Insulin A to Z: A Guide on Different Types of Insulin". In: (2016). URL: http://www.joslin.org/info/insulin_a_to_z_a_guide_on_different_types_of_insulin.html (visited on 07/09/2018).

[191] Diabetes Health Center. “Types of Insulin for Diabetes Treatment”. In: (2016). URL: http://www.webmd.com/diabetes/guide/diabetes-types-insulin (visited on 07/09/2018).

[192] J.B. Lee, E. Dassau, D.E. Seborg, and F.J. Doyle. “Model-based personalization scheme of an artificial pancreas for type 1 diabetes applications”. In: *The 2013 American Control Conference (ACC 2013)*. bibtex*[eventdate=2013-07-17/2013-07-19;venue=Washington DC, USA;organization=IEEE] event-place: USA. IEEE, 2013, pp. 2911–2916.

[193] F.J. Doyle, E. Dassau, D.E. Seborg, and J.B. Lee. “Model-Based Personalization Scheme of an Artificial Pancreas for Type I Diabetes Applications”. In: (2015). US Patent App. 14/792,524 bibtex*[publisher=Google Patents]. URL: https://www.google.com/patents/US20150306314.

[194] R. Nimri, A. Murray N. abd Ochs, J.E. Pinsker, and E. Dassau. “Closing the Loop”. In: *Diabetes Technol The* 19.1 (2017), s27–s41.

[195] V. Gingras, R. Rabasa-Lhoret, V. Messier, M. Ladouceur, L. Legault, and A. Haidar. “Efficacy of dual-hormone artificial pancreas to alleviate the carbohydrate-counting burden of type 1 diabetes: A randomized crossover trial”. In: *Diabetes Metab* (2015). bibtex*[supply=S1262], p. 3636.

[196] R.E. Pollock. *Advanced therapy in surgical oncology*. 1st. Hamilton, USA: Decker Inc., 2008.

[197] Protocol Online. “Xenograft Tumor Model Protocol”. In: (2005). URL: http://www.protocol-%20online.org/prot/Protocols/Xenograft-Tumor-Model-Protocol-3810.html (visited on 07/09/2018).

[198] ACS, American Cancer Society. “The History of Cancer”. In: (2011). URL: http://www.cancer.org/acs/groups/cid/documents/webcontent/002048-pdf.pdf (visited on 07/09/2018).

[199] D.J. Samson, T.A. Ratko, B.M. Rothenberg, H.M. Brown, C.J. Bonnell, K.M. Ziegler, and N. Aronson. “Comparative effectiveness and safety of radiotherapy treatments for head and neck cancer”. In: (2010). bibtex*[publisher=Agency for Healthcare Research and Quality;location=Rockville, USA].

[200] M.C. Perry. *The chemotherapy source book*. 5th. Philadelphia, USA: Lippincott Williams & Wilkins, 2008.

[201] D.W. Kufe, W. Hait, J.F. Holland, E. Frei, and R.E. Pollock, eds. *Holland Frei Cancer Medicine 8*. Vol. 8. Shelton, USA: PMPH, 2010.

[202] A. Toss, M. Venturelli, C. Peterle, F. Piacentini, S. Cascinu, and L. Cortesi. "Molecular biomarkers for prediction of targeted therapy response in metastatic breast cancer: trick or treat?" In: *Int J Mol Sci* 18.1 (2017). bibtex*[publisher=Multidisciplinary Digital Publishing Institute], p. 85.

[203] M. Goitein and M. Jermann. "The relative costs of proton and X-ray radiation therapy". In: *Clin Oncol (R Coll Radiol)* 15.1 (2003), S37–50.

[204] T.E. Goffman and E. Glatstein. "Intensity-modulated radiation therapy". In: *Radiat Res* 158.1 (2002), pp. 115–117.

[205] A.J. Karayiannakis, K.N. Syrigos, A. Polychronidis, A. Zbar, G. Kouraklis, C. Simopoulos, and G. Karatzas. "Circulating VEGF levels in the serum of gastric cancer patients: correlation with pathological variables, patient survival, and tumor surgery". In: *Ann Surg* 236.1 (2002), pp. 37–42.

[206] K. Dredge, A.G. Dalgleish, and J.B. Marriott. "Angiogenesis inhibitors in cancer therapy". In: *Curr Opin Investig Drugs* 4 (2003), pp. 667–674.

[207] L.M. Ellis and D.G. Haller. "Bevacizumab Beyond Progression: Does This Make Sense?" In: *J Clin Oncol* 26.33 (2008), pp. 5313–5315.

[208] J.L. Marshall, ed. *Cancer Therapeutic Targets*. New York, USA: Springer New York, 2017.

[209] J.E. Pinsker, A.J. Laguna Sanz, J.B. Lee, M.M. Church, C. Andre, L.E. Lindsey, F.J. Doyle III, and E. Dassau. "Evaluation of an Artificial Pancreas with Enhanced Model Predictive Control and a Glucose Prediction Trust Index with Unannounced Exercise". In: *Diab Techn Ther* 20.7 (2018). bibtex*[publisher=Mary Ann Liebert], pp. 455–464.

[210] R. Gondhalekar, E. Dassau, and F.J. Doyle. "Velocity-weighting & velocity-penalty MPC of an artificial pancreas: Improved safety & performance". In: *Automatica* 91 (2018). bibtex*[publisher=Elsevier], pp. 105–117.

[211] S. Zavitsanou, A. Chakrabarty, E. Dassau, and F.J. Doyle. "Embedded control in wearable medical devices: application to the artificial pancreas". In: *Processes* 4.4 (2016). bibtex*[publisher=Multidisciplinary Digital Publishing Institute], p. 35.

[212] P. Colmegna, F. Garelli, H. De Battista, and R. Sánchez-Peña. "Automatic regulatory control in type 1 diabetes without carbohydrate counting". In: *Control Eng Pract* 74 (2018). bibtex*[publisher=Elsevier], pp. 22–32.

[213] A. Haidar, R. Rabasa-Lhoret, L. Legault, L.E. Lovblom, R. Rakheja, V. Messier, É. D'aoust, C.M. Falappa, T. Justice, and A. Orszag. "Single-and dual-hormone artificial pancreas for overnight glucose control in type 1 diabetes". In: *J Clin Endocrinol* 101.1 (2016). bibtex*[publisher=Endocrine Society], pp. 214–223.

[214] P. Colmegna, R.S. Sánchez-Peña, and R. Gondhalekar. "Linear parameter-varying model to design control laws for an artificial pancreas". In: *Biomed Signal Proces* 40 (2018). bibtex*[publisher=Elsevier], pp. 204–213.

[215] B.W. Bequette, F. Cameron, B.A. Buckingham, D.M. Maahs, and J. Lum. "Overnight Hypoglycemia and Hyperglycemia Mitigation for Individuals with Type 1 Diabetes: How Risks Can Be Reduced". In: *IEEE Contr Syst* 38.1 (2018). bibtex*[publisher=IEEE], pp. 125–134.

[216] K. Turksoy, E. Littlejohn, and A. Cinar. "Multimodule, Multivariable Artificial Pancreas for Patients with Type 1 Diabetes: Regulating Glucose Concentration Under Challenging Conditions". In: *IEEE Contr Syst* 38.1 (2018). bibtex*[publisher=IEEE], pp. 105–124.

[217] M. Messori, G.P. Incremona, C. Cobelli, and L. Magni. "Individualized model predictive control for the artificial pancreas: In silico evaluation of closed-loop glucose control". In: *IEEE Contr Syst* 38.1 (2018). bibtex*[publisher=IEEE], pp. 86–104.

[218] A. El Fathi, M.R. Smaoui, V. Gingras, B. Boulet, and A. Haidar. "The Artificial Pancreas and Meal Control: An Overview of Postprandial Glucose Regulation in Type 1 Diabetes". In: *IEEE Contr Syst* 38.1 (2018). bibtex*[publisher=IEEE], pp. 67–85.

[219] J. Bondia, S. Romero-Vivo, B. Ricarte, and J.L. Diez. "Insulin Estimation and Prediction: A Review of the Estimation and Prediction of Subcutaneous Insulin Pharmacokinetics in Closed-Loop Glucose Control". In: *IEEE Contr Syst* 38.1 (2018). bibtex*[publisher=IEEE], pp. 47–66.

[220] L.M. Huyett, E. Dassau, H.C. Zisser, and F.J. Doyle III. "Glucose Sensor Dynamics and the Artificial Pancreas: The Impact of Lag on Sensor Measurement and Controller Performance". In: *IEEE Contr Syst* 38.1 (2018). bibtex*[publisher=IEEE], pp. 30–46.

[221] L. Bally, H. Thabit, and R. Hovorka. "Glucose-responsive insulin delivery for type 1 diabetes: The artificial pancreas story". In: *Int J Pharm* 544.2 (2018). bibtex*[publisher=Elsevier], pp. 309–318.

[222] F. Cacace, V. Cusimano, A. Germani, P. Palumbo, and F. Papa. “Closed-loop control of tumor growth by means of anti-angiogenic administration”. In: *Math Biosc Eng* 15.4 (2018), pp. 827–839.

[223] A.E. Glick and A. Mastroberardino. “An Optimal Control Approach for the Treatment of Solid Tumors with Angiogenesis Inhibitors”. In: *Mathematics* 5.4 (2017). bibtex*[publisher=Multidisciplinary Digital Publishing Institute], p. 49.

[224] V. Cusimano, P. Palumbo, and F. Papa. “Closed-loop control of tumor growth by means of anti-angiogenic administration”. In: *2015 IEEE 54th Annual Conference on Decision and Control (CDC)*. bibtex*[organization=IEEE]. 2015, pp. 7789–7794.

[225] U. Ledzewicz and H. Schättler. “Optimal controlled trajectories for a mathematical model of anti-angiogenic therapy in cancer”. In: *Proceedings of the 48th IEEE Conference on Decision and Control, 2009 held jointly with the 2009 28th Chinese Control Conference. CDC/CCC 2009*. bibtex*[organization=IEEE]. 2009, pp. 1201–1206.

[226] H.M. Schättler, U. Ledzewicz, and B. Cardwell. *Robustness of optimal controls for a class of mathematical models for tumor anti-angiogenesis*. American Institute of Mathematical Sciences, 2011.

[227] U. Hasirci, T.E. Burg, and R.E. Groff. “Closed-loop nonlinear smooth robust control of anti-angiogenic tumor therapy”. In: *2013 American Control Conference*. IEEE, 2013.

[228] G.W. Swan. “Role of optimal control theory in cancer chemotherapy”. In: *Math Biosc* 101.2 (1990). bibtex*[publisher=Elsevier], pp. 237–284.

[229] J.C. Panetta and K.R. Fister. “Optimal control applied to cell-cycle-specific cancer chemotherapy”. In: *SIAM J Appl Math* 60.3 (2000). bibtex*[publisher=SIAM], pp. 1059–1072.

[230] P. Khalili, R. Vatankhah, and S. Taghvaei. “Optimal sliding mode control of drug delivery in cancerous tumour chemotherapy considering the obesity effects”. In: *IET Systems Biology* (2018). bibtex*[publisher=IET].

[231] H. Moradi, G. Vossoughi, and H. Salarieh. “Optimal robust control of drug delivery in cancer chemotherapy: a comparison between three control approaches”. In: *Comp Meth Prog Biomed* 112.1 (2013). bibtex*[publisher=Elsevier], pp. 69–83.

[232] H. Moradi, M. Sharifi, and G. Vossoughi. “Adaptive robust control of cancer chemotherapy in the presence of parametric uncertainties: A comparison between three hypotheses”. In: *Comp Biol and Med* 56 (2015). bibtex*[publisher=Elsevier], pp. 145–157.

[233] N. Babaei and M.U. Salamci. “Controller design for personalized drug administration in cancer therapy: Successive approximation approach”. In: *Optimal Cont Appl Meth* 39.2 (2018). bibtex*[publisher=Wiley Online Library], pp. 682–719.

[234] S. Rooka and R. Ghasemi. “Fuzzy fractional sliding mode observer design for a class of nonlinear dynamics of the cancer disease”. In: *Int J Aut Cont* 12.1 (2018). bibtex*[publisher=Inderscience Publishers (IEL)], pp. 62–77.

[235] L. Kovács, P. Szalay, Zs. Almássy, Z. Benyo, and L. Barkai. “Quasi In-Silico Validations of a Nonlinear LPV Model-based Robust Glucose Control Algorithm for Type I Diabetes”. In: *IFAC Proc Vol* 44.1 (2011). bibtex*[publisher=Elsevier BV], pp. 7114–7119.

[236] P.H. Colmegna, R.S. Sánchez-Peña, R. Gondhalekar, E. Dassau, and F.. Doyle. “Reducing Glucose Variability Due to Meals and Postprandial Exercise in T1DM Using Switched LPV Control”. In: *J Diab Scien Techn* 10.3 (2016). bibtex*[publisher=SAGE Publications], pp. 744–753.

[237] Alberto Isidori. *Nonlinear Control Systems*. Springer London, 1995.

[238] A. Facchinetti, S. Favero, G. Sparacino, and C. Cobelli. “An Online Failure Detection Method of the Glucose Sensor-Insulin Pump System: Improved Overnight Safety of Type-1 Diabetic Subjects”. In: *IEEE Transactions on Biomedical Engineering* 60.2 (2013). bibtex*[publisher=Institute of Electrical and Electronics Engineers (IEEE)], pp. 406–416.

[239] P. Colmegna and R.S. Sánchez Peña. “Analysis of three T1DM simulation models for evaluating robust closed-loop controllers”. In: *Comp Meth Progr Biomed* 113.1 (2014). bibtex*[publisher=Elsevier BV], pp. 371–382.

[240] C. Luni, J.E. Shoemaker, K.R. Sanft, L.R. Petzold, and F.J. Doyle. “Confidence from uncertainty - A multi-target drug screening method from robust control theory”. In: *BMC Syst Biol* 4.1 (2010). bibtex*[publisher=Springer Nature], p. 161.

[241] M. Phillip, T. Battelino, E. Atlas, O. Kordonouri, N. Bratina, S. Miller, T. Biester, M.A. Stefanija, I. Muller, R. Nimri, and T. Danne. “Nocturnal Glucose Control with an Artificial Pancreas at a Diabetes Camp”. In: *New Engl J Med* 368.9 (2013).

bibtex*[publisher=New England Journal of Medicine (NEJM/MMS)], pp. 824–833.

[242] C. Ionescu and R. De Keyser. “EPSAC Predictive Control of Blood Glucose Level in Type I Diabetic Patients”. In: *Proceedings of the 44th IEEE Conference on Decision and Control*. IEEE, 2005.

[243] C. Ionescu, R. Hodrea, and R. De Keyser. “Impact of disturbance filter in nonlinear EPSAC predictive control of blood glucose level in type I diabetic patients”. In: *2008 IEEE International Conference on Control Applications*. IEEE, 2008.

[244] B.P. Kovatchev, E. Renard, C. Cobelli, H.C. Zisser, P. Keith-Hynes, S.M. Anderson, S.A. Brown, D.R. Chernavvsky, M.D. Breton, L.B. Mize, A. Farret, J. Place, D. Bruttomesso, S. Del Favero, F. Boscari, S. Galasso, A. Avogaro, L. Magni, F. Di Palma, C. Toffanin, M. Messori, E. Dassau, and F.J. Doyle. “Safety of Outpatient Closed-Loop Control: First Randomized Crossover Trials of a Wearable Artificial Pancreas”. In: *Diab Care* 37.7 (2014). bibtex*[publisher=American Diabetes Association], pp. 1789–1796.

[245] L. Magni, D.M. Raimondo, C. Dalla Man, G. De Nicolao, B. Kovatchev, and C. Cobelli. “Model predictive control of glucose concentration in type I diabetic patients: An in silico trial”. In: *Biomed Sign Proc Cont* 4.4 (2009). bibtex*[publisher=Elsevier BV], pp. 338–346.

[246] J.T. Sorensen. “A physiologic model of glucose metabolism in man and its use to design and assess improved insulin therapies for diabetes”. PhD thesis. Massachusetts Institute of Technology, 1985.

[247] R.N. Bergman, L.S. Phillips, and C. Cobelli. “Physiologic evaluation of factors controlling glucose tolerance in man: measurement of insulin sensitivity and beta-cell glucose sensitivity from the response to intravenous glucose.” In: *J Clin Invest* 68.6 (1981). bibtex*[publisher=American Society for Clinical Investigation], pp. 1456–1467.

[248] C. Cobelli, E. Renard, and B. Kovatchev. “Artificial Pancreas: Past, Present, Future”. In: *Diabetes* 60.11 (2011). bibtex*[publisher=American Diabetes Association], pp. 2672–2682.

[249] R.A. Harvey, Youqing Wang, B. Grosman, M.W. Percival, W. Bevier, D.A. Finan, H. Zisser, D.E. Seborg, L. Jovanovic, F.J. Doyle, and E. Dassau. “Quest for the Artificial Pancreas: Combining Technology with Treatment”. In: *IEEE Eng Med*

Biol Mag 29.2 (2010). bibtex*[publisher=Institute of Electrical and Electronics Engineers (IEEE)], pp. 53–62.

[250] J.E. Shaw, R.A. Sicree, and P.Z. Zimmet. "Global estimates of the prevalence of diabetes for 2010 and 2030". In: *Diab Res Clin Prac* 87.1 (2010). bibtex*[publisher=Elsevier BV], pp. 4–14.

[251] S. Wild, G. Roglic, A. Green, R. Sicree, and H. King. "Global prevalence of diabetes: estimates for the year 2000 and projections for 2030". In: *Diab Care* 27.5 (May 2004), pp. 1047–1053.

[252] William Sansum Diabetes Center. "Feasibility study using run-to-run control to optimize continuous glucose sensor bias". In: (2014).

[253] J.C. Maxwell. *A Treatise on Electricity and Magnetism*. 3rd. Clarendon, Oxford, UK, 1892.

[254] J.C. Maxwell. "On Governors". In: *Proceedings of the Royal Society* 100 (1868).

[255] B. Davies. *Integral Transforms and Their Applications*. Springer Science & Business Media, 2002.

[256] B. Davies. *Integráltranszformációk és alkalmazásaik (in Hungarian)*. Műszaki Könyvkiadó, Budapest, Hungary, 1983.

[257] V. Jurdjevic. *Geometric Control Theory*. Cambridge University Press, Cambrigde, UK, 1997.

[258] L. Lapicque. "Recherches quantitatives sur l'excitation électrique des nerfs traitée comme une polarisation". In: *J. Physiol. Pathol.* 9 (1907), pp. 620–635.

[259] A.L. Hodgkin and A.F. Huxley. "A quantitative description of membrane current and its application to conduction and excitation in nerve". In: *The Journal of Physiology* 117.4 (1952), pp. 500–544.

[260] R. FitzHugh. "Impulses and Physiological States in Theoretical Models of Nerve Membrane". In: *Biophys J.* 1.6 (1961), pp. 445–466.

[261] J. Nagumo, S. Arimoto, and S. Yoshizawa. "An active pulse transmission line simulating nerve axon". In: *Proc. of IRE* 50 (1962), pp. 2061–2070.

[262] Y. Che, J. Wang, W.L. Chan, and K.M. Tsang. "Chaos synchronization of coupled neurons under electrical stimulation via robust adaptive fuzzy control". In: *Nonlinear Dyn* 61 (2010), pp. 847–857.

[263] T. Matsumoto. "A Chaotic Attractor from Chua's Circuit". In: *IEEE Transactions on Circuits and Systems* CAS-31.12 (1984), pp. 1055–1058.

[264] L. Glass. *Chaos in neural systems. In: Arbib, M. (ed.) The Handbook of Brain Theory and Neural Networks*. MIT, Cambridge, 1995. 186-189.

[265] M.I. Rabinovich and H.D.I. Abarbanel. "The role of chaos in neural systems". In: *Neuroscience* 87.1 (1998), pp. 5–14.

[266] P. Dayan and L. F. Abbott. *Theoretical Neuroscience - Computational and Mathematical Modeling of Neural Systems*. MIT Press, 2001. ISBN: 978-0-262-54185-5.

[267] J. Guckenheimer and R.A. Oliva. "Chaos in the Hodgkin–Huxley Model". In: *SIAM J. APPLIED DYNAMICAL SYSTEMS* 1.1 (2002), pp. 105–114.

[268] E.M. Izhikevich. *Dynamical Systems in Neuroscience - The Geometry of Excitability and Bursting*. MIT Press, 2007.

[269] Changsong Zhou and J. Kurths. "Noise-induced synchronization and coherence resonance of a Hodgkin – Huxley model of thermally sensitive neurons". In: *CHAOS* 13.1 (2003), pp. 401–409.

[270] T.A. Várkonyi, J.K. Tar, and I.J. Rudas. "Robust Fixed Point Transformations in Chaos Synchroniztion". In: *In Proc. of the 11th Intl. Symp. of Hungarian Researchers on Computational Intelligence and Informatics, Budapest* (2010), pp. 219–224.

[271] X.J. Yang, J.A. Tenreiro Machado, and H.M. Srivastava. "Nonlinear dynamics for local fractional Burgers' equation arising in fractal flow". In: *Nonlinear Dynamics* 84.1 (2015), pp. 3–7.

[272] A.M. Zhabotinsky. "Periodic processes of malonic acid oxidation in a liquid phase". In: *Biophysika* 9 (1964), pp. 306–311.

[273] R.J. Field, E. Koros, and R.M. Noyes. "Oscillations in Chemical Systems. II. Thorough Analysis of Temporal Oscillation in the Bromate-cerium-malonic Acid System". In: *J. Am. Chem. Soc.* 94.25 (1972), pp. 8649–8664.

[274] J.J. Tyson. *The Belousov-Zhabotinskii Reaction - Lecture Notes in Biomathematics 10*. Springer–Verlag, Heidelberg, 1976.

[275] D. Kondepudi and I Prigogine. *Modern Thermodynamics: From Heat Engines to Dissipative Structures*. 2nd. Chichester, UK: John Wiley & Sons, 2014.

[276] I. Prigogine and I. Stengers. *La nouvelle alliance. Métamorphose de la science*. Gallimard, Paris, 1986.

[277] J.K. Tar, I.J. Rudas, L. Nádai, and K. Kósi. "Adaptive Controllability of the Brusselator Model with Input Coupling". In: *In Proc of the 4th IEEE Intl. Symp. on Logistics and Industrial Informatics (LINDI), Smolenice, Slovakia* (2012), pp. 157–162.

[278] A.M. Lyapunov. "A General Task About the Stability of Motion (in Russian)". PhD thesis. Kharokov, Russia: University of Kharkov, 1892.

[279] A.M. Lyapunov. *Stability of Motion*. New York, USA: Academic Press, 1966.

[280] B. Lantos. *Theory and design of control systems [in Hungarian]*. 2nd. Budapest, Hungary: Akademia Press, 2005.

[281] J.Y Tjalling. "Historical development of the Newton-Raphson method". In: *SIAM Review* 37.4 (1995), pp. 531–551.

[282] P. Deuflhard. *Newton Methods for Nonlinear Problems. Affine Invariance and Adaptive Algorithms, Springer Series in Computational Mathematics, Vol. 35*. Berlin, Germany: Springer, 2004.

[283] C.T. Kelley. *Solving Nonlinear Equations with Newton's Method, no 1 in Fundamentals of Algorithms*. SIAM, 2003.

[284] M. Abedini, M.A Nojoumian, H. Salarieh, and A. Meghdari. "Model reference adaptive control in fractional order systems using discrete-time approximation methods". In: *Commun Nonlinear Sci* 25 (2015). bibtex*[issues=1-3], pp. 27–40.

[285] Q. Shen and T. Zhang. "A novel adaptive synchronization control of a class of master–slave large-scale systems with unknown channel time-delay". In: *Commun Nonlinear Sci* 22 (2015). bibtex*[issues=1-3], pp. 83–91.

[286] S. Banach. "Sur les opérations dans les ensembles abstraits et leur application aux équations intégrales (About the Operations in the Abstract Sets and Their Application to Integral Equations)". In: *Fund Math* 3 (1922), pp. 133–181.

[287] Gy. Eigner, P. Horváth, J.K. Tar, I. Rudas, and L. Kovács. "Application of Robust Fixed Point control in case of T1DM". In: *IEEE International Conference on Systems, Man, and Cybernetics 2015: IEEE SMC 2015*. Ed. by S. Kwong and D. Yeung. bibtex*[eventdate=2015-10-09/2015-10-12;venue=Hong Kong, China]. IEEE SMC, 2015, pp. 2459–2464.

[288] M. Hazewinkel (Ed.) *Encyclopaedia of Mathematics (set)*. Kluwer, 1994.

[289] F. Riesz. "Sur les systèmes orthogonaux de fonctions". In: *Comptes rendus de l'Académie des sciences* 144 (1907), pp. 615–619.

[290] E. Fisher. “Sur la convergence en moyenne”. In: *Comptes rendus de l’Académie des sciences* 144 (1907), pp. 1022–1024.

[291] A. Dineva, J.K. Tar, A. VáJablonskirkonyi-Kóczy, and V. Piuri. “Generalization of a Sigmoid Generated Fixed Point Transformation from SISO to MIMO systems”. In: *2015 IEEE 19th International Conference on Intelligent Engineering Systems (INES 2015)* (2015), pp. 135–140.

[292] L. Grüne and J. Pannek. *Nonlinear Model Predictive Control*. Springer, 2011.

[293] A. Grancharova and T.A. Johansen. *Explicit Nonlinear Model Predictive Control*. Springer, 2012.

[294] A. Levant. “Arbitrary-order Sliding Modes with Finite Time Convergence”. In: *In Proc. 6th IEEE Mediterranean Conference on Control and Systems (MED 1998), Alghero, Italy* (1998), pp. 349–354.

[295] S.A Billings. *Nonlinear System Identification*. 1st. Chichester, UK: John Wiley & Sons, 2013.

[296] D. Drexler, J. Sápi, and L. Kovács. “A minimal model of tumor growth with angiogenic inhibition using bevacizumab”. In: *SAMI 2017 - IEEE 15th International Symposium on Applied Machine Intelligence and Informatics*. bibtex*[venue=Herl’any, Slovakia;eventdate=2017-01-26/2017-01-28]. IEEE, 2017, pp. 185–190.

[297] D.A. Drexler, J. Sápi, and L. Kovács. “Positive control of a minimal model of tumor growth with bevacizumab treatment”. In: *Proceedings of the 12th IEEE Conference on Industrial Electronics and Applications*. 2017, pp. 2081–2084.

[298] Y. Akatsu, Y. Yoshimatsu, T. Tomizawa, K. Takahashi, A. Katsura, K. Miyazono, and T. Watabe. “Dual targeting of vascular endothelial growth factor and bone morphogenetic protein-9/10 impairs tumor growth through inhibition of angiogenesis”. In: *Cancer Science* 108.1 (2017). bibtex*[publisher=Wiley-Blackwell], pp. 151–155.

[299] J. Sápi, L. Kovács, D.A. Drexler, P. Kocsis, D. Gaári, and Z. Sápi. “Tumor volume estimation and quasi-continuous administration for most effective bevacizumab therapy”. In: *PLoS ONE* 10.11 (2015).

[300] C. Briat. “Linear parameter-varying and time-delay systems”. In: *Analysis, Observation, Filtering & Control* 3 (2014). bibtex*[publisher=Springer].

[301] B. Siciliano, L. Sciavicco, L. Villani, and G. Oriolo. *Robotics–Modelling, Planning and Control. Advanced Textbooks in Control and Signal Processing Series*. Springer-Verlag, 2009.

[302] Y. Tagawa, J.Y. Tu, and D.P. Stoten. "Inverse dynamics compensation via simulation of feedback control systems". In: *Proceedings of the institution of mechanical engineers, Part I: Journal of systems and control engineering* 225.1 (2011). bibtex*[publisher=SAGE Publications Sage UK: London, England], pp. 137–153.

[303] J. Cui, K. Zhang, and T. Ma. "An efficient algorithm for the tensor product model transformation". In: *Int J Control Autom* 14.5 (2016). bibtex*[publisher=Springer], pp. 1205–1212.

[304] Sz. Nagy, Z. Petres, P. Baranyi, and H. Hashimoto. "Computational relaxed TP model transformation: restricting the computation to subspaces of the dynamic model". In: *Asian J Control* 11.5 (2009). bibtex*[publisher=Wiley Online Library], pp. 461–475.

[305] A. Szollosi and P. Baranyi. "Influence of the Tensor Product model representation of qLPV models on the feasibility of Linear Matrix Inequality". In: *Asian J Control* 18.4 (2016). bibtex*[publisher=Wiley Online Library], pp. 1328–1342.

[306] A. Szollosi and P. Baranyi. "Improved control performance of the 3-DoF aeroelastic wing section: a TP model based 2D parametric control performance optimization". In: *Asian J Control* 19.2 (2017). bibtex*[publisher=Wiley Online Library], pp. 450–466.

[307] A. Szollosi and P. Baranyi. "Influence of the Tensor Product Model Representation of qLPV Models on the Feasibility of Linear Matrix Inequality Based Stability Analysis". In: *Asian J Control* 20.1 (2018). bibtex*[publisher=Wiley Online Library], pp. 531–547.

[308] X. Liu, Y. Yu, Z. Li, Herbert H.C. Iu, and T. Fernando. "An Efficient Algorithm for Optimally Reshaping the TP Model Transformation". In: *IEEE T Circuits-II* 64.10 (2017). bibtex*[publisher=IEEE], pp. 1187–1191.

[309] P. Várkonyi, D. Tikk, P. Korondi, and P. Baranyi. "A new algorithm for RNO-INO type tensor product model representation". In: *2005 IEEE International Conference on Intelligent Engineering Systems, INES*. Vol. 5. 2005, pp. 263–266.

[310] X. Liu, X. Xin, Z. Li, and Z. Chen. "Near Optimal Control Based on the Tensor-Product Technique". In: *IEEE T Circuits-II* 64.5 (2017). bibtex*[publisher=IEEE], pp. 560–564.

[311] X. Liu, Y. Yu, H. Li Z.and Iu, and Ty. Fernando. “A novel constant gain Kalman filter design for nonlinear systems”. In: *Signal Process* 135 (2017). bibtex*[publisher=Elsevier], pp. 158–167.

[312] X. Liu, Y. Yu, Z. Li, and H. Iu. “Polytopic H_∞ filter design and relaxation for nonlinear systems via tensor product technique”. In: *Signal Process* 127 (2016). bibtex*[publisher=Elsevier], pp. 191–205.

[313] P.S. Saikrishna, R. Pasumarthy, and N.P. Bhatt. “Identification and multivariable gain-scheduling control for cloud computing systems”. In: *IEEE T Cont Syst T* 25.3 (2017). bibtex*[publisher=IEEE], pp. 792–807.

[314] G. Zhao, D. Wang, and Z. Song. “A novel tensor product model transformation-based adaptive variable universe of discourse controller”. In: *J Frankl Inst* 353.17 (2016). bibtex*[publisher=Elsevier], pp. 4471–4499.

[315] W. Qin, B. He, Q. Qin, and G. Liu. “Robust active controller of hypersonic vehicles in the presence of actuator constraints and input delays”. In: *2016 35th Chinese Control Conference (CCC)*. bibtex*[organization=IEEE]. 2016, pp. 10718–10723.

[316] Q. Weiwei, H. Bing, L. Gang, and Z. Pengtao. “Robust model predictive tracking control of hypersonic vehicles in the presence of actuator constraints and input delays”. In: *J Frankl Inst* 353.17 (2016). bibtex*[publisher=Elsevier], pp. 4351–4367.

[317] T. Wang and B. Liu. “Different polytopic decomposition for visual servoing system with LMI-based Predictive Control”. In: *2016 35th Chinese Control Conference (CCC)*. bibtex*[organization=IEEE]. 2016, pp. 10320–10324.

[318] T. Wang and W. Zhang. “The visual-based robust model predictive control for two-DOF video tracking system”. In: *2016 Chinese Control and Decision Conference (CCDC)*. bibtex*[organization=IEEE]. 2016, pp. 3743–3747.

[319] T. Jiang and D. Lin. “Tensor Product Model-Based Gain Scheduling of a Missile Autopilot”. In: *T Jpn Soc Aeronaut S* 59.3 (2016). bibtex*[publisher=The Japan Society for Aeronautical and Space Sciences], pp. 142–149.

[320] V.CS. Campos, F.O. Souza, L.AB. Torres, and R.M. Palhares. “New stability conditions based on piecewise fuzzy Lyapunov functions and tensor product transformations”. In: *IEEE T Fuzzy Syst* 21.4 (2013). bibtex*[publisher=IEEE], pp. 748–760.

[321] S. Kuntanapreeda. “Tensor Product Model Transformation Based Control and Synchronization of a Class of Fractional-Order Chaotic Systems”. In: *Asian J Control* 17.2 (2015). bibtex*[publisher=Wiley Online Library], pp. 371–380.

[322] R-E. Precup, E.M. Petriu, M-B. Rădac, S. Preitl, L-O. Fedorovici, and C-A. Dragoş. “Cascade Control System-Based Cost Effective Combination of Tensor Product Model Transformation and Fuzzy Control”. In: *Asian J Control* 17.2 (2015). bibtex*[publisher=Wiley Online Library], pp. 381–391.

[323] G. Zhao, H. Li, and Z. Song. “Tensor product model transformation based decoupled terminal sliding mode control”. In: *Int J Syst Sci* 47.8 (2016). bibtex*[publisher=Taylor & Francis], pp. 1791–1803.

[324] P. Korondi. “Tensor product model transformation-based sliding surface design”. In: *Acta Polytech Hung* 3.4 (2006), pp. 23–35.

[325] T.T. Wang, W.F. Xie, G.D. Liu, and Y.M. Zhao. “Quasi-Min-Max Model Predictive Control for Image-Based Visual Servoing with Tensor Product Model Transformation”. In: *Asian J Control* 17.2 (2015). bibtex*[publisher=Wiley Online Library], pp. 402–416.

[326] J. Kuti, P. Galambos, and Á. Miklós. “Output Feedback Control of a Dual-Excenter Vibration Actuator via qLPV Model and TP Model Transformation”. In: *Asian J Control* 17.2 (2015). bibtex*[publisher=Wiley Online Library], pp. 432–442.

[327] J. Pan and L. Lu. “TP Model Transformation Via Sequentially Truncated Higher-Order Singular Value Decomposition”. In: *Asian J Control* 17.2 (2015). bibtex*[publisher=Wiley Online Library], pp. 467–475.

[328] S. Campos, V. Costa, L. Tôrres, and R. Palhares. “Revisiting the TP model transformation: Interpolation and rule reduction”. In: *Asian J Control* 17.2 (2015). bibtex*[publisher=Wiley Online Library], pp. 392–401.

[329] G. Zhao, K. Sun, and H. Li. “Tensor product model transformation based adaptive integral-sliding mode controller: Equivalent control method”. In: *Scien World J* 2013 (2013). bibtex*[publisher=Hindawi].

[330] S. Chumalee and J. Whidborne. “Gain-Scheduled H_∞ Control for Tensor Product Type Polytopic Plants”. In: *Asian J Control* 17.2 (2015). bibtex*[publisher=Wiley Online Library], pp. 417–431.

[331] J. Klespitz, I. Rudas, and L. Kovács. “LMI-based feedback regulator design via TP transformation for fluid volume control in blood purification therapies”. In: *2015 IEEE International Conference on Systems, Man, and Cybernetics (SMC)*. bibtex*[organization=IEEE]. 2015, pp. 2615–2619.

[332] Á. Takács, T. Haidegger, P. Galambos, J. Kuti, and I. Rudas. “Nonlinear soft tissue mechanics based on polytopic tensor product modeling”. In: *2016 IEEE 14th International Symposium on Applied Machine Intelligence and Informatics (SAMI)*. bibtex*[organization=IEEE]. 2016, pp. 211–215.

[333] J. Matuško, Š. Ileš, F. Kolonić, and V. Lešić. “Control of 3d tower crane based on tensor product model transformation with neural friction compensation”. In: *Asian J Control* 17.2 (2015). bibtex*[publisher=Wiley Online Library], pp. 443–458.

[334] Arthur Bertachi, Charrise M Ramkissoon, Jorge Bondia, and Josep Vehí. “Automated blood glucose control in type 1 diabetes: A review of progress and challenges”. In: *Endocrinología, Diabetes y Nutrición (English ed.)* 65.3 (2018). bibtex*[publisher=Elsevier], pp. 172–181.

[335] D. Barry Keenan, John J. Mastrototaro, Stuart A. Weinzimer, and Garry M. Steil. “Interstitial fluid glucose time-lag correction for real-time continuous glucose monitoring”. In: *Biomedical Signal Processing and Control* 8.1 (Jan. 2013), pp. 81–89. ISSN: 17468094. DOI: 10.1016/j.bspc.2012.05.007. URL: http://linkinghub.elsevier.com/retrieve/pii/S1746809412000687 (visited on 03/05/2018).

[336] Alexander Hildenbrand Hansen, Anne Katrine Duun-Henriksen, Rune Juhl, Signe Schmidt, Kirsten Nørgaard, John Bagterp Jørgensen, and Henrik Madsen. “Predicting Plasma Glucose From Interstitial Glucose Observations Using Bayesian Methods”. In: *Journal of Diabetes Science and Technology* 8.2 (Mar. 2014), pp. 321–330. ISSN: 1932-2968, 1932-2968. DOI: 10.1177/1932296814523878. URL: http://journals.sagepub.com/doi/10.1177/1932296814523878 (visited on 03/05/2018).

[337] Andrea Facchinetti, Giovanni Sparacino, and Claudio Cobelli. *Reconstruction of glucose in plasma from interstitial fluid continuous glucose monitoring data: role of sensor calibration*. SAGE Publications, 2007.

[338] E. Campos-Náñez, O. Chen, C. Fabris, A. DeHennis, M. Breton, and B. Kovatchev. “Modeling & Simulation of the Eversense Implantable Sensor”. In: (). URL: http://www.senseonics.com/~/media/Files/S/Senseonics-IR/reports-and-

presentations/modelingsimulationoftheeversenseimplantablesensor.pdf (visited on 03/05/2018).

[339] Roland Tóth, Marco Lovera, Peter SC Heuberger, Matteo Corno, and Paul MJ Van den Hof. "On the discretization of linear fractional representations of LPV systems". In: *IEEE Transactions on Control Systems Technology* 20.6 (2012). bibtex*[publisher=IEEE], pp. 1473–1489.

[340] Roland Tóth, Peter SC Heuberger, and Paul MJ Van den Hof. "Discretisation of linear parameter-varying state-space representations". In: *IET control theory & applications* 4.10 (2010). bibtex*[publisher=IET], pp. 2082–2096.

[341] Roland Tóth. *Modeling and identification of linear parameter-varying systems*. Vol. 403. Springer, 2010.

[342] Wei Xie. "An equivalent LMI representation of bounded real lemma for continuous-time systems". In: *Journal of Inequalities and Applications* 2008.1 (2008). bibtex*[publisher=Springer], p. 672905.

[343] Thomas Donner. "Insulin–pharmacology, therapeutic regimens and principles of intensive insulin therapy". In: (2015). bibtex*[publisher=MDText. com, Inc.]

[344] Andrea Facchinetti, Simone Del Favero, Giovanni Sparacino, Jessica R Castle, W Kenneth Ward, and Claudio Cobelli. "Modeling the glucose sensor error". In: *IEEE T Biomed Eng* 61.3 (2014). bibtex*[publisher=IEEE], pp. 620–629.

[345] D. Copot, R. De Keyser, J. Juchem, and C.M. Ionescu. "Fractional Order Impedance Model to Estimate Glucose Concentration: in Vitro Analysis". In: *ACTA Pol Hung* 14.1 (2017). bibtex*[publisher=BUDAPEST TECH BECSI UT 96-B, BUDAPEST, H-1034, HUNGARY], pp. 207–220.

[346] Kamuran Turksoy and Ali Cinar. "Adaptive control of artificial pancreas systems: a review". In: *J Health Eng* 5.1 (2014). bibtex*[publisher=Hindawi], pp. 1–22.

[347] Dimitri Boiroux, Anne Katrine Duun-Henriksen, Signe Schmidt, Kirsten Nørgaard, Niels Kjølstad Poulsen, Henrik Madsen, and John Bagterp Jørgensen. "Adaptive control in an artificial pancreas for people with type 1 diabetes". In: *Cont Eng Prac* 58 (2017). bibtex*[publisher=Elsevier], pp. 332–342.

[348] Dimitri Boiroux, Morten Hagdrup, Zeinab Mahmoudi, Kjølstad Poulsen, Henrik Madsen, and John Bagterp Jørgensen. "An ensemble nonlinear model predictive control algorithm in an artificial pancreas for people with type 1 diabetes". In: *2016 European Control Conference (ECC)*. bibtex*[organization=IEEE]. 2016, pp. 2115–2120.

[349] D.A. Drexler, J. Sápi, and L. Kovács. “Modeling of Tumor Growth Incorporating the Effects of Necrosis and the Effect of Bevacizumab”. In: *Complexity* 2017 (2017). bibtex*[publisher=Hindawi].

[350] Dan Wu, Di Cao, Tengteng Wang, Yunmei Fang, and Juntao Fei. “Adaptive Neural LMI-Based H-Infinity Control for MEMS Gyroscope”. In: *IEEE Access* 4 (2016). bibtex*[publisher=IEEE], pp. 6624–6630.

[351] Tamás Ferenci, Johanna Sápi, and Levente Kovács. “Modelling Tumor Growth Under Angiogenesis In-hibition with Mixed-effects Models”. In: *ACTA Pol Hung* 14.1 (2017).

[352] Jordan E Pinsker, Joon Bok Lee, Eyal Dassau, Dale E Seborg, Paige K Bradley, Ravi Gondhalekar, Wendy C Bevier, Lauren Huyett, Howard C Zisser, and Francis J Doyle. “Randomized Crossover Comparison of Personalized MPC and PID Control Algorithms for the Artificial Pancreas”. In: *Diab Care* 39 (2016). bibtex*[publisher=Diab Care], pp. 1135–1142.

[353] Amira Gharbi, Mohamed Benrejeb, and Pierre Borne. “Study of the Stabilization of Uncertain Nonlinear Systems Controlled by State Feedback”. In: *ACTA Pol Hung* 13.4 (2016), pp. 21–38.

[354] Ahmad Haidar. “The Artificial Pancreas: How Closed-Loop Control Is Revolutionizing Diabetes”. In: *IEEE Contr Syst Mag* 36.5 (2016), pp. 28–47.

[355] International Diabetes Federation. *IDF Diabetes Atlas*. 6th ed. Brussel, Belgium: International Diabetes Federation, 2013.

[356] Tamás Ferenci, Anna Körner, and Levente Kovács. “The interrelationship of HbA1c and real-time continuous glucose monitoring in children with type 1 diabetes”. In: *Diab Res Clin Pr* 108.1 (2015), pp. 38–44.

[357] Istvan Nagy. “From Exploring to Optimal Path Planning: Considering Error of Navigation in Multi-Agent Mobile Robot Domain”. In: *ACTA Pol Hung* 11.6 (2014), pp. 39–55.

[358] J.H. Lee. “Model predictive control: Review of the three decades of development”. In: *International Journal of Control, Automation and Systems* 9.3 (2011), p. 415.

[359] M. E. Villanueva, R. Quirynen, M. Diehl, B. Chachuat, and B. Houska. “Robust MPC via min-max differential inequalities”. In: *Automatica* 77 (Mar. 2017), pp. 311–321.

[360] M. Morari and J.H. Lee. “Model Predictive Control: Past, Present and Future”. In: *Comp Chem Eng* 23 (1997), pp. 667–682.

[361] C. E. Garcia, D. M. Prett, and M. Morari. “Model Predictive Control: Theory and Practice&Mdash;a Survey”. In: *Automatica* 25.3 (1989). bibtex*[publisher=Pergamon Press, Inc.;location=Tarrytown, NY, USA;numpages=14], pp. 335–348.

[362] C. Ionescu, Y. Zhou, and J.A.T. Machado. “Special Issue: Advances in Fractional Dynamics and Control”. In: *J Vib Control* 22.8 (2016), pp. 1969–1971.

[363] C-K. Chui, B.P. Nguyen, Y. Ho, Z. Wu, M. Nguyen, G-S. Hong, D. Mok, S. Sun, and S. Chang. “Embedded Real-Time Model Predictive Control for Glucose Regulation”. In: *World Congress on Medical Physics and Biomedical Engineering May 26-31, 2012, Beijing, China*. Ed. by M. Long. Berlin, Heidelberg: Springer Berlin Heidelberg, 2013, pp. 1437–1440.

[364] K. Soltesz, K. van Heusden, M. Hast, J.M. Ansermino, and G.A. Dumont. “A Synthesis Method for Automatic Handling of Inter-patient Variability in Closed-loop Anesthesia”. In: *2016 American Control Conference (ACC)*. bibtex*[eventdate=2016-07-08/2016-07-08;venue=Boston, MA, USA] event-place: Boston. ACC, 2016, pp. 4877–4882.

[365] R.N. Bergman and J. Urquhart. “The pilot gland approach to the study of insulin secretory dynamics”. In: *Recent Prog Horm Res* 27 (1971), pp. 583–605.

[366] R.N. Bergman, L.S. Phillips, and C. Cobelli. “Physiological evaluation of factors controlling glucose tolerance in man”. In: *J Clin Invest* 68 (1981), pp. 1456–1467.

[367] B. Takarics and P. Baranyi. “TP Model-based Robust Stabilization of the 3 Degrees-of-Freedom Aeroelastic Wing Section”. In: *ACTA Pol Hung* 12.1 (2015), pp. 209–228.

[368] D.W. Gu, P.H. Petkov, and M.M. Konstantinov. *Robust Control Design with Matlab*. 2nd. London: Springer, 2013.

[369] F.A. Möbius. *The Barycentric Calculus (in German)*. 1st. Leipzig: Verlag von Johann Ambrosius Barth, 1827.

[370] J. Fauvel, F. Raymond, and R. Wilson, eds. *Möbius and his Band*. 1st. Oxford: Oxford University Press, 1993.

[371] J. Warren, S. Schaefer, A.N. Hirani, and M. Desbrun. “Barycentric coordinates for convex sets”. In: *Adv Comp Math* 27 (2007), pp. 319–338.

[372] J.W. Haefner. *Modeling biological systems: Principles and applications*. 2nd. New York: Springer, 2005.

[373] B. Hannon and M. Ruth. *Modeling Dynamic Biological Systems*. 2nd ed. Modeling Dynamic Systems. New York: Springer International Publishing, 2014.

[374] P. Szalay, Gy. Eigner, and L. Kovács. “Linear Matrix Inequality-based Robust Controller design for Type-1 Diabetes Model”. In: *IFAC 2014 – 19th World Congress of The International Federation of Automatic Control*. bibtex*[eventdate=2014-08-24/2014-08-29;venue=Cape Town, South Africa] event-place: Cape Town. IFAC, 2014, pp. 9247–9252.

[375] X.W. Wong, J.G. Chase, G.M. Shaw, C.E. Hanna, T. Lotz, J. Lin, I. Singh-Levett, L.J. Hollingsworth, and O.S.W. Wong. “Model predictive glycaemic regulation in critical illness using insulin and nutrition input: A pilot study”. In: *Med Eng Phys* 28 (2006), pp. 665–681.

[376] X.W. Wong, J.G. Chase, G.M. Shaw, C.E. Hann, J. Lin, and T. Lotz. “Comparison of adaptive and sliding-scale glycaemic control in critical care and the impact of nutritional inputs”. In: *12th International Conference On Biomedical Engineering*. bibtex*[eventdate=2005-12-07/2005-12-10;venue=Singapore,Singapore] event-place: Singapore. 2005, pp. 1–4.

[377] L. Kovács, A. György, B. Kulcsar, P. Szalay, B. Benyó, and Z. Benyó. “Robust control of type 1 diabetes using μ-synthesis”. In: *UKACC International Conference on Control 2010*. bibtex*[eventdate=2010-09-07/2010-09-10;venue=Coventry, UK] event-place: Coventry. 2010, pp. 1–6.

[378] R.S. Burns. *Advanced Control Engineering*. 1st. Oxford, UK: Butterworth – Heinemann, 2001.

[379] D.J. Leith and W.E. Leithead. “Survey of Gain-Scheduling Analysis Design”. In: *Int J Contr* 73 (1999), pp. 1001–1025.

[380] P. Galambos, J. Kuti, P. Baranyi, G. Szögi, and I.J Rudas. “Tensor Product based Convex Polytopic Modeling of Nonlinear Insulin-Glucose Dynamics”. In: *Proceedings of the 2015 IEEE International Conference on Systems, Man, and Cybernetics*. bibtex*[eventdate=2015-10-09/2015-10-12;venue=Hong Kong, China]. IEEE SMC, 2015, pp. 2597–2602.

[381] J. Kuti, P. Galambos, and P. Baranyi. “Minimal Volume Simplex (MVS) approach for convex hull generation in TP Model Transformation”. In: *2014 18th International Conference on Intelligent Engineering Systems (INES 2014)*. bibtex*[venue=Tihany, Hungary]. IEEE Hungary Section, 2014, pp. 187–192.

[382] M. Messori, C. Cobelli, and L. Magni. “Artificial Pancreas: from in-silico to in-vivo”. In: *9th International Symposium on Advanced Control of Chemical Processes*.

bibtex*[eventdate=2015-06-07/2015-06-10;venue=Whistler, Canada]. IFAC, 2014, pp. 1301–1309.

[383] RC. Roman, MB. Radac, RE. Precup, and EM. Petriu. "Data-driven Model-Free Adaptive Control Tuned by Virtual Reference Feedback Tuning". In: *ACTA Pol Hung* 13.1 (2016), pp. 83–96.

[384] J.G. Chase, A.J. Le Compte, J.G. Preiser, G.M. Shaw, S. Penning, and T. Desaive. "Physiological modeling, tight glycemic control, and the ICU clinician: what are models and how can they affect practice?" In: *Ann Intens Care* 1.11 (2011), P1–8.

[385] L. Kovács and B. Paláncz. "Algebraic Biology: Second International Conference, AB 2007, Castle of Hagenberg, Austria, July 2-4, 2007. Proceedings". In: ed. by H. Anai, Katsuhisa Horimoto, and Temur Kutsia. bibtex*[chapter=Glucose-Insulin Control of Type1 Diabetic Patients in H_2/H_∞ Space Via Computer Algebra]. Berlin, Heidelberg: Springer Berlin Heidelberg, 2007, pp. 95–109.

[386] J.K. Tar, L. Nádai, I. Felde, and I.J. Rudas. In: *Advances in Robot Design and Intelligent Control: Proceedings of the 24th International Conference on Robotics in Alpe-Adria-Danube Region (RAAD)*. Ed. by T. Borangiu. bibtex*[chapter=Cost Function-Free Optimization in Inverse Kinematics of Open Kinematic Chains]. Springer International Publishing, 2016, pp. 137–145.

[387] F. Wettl. *Linear Algebra [in Hungarian]*. 1nd. Budapest, Hungary: Budapest University of Technology and Economy, Faculty of Natural Sciences, 2011.

[388] R.A. Beezer. *A First Course in Linear Algebra*. Version 3.40. Washington, USA: Congruent Press, 2014.

[389] MATLAB. *Control System Toolbox Getting Started Guide*. bibtex*[version=Version 2016a;organization=The MathWorks, Inc]. 196 pp.

[390] R. Hovorka, F. Shojaee-Moradie, P.V Carroll, L.J Chassin, I.J Gowrie, N.C Jackson, R.S Tudor, M. Umpleby, and D.H Jones. "Partitioning glucose distribution/transport, disposal, and endogenous production during IVGTT". In: *Am J Physiol Endocr Metab* 282.5 (2002), E992–1007.

[391] M. Naerum. *Model Predictive Control for Insulin Administration in People with Type 1 Diabetes*. Technical University of Denmark, 2010.

[392] K.P. Sucher, M. Nelms, S. Long-Roth, and K. Lacey. *Nutrition Therapy and Pathophysiology*. Cengage Learning, 2011.

[393] L. Magni, D.M. Raimondo, C. Dalla Man, G. De Nicolao, B. Kovatchev, and C. Cobelli. "Model Predictive Control of glucose concentration in subjects with type 1 diabetes: an in silico trial". In: *Proceedings of the 17th World Congress The International Federation of Automatic Control*. Ed. by M.J Chung and P Misra. bibtex*[eventdate=2008-07-06/2008-07-11;venue=Seoul, Korea]. International Federation of Automatic Control, 2008, pp. 4246–4251.

[394] C. Dalla Man, R.A. Rizza, and C. Cobelli. "Mixed Meal Simulation Model of Glucose-Insulin System". In: *Proceedings of the 28th IEEE EMBS Annual International Conference*. bibtex*[eventdate=2006-08-30/2006-09-03;venue=New York City, USA]. IEEE EMBS, 2006, pp. 307–310.

[395] C. Dalla Man, G. Toffolo, R. Basu, R.A. Rizza, and C. Cobelli. "A Model of Glucose Production During a Meal". In: *Proceedings of the 28th IEEE EMBS Annual International Conference*. bibtex*[eventdate=2006-08-30/2006-09-03;venue=New York City, USA]. IEEE EMBS, 2006, pp. 5647–5652.

[396] C. Dalla Man, F. Micheletto, D. Lv, M. Breton, B. Kovatchev, and C. Cobelli. "The UVA/PADOVA Type 1 Diabetes Simulator: New Features." In: *J Diab Sci Tech* 8.8 (2014), pp. 26–34.

[397] A. Fonyó and E. Ligeti. *Physiology (in Hungarian)*. 3rd. Budapest, Hungary: Medicina, 2008.

[398] P. Palumbo, S. Ditlevsen, A. Bertuzzi, and A. de Gaetano. "Mathematical modeling of the glucose-insulin system A review". In: *Math Biosci* 244.2 (2013), pp. 69–81.

[399] International Diabetes Federation. *IDF Diabetes Atlas*. 7th. London, United Kongdom: International Diabetes Federation, 2015.

[400] Novo Nordisk. "Novo Nordisk Website". In: (2016). URL: https://www.novonordisk.com (visited on 08/08/2016).

[401] V. Bátora, M. Tŕnik, J. Murgas, S. Schmidt, K. Nogaard, N.K. Poulsen, H. Madsen, and J.B. Jorgensen. "Bihormonal Control of Blood Glucose in People with Type 1 Diabetes". In: *2015 European Control Conference (ECC)*. bibtex*[booksubtitle=;booktitleaddon=;even 07-15/2015-07-17;venue=Linz, Austria] event-place: Linz. IFAC, 2015, pp. 25–30.

[402] Gy. Eigner, J.K. Tar, and L. Kovács. "Adaptive Control Solution for T1DM Control". In: *Proceedings of the 10th Jubilee IEEE International Symposium on Applied Computational Intelligence and Informatics (SACI 2015)*. Ed. by A.

Szakál. bibtex*[eventdate=2015-01-22/2015-01-24;venue=Timisoara, Romania]. IEEE Hungary Section, 2015, pp. 215–220.

[403] Gy. Eigner, Tar J.K., and L. Kovács. “Fixed Point Transformation-based Adaptive Control for Type 1 Diabetes Mellitus”. In: *Scientific Bulletin of Politechnica University of Timisoara Transactions on Automatic Control and Computer Science* 60.1 (2015), pp. 1–9.

[404] L. Kovács and Gy. Eigner. “Opportunities of using Robust Fixed Point Transformation-based controller design in case of Type 1 Diabetes Mellitus”. Manuscript in preparation. 2016.

[405] Gy. Eigner, J.K. Tar, and L. Kovács. “Novel Error Interpretation in case of Linear Parameter Varying Systems”. In: *16th IEEE International Symposium on Computational Intelligence and Informatics, CINTI 2015*. Ed. by A. Szakál. bibtex*[eventdate=2015-11-19/2015-11-19;venue=Budapest, Hungary]. IEEE Hungary Section, 2015, pp. 243–248.

[406] Gy. Eigner. “Novel LPV-based control approach for nonlinear physiological systems”. In: *ACTA Pol Hung* 14.1 (2017), pp. 45–61.

[407] Gy. Eigner, P. Pausits, and L. Kovács. “A novel completed LPV controller and observer scheme in order to control nonlinear compartmental systems”. In: *14th IEEE International Symposium on Intelligent Systems and Informatics, CINTI 2015*. Ed. by A. Szakál. bibtex*[eventdate=2016-08-29/2016-08-31;venue=Subotica, Serbia]. IEEE Hungary Section, 2016, pp. 85–92.

[408] L. Kovács and Gy. Eigner. “Usability of the Tensor Product based modeling in the modeling of Diabetes Mellitus”. Manuscript in preparation. 2016.

[409] Gy. Eigner, I. Rudas, and L. Kovács. “Investigation of the TP-based modeling possibility of a nonlinear ICU diabetes model”. In: *IEEE International Conference on Systems, Man, and Cybernetics 2016: IEEE SMC 2016*. bibtex*[eventdate=2016-10-09/2016-10-12;venue=Budapest, Hungary]. IEEE SMC, 2016, pp. 3405–3410.

[410] L. Kovács and Gy. Eigner. “Convex Polytopic Modeling of Diabetes Mellitus: A Tensor Product based approach”. In: *IEEE International Conference on Systems, Man, and Cybernetics 2016: IEEE SMC 2016*. bibtex*[eventdate=2016-10-09/2016-10-12;venue=Budapest, Hungary]. IEEE SMC, 2016, pp. 3393–3398.

[411] M. Kozlovszky, K. Hegedűs, S. Szénási, G. Kiszler, B. Wichmann, I. Bándi, Gy. Eigner, P.I Sas, L. Kovács, Z. Garaguly, V. Jónás, G. Kiss, G. Valcz, and B. Molnár. "Parameter assisted HE colored tissue image classification". In: *IEEE 17th International Conference on Intelligent Engineering Systems (INES)*. Ed. by IEEE. bibtex*[eventdate=2013-06-19/2013-06-21;venue=San Jose, Costa Rica]. IEEE Hungary Section, 2013, pp. 203–207.

[412] M. Kozlovszky, L. Kovács, M. Törőcsik, G. Windisch, S. Ács, D. Prém, Gy. Eigner, P.I. Sas, T. Schubert, and V. Póserné. "Cloud security monitoring and vulnerability management". In: *IEEE 17th International Conference on Intelligent Engineering Systems (INES)*. Ed. by IEEE. bibtex*[eventdate=2013-06-19/2013-06-21;venue=San Jose, Costa Rica]. IEEE Hungary Section, 2013, pp. 265–269.

[413] L. Kovács, J. Sápi, T. Ferenci, P. Szalay, D. Drexler, Gy. Eigner, P.I. Sas, I. Harmati, M. Kozlovszky, and Z. Sápi. "Model-based optimal therapy for high-impact diseases". In: *IEEE 17th International Conference on Intelligent Engineering Systems (INES)*. Ed. by IEEE. bibtex*[eventdate=2013-06-19/2013-06-21;venue=San Jose, Costa Rica]. IEEE Hungary Section, 2013, pp. 209–214.

[414] L. Kovács, P. Szalay, P.I. Sas, Gy. Eigner, Zs. Almássy, E. Felszeghy, Gy. Kocsis, J. Fövényi, A. Körner, L. Kautzky, H. Soós, A. Orbán, T. Niederland, A. Juhászné Tuifel, T. Tóthné Sebestyén, A. Soós, A. Török, and L. Barkai. "Preliminary model-free results of a Hungarian robust artificial pancreas algorithm: Abstracts of 6th International Conference on Advanced Technologies & Treatment for Diabetes, Paris, France". In: *Diab Techn Theap* 15 (Suppl1 2013), A–96–A–97.

[415] Gy. Eigner, P.I. Sas, and L. Kovács. "Insulin pump testing platform for robust control framework". In: *Proceedings of IEEE 9th International Conference on Computational Cybernetics*. Ed. by A. Szakál. bibtex*[eventdate=2013-07-08/2013-07-10;venue=Tihany, Hungary]. IEEE Hungary Section, 2013, pp. 201–205.

[416] P. Szalay, Gy. Eigner, Z. Benyó, I. Rudas, and L. Kovács. "Comparison of sigma-point filters for state estimation of diabetes models". In: *2014 IEEE International Conference on Systems, Man and Cybernetics (SMC)*. Ed. by W.A Gruver. bibtex*[eventdate=2014-10-05/2014-10-08;venue=San Diego, USA]. IEEE SMC, 2014, pp. 2476–2481.

[417] L. Kovács, J. Sápi, Gy. Eigner, T. Ferenci, P. Szalay, J. Klespitz, B. Kurtán, M. Kozlovszky, D. Drexler, P. Pausits, I. Harmati, Z. Sápi, and I. Rudas. "Model-based healthcare applications at Obuda University". In: *9th IEEE International Symposium on Applied Computational Intelligence and Informatics*. Ed. by A.

Szakál. bibtex*[eventdate=2014-05-15/2014-05-17;venue=Timisoara, Romania]. IEEE Hungary Section, 2014, pp. 183–187.

[418] L. Kovács, M. Kozlovszky, P. Szalay, Gy. Eigner, P. Sas, T. Ferenci, Zs. Almássy, E. Felszeghy, G. Kocsis, J. Fövényi, K. Wudi, A. Körner, L. Kautzky, H. Soós, A. Orbán, T. Niederland, A. Juhászné Tuifel, M. Tóthné Sebestyén Hocsi, A. Soós, A. Török, and L. Barkai. "relax Magyar mesterséges hasnyálmirigy projekt. Eredmények és távlatok - in Hungarian". In: *Diabetologia Hungarica XXII*. bibtex*[eventdate=2014-04-24/2014-04-27;venue=Szeged, Hungary]. Hungarian Diabetes Associasion, 2014, pp. 73–76.

[419] L. Kovács, M. Kozlovszky, P. Szalay, Gy. Eigner, P. Sas, Zs. Almássy, E. Felszeghy, G. Kocsis, J. Fövényi, A. Körner, L. Kautzky, H. Soós, A. Orbán, T. Niederland, A. Juhászné Tuifel, M. Tóthné Sebestyén Hocsi, A. Soós, A. Török, and L. Barkai. "relax Newest results of the Hungarian artificial pancreas project". In: *7th International Conference on Advanced Technologies & Treatment for Diabetes*. Ed. by M. Phillip and T. Battelino. bibtex*[eventdate=2014-02-05/2014-02-08;venue=Wien, Austria]. Mary Ann Liebert, 2014, A–149–A–150.

[420] Gy. Eigner, P.I. Sas, and L. Kovács. "Continuous glucose monitoring systems in the service of artificial pancreas". In: *9th IEEE International Symposium on Applied Computational Intelligence and Informatics*. Ed. by A. Szakál. bibtex*[eventdate=2014-05-15/2014-05-17;venue=Timisoara, Romania]. IEEE Hungary Section, 2014, pp. 117–122.

[421] L. Kovács, P. Szalay, Gy. Eigner, P. Sas, Zs. Almássy, and L. Barkai. "LPV-based robust control for Artificial Pancreas". In: (2014). Online Abstract bibtex*[booktitle=European Associasion for Study of Diabetes;publisher=OASIS - The Online Abstract Submission System].

[422] L. Kovács, T. Ferenci, J. Sápi, Gy. Eigner, J. Klespitz, P. Szalay, M. Kozlovszky, and I. Rudas. "Physiological Modeling and Control at Obuda University". In: *Proceedings of the 10th Jubilee IEEE International Symposium on Applied Computational Intelligence and Informatics (SACI 2015)*. Ed. by A. Szakál. bibtex*[eventdate=2015-01-22/2015-01-24;venue=Timisoara, Romania]. IEEE Hungary Section, 2015, pp. 21–25.

[423] Gy. Eigner, B. Kurtán, I. Rudas, C.K. Chui, and L. Kovács. "Examination of a novel double diabetes model". In: *IEEE 13th International Symposium on Applied Machine Intelligence and Informatics - SAMI 2015*. Ed. by A. Szakál.

bibtex*[eventdate=2015-01-22/2015-01-24;venue=Herlany, Slovakia]. IEEE Hungary Section, 2015, pp. 41–46.

[424] L. Kovács, B. Kurtán, Gy. Eigner, I. Rudas, and C.K. Chui. "Analyzing of a Novel Time Delay Diabetes Model". In: *ECC 2015 - 14th Annual European Control Conference*. bibtex*[eventdate=2015-07-15/2015-07-17;venue=Linz, Austria]. European Control Association (EUCA), 2015, pp. 13–18.

[425] P. Balla, P. Kocsis, Gy. Eigner, and Á. Antal. "Surface reconstruction with Wavelet transformation". In: *20th Jubilee IEEE International Conference on Intelligent Engineering Systems 2016*. Ed. by A. Szakál. bibtex*[eventdate=2016-06-30/2016-07-01;venue=Budapest, Hungary]. IEEE Hungary Section, 2016, pp. 201–206.

[426] L. Kovács and Gy. Eigner. "Clinical decision support systems for personalized healthcare". In: *International Conference on Automation, Quality and Testing, Robotics, AQTR 2016*. bibtex*[eventdate=2016-05-19/2016-05-21;venue=Cluj-Napoca, Romania]. IEEE Hungary Section, 2016, pp. 1–6.

[427] Á. Takács, Gy. Eigner, L. Kovács, I. Rudas, and T. Haidegger. "Teachers Kit: Development, Usability and Communities of Modular Robotic Kits for Classroom Education". In: *IEEE Robot Autom Mag* 23.2 (2016), pp. 2–11.

[428] I. Rudas, Gy. Eigner, and L. Kovács. "SMC 2016 and SMC Junior 2016". In: *IEEE SMC Mag* 2.1 (2016), pp. 41–44.

[429] Y. Kubota. "Tumor angiogenesis and antiangiogenic therapy". In: *Keio J Med* 61.2 (2012), pp. 47–56.

[430] Guido Herrmann, Matthew C Turner, and Ian Postlethwaite. "Linear matrix inequalities in control". In: *Mathematical methods for robust and nonlinear control*. Springer, 2007, pp. 123–142.

[456] P. Sas, L. Lukács, A. Kovács, E. Borbléy, and L. Kovács. "Monitoring drivers' vital parameters". In: *4th IEEE International Symposium on Logistics and Industrial Informatics: LINDI 2012*. Ed. by Anikó Szakál. Smolenice: IEEE, 2012, pp. 255–259.

[457] P. Patrícia, L. Vajda, and L. Kovács. "Developing a decision support system to determine carbohydrate intake of diabetic patients". In: *IEEE 10th Jubilee International Symposium on Applied Machine Intelligence and Informatics, SAMI 2012: Proceedings*. Ed. by IEEE. Budapest: IEEE Hungary Section, 2012, pp. 427–430.

[458] Drexler Dániel András, Sápi Johanna, Szeles Annamária, Harmati István, Kovács Adalbert, and Kovács Levente. “Flat control of tumor growth with angiogenic inhibition”. In: *Proceedings of the 7th IEEE International Symposium on Applied Computational Intelligence and Informatics (SACI), 2012*. Ed. by Szakál Anikó. New York: IEEE, 2012, pp. 179–183.

[459] Kovács Levente, Szalay Péter, Ferenci Tamás, Sápi Johanna, Sas Péter István, Drexler Dániel, Harmati István, Benyó Balázs, and Kovács Adalbert. “Model-based control algorithms for optimal therapy of high-impact public health diseases”. In: *Proceedings of the IEEE 16th International Conference on Intelligent Engineering Systems 2012*. Ed. by Szakál Anikó. Lisszabon: Institute of Electrical and Electronics Engineers (IEEE), 2012, pp. 531–536.

[460] Kovács Levente, Ferenci Tamás, Sápi Johanna, and Szalay Péter. “Népegészségügyi problémák számítógépes modellezése”. In: *IME: INTERDISZCIPLINÁRIS MAGYAR EGÉSZSÉGÜGY / INFORMATIKA ÉS MENEDZSMENT AZ EGÉSZSÉGÜGYBEN* XI.8 (2012), pp. 49–55. ISSN: 1588-6387.

[461] Kovács Levente, Szalay Péter, Sas Péter István, Eigner György, Almássy Zsuzsa, Felszeghy Enikő, Soós Hajnalka, Orbán Andrea, Körner Anna, Niederland Tamás, Juhászné Tuifel Andrea, Tóthné Sebestyén Tímea, Soós Andrea, Török András, and Barkai László. “Magyar mesterséges hasnyálmirigy algoritmusának előzetes modell-független eredményei”. In: ed. by Felszeghy Enikő. 2012, pp. 21–22.

[462] L Kovács, T Haidegger, and I Rudas. “Surgery from a Distance—Application of Intelligent Control for Telemedicine”. In: *Proceedings of the IEEE 11th International Symposium on Applied Machine Intelligence and Informatics (SAMI 2013)*. Ed. by Anikó Szakál. Budapest: IEEE Hungary Section, 2013, pp. 125–129.

[463] L Kovács. “Modern Robust Control in Patophysiology: From Theory to Application: (Plenary Talk)”. In: *Proceedings of the IEEE 11th International Symposium on Applied Machine Intelligence and Informatics (SAMI 2013)*. Ed. by Anikó Szakál. Budapest: IEEE Hungary Section, 2013, pp. 13–14.

[464] L Kovács, P Szalay, P I Sas, Gy Eigner, Zs Almássy, E Felszeghy, Gy Kocsis, J Fövényi, A Körner, L Kautzky, H Soós, A Orbán, T Niederland, A Juhászné Tuifel, T Tóthné Sebestyén, A Soós, A Török, and L Barkai. “Preliminary model-free results of a Hungarian robust artificial pancreas algorithm: Abstracts of 6th International Conference on Advanced Technologies & Treatment for Diabetes, Paris, France”. In: *DIABETES TECHNOLOGY AND THERAPEUTICS* 15 (Suppl1 2013), A–96.

[465] D A Drexler, J Sápi, A Szeles, I Harmati, and L Kovács. “Comparison of Path Tracking Flat Control and Working Point Linearization Based Set Point Control of Tumor Growth with Angiogenic Inhibition”. In: *BULETINUL STIINTIFIC AL UNIVERSITATII POLITEHNICA DIN TIMISOARA ROMANIA SERIA AUTOMATICA SI CALCULATORAE* 57 (71).2 (2012), pp. 113–120.

[466] T Ferenci, B Benyó, L Kovács, L Fisk, G M Shaw, and G J Chase. “Daily Evolution of Insulin Sensitivity Variability with Respect to Diagnosis in the Critically Ill”. In: *PLOS ONE* 8.2 (2013).

[467] Laura Kovács, Béla Paláncz, and Levente Kovács. “Solving Robust Glucose-Insulin Control by Dixon Resultant Computations”. In: *Symbolic and Numeric Algorithms for Scientific Computing (SYNASC), 2012 14th International Symposium on*. Ed. by Andrei Voronkov, Viorel Negru, Tetsuo Ida, Tudor Jebelean, Dana Petcu, Stephen Watt, and Daniela Zaharie. Seattle (WA): IEEE, 2012, pp. 53–61.

[468] Ferenci Tamás, Kovács Levente, Benyó Balázs, and Kovács Adalbert. “Using Support Vector Machines to Recognize Changes Characteristic to Obesity in Laboratory Results”. In: *Proceedings of the 5th European Conference of the International Federation for Medical and Biological Engineering*. Ed. by Jobbágy Á. Berlin; Heidelberg: Springer Verlag, 2012, pp. 215–218.

[469] Ferenci Tamás, Kovács Levente, Benyó Balázs, Aaron Le Compte, Geoffrey M. Shaw, and Geoffrey J. Chase. “Effect of Diagnosis on Variability of ICU Patients in Insulin Sensitivity”. In: *Proceedings of 8th IFAC Symposium on Biological and Medical Systems*. Ed. by Balazs Benyo, David Feng, J Geoffrey Chase, Steen Andreassen, Ewart Carson, and Levente Kovacs. New York: Curran, 2012, pp. 462–466.

[470] Kovács L, Szalay P, Benyó B, and Chase JG. “Optimal tight glycaemic control supported by differential geometric methodsa”. In: *Proceedings of the 5th European Conference of the International Federation for Medical and Biological Engineering*. Ed. by Jobbágy Á. Berlin; Heidelberg: Springer Verlag, 2012, pp. 351–354.

[471] Szeles Annamária, Sápi Johanna, Drexler Dániel, Harmati István, Sápi Zoltán, and Kovács Levente. “Model-based Angiogenic Inhibition of Tumor Growth using Modern Robust Control Method”. In: *Proceedings of 8th IFAC Symposium on Biological and Medical Systems*. Ed. by Balazs Benyo, David Feng, J Geoffrey Chase, Steen Andreassen, Ewart Carson, and Levente Kovacs. New York: Curran, 2012, pp. 113–118.

[472] A Kovács, L Kovács, and L Kovács. “The boundary element method in the study of the fluid’s non-stationary motion through network profiles”. In: ed. by Ioan Cuculescu, Jovo Jaric, Pasc Gavruta, Ioan Golet, and Liviu Cadariu. Editura Politehnica, 2012, pp. 241–248.

[473] L Kovács, T Ferenci, B Benyó, A Kovács, and J G Chase. “Short- and long-term evolution of insulin sensitivity variability in critically ill patients”. In: ed. by Ioan Cuculescu, Jovo Jaric, Pasc Gavruta, Ioan Golet, and Liviu Cadariu. Editura Politehnica, 2012, pp. 329–334.

[474] L Kovács, P Szalay, Zs Almássy, and L Barkai. “Applicability Results of a Nonlinear Model-Based Robust Blood Glucose Control Algorithm”. In: *JOURNAL OF DIABETES SCIENCE AND TECHNOLOGY* 7.3 (2013), pp. 708–716.

[475] J Sápi, D A Drexler, I Harmati, A Szeles, B Kiss, Z Sápi, and L Kovács. “Tumor growth model identification and analysis in case of C38 colon adenocarcinoma and B16 melanoma”. In: *IEEE 8th International Symposium on Applied Computational Intelligence and Informatics: SACI 2013*. Ed. by Szakál Anikó. New York: IEEE, 2013, pp. 303–308.

[476] T Ferenci, A Körner, and L Kovács. “Correlation investigations between HbA1c and blood glucose indicators on type 1 diabetic Hungarian children”. In: *IEEE 8th International Symposium on Applied Computational Intelligence and Informatics: SACI 2013*. Ed. by Szakál Anikó. New York: IEEE, 2013, pp. 443–447.

[477] M Kozlovszky, L Kovács, M Törőcsik, G Windisch, S Ács, D Prém, Gy Eigner, P I Sas, T Schubert, and V Póserné. “Cloud security monitoring and vulnerability management”. In: *IEEE 17th International Conference on Intelligent Engineering Systems (INES), 2013*. Ed. by IEEE. Piscataway (NJ): IEEE, 2013, pp. 265–269.

[478] M Kozlovszky, K Hegedűs, S Szénási, G Kiszler, B Wichmann, I Bándi, Gy Eigner, P I Sas, L Kovács, Z Garaguly, V Jónás, G Kiss, G Valcz, and B Molnár. “Parameter assisted HE colored tissue image classification”. In: *IEEE 17th International Conference on Intelligent Engineering Systems (INES), 2013*. Ed. by IEEE. Piscataway (NJ): IEEE, 2013, pp. 203–207.

[479] L Kovács, J Sápi, T Ferenci, P Szalay, D Drexler, Gy Eigner, P I Sas, I Harmati, M Kozlovszky, and Z Sápi. “Model-based optimal therapy for high-impact diseases”. In: *IEEE 17th International Conference on Intelligent Engineering Systems (INES), 2013*. Ed. by IEEE. Piscataway (NJ): IEEE, 2013, pp. 209–214.

[480] Gyorgy Eigner, Peter Istvan Sas, and Levente Kovács. “Insulin pump testing platform for robust controller”. In: *ICCC 2013, Proceedings of IEEE 9th International Conference on Computational Cybernetics*. Ed. by Anikó Szakál. Tihany: IEEE Hungary Section, 2013, pp. 201–205.

[481] S Jordán, T Haidegger, L Kovács, I Felde, and I Rudas. “The Rising Prospects of Cloud Robotic Applications”. In: *ICCC 2013, Proceedings of IEEE 9th International Conference on Computational Cybernetics*. Ed. by Anikó Szakál. Tihany: IEEE Hungary Section, 2013, pp. 327–332.

[482] P Szalay, Gy Eigner, M Kozlovszky, I Rudas, and L Kovács. “The significance of LPV modeling of a widely used T1DM model”. In: *EMBC 2013 – 35th Annual International Conference of the IEEE Engineering in Medicine and Biology Society*. Ed. by K Sunagawa. Seattle (WA): IEEE, 2013, pp. 3531–3534.

[483] Balazs Benyo, David Feng, J Geoffrey Chase, Steen Andreassen, Ewart Carson, and Levente Kovacs, eds. *Proceedings of 8th IFAC Symposium on Biological and Medical Systems*. New York: Curran, 2012.

[484] Benyo B, Illyés A, Némedi NS, Le Compte AJ, Havas A, Kovacs L, Fisk L, Shaw GM, and Chase JG. “Pilot study of the SPRINT glycemic control protocol in a Hungarian medical intensive care unit.” In: *JOURNAL OF DIABETES SCIENCE AND TECHNOLOGY* 6.6 (2012), pp. 1464–1477.

[485] T Ferenci, L Kovács, and A Körner. “Az életkor, diabetestartam, HBA1C és a vércukorszint alakulásának jellemzői közti összefüggések CGM adatok alapján”. In: ed. by Soós Hajnalka and Nagyné Orbán Andrea. Magyar Diabetes Társaság, 2013, pp. 18–19.

[486] L Kovács, M Kozlovszky, P Szalay, Gy Eigner, P I Sas, Zs Almássy, E Felszeghy, H Soós, A Orbán, A Körner, T Niederland, A Juhászné Tuifel, T Tóthné Sebestyén, A Soós, A Török, and L Barkai. “A magyar mesterséges hasnyálmirigy projekt legújabb eredményei”. In: ed. by Soós Hajnalka and Nagyné Orbán Andrea. Magyar Diabetes Társaság, 2013, pp. 16–17.

[487] B Kiss, J Sápi, and L Kovács. “Imaging method for model-based control of tumor diseases”. In: *SISY 2013: IEEE 11th International Symposium on Intelligent Systems and Informatics : proceedings*. Ed. by Szakál Anikó. Budapest: IEEE Hungary Section, 2013, pp. 271–275.

[488] J Sápi, D A Drexler, and L Kovács. "Parameter optimization of H_∞ controller designed for tumor growth in the light of physiological aspects". In: *CINTI 2013 : Proceeding of the 14th IEEE International Symposium on Computational Intelligence and Informatics*. Ed. by Anikó Szakál. Budapest: IEEE Hungary Section, 2013, pp. 19–24.

[489] J Klespitz and L Kovács. "Identification and control of peristaltic pumps in hemodialysis machines". In: *CINTI 2013 : Proceeding of the 14th IEEE International Symposium on Computational Intelligence and Informatics*. Ed. by Anikó Szakál. Budapest: IEEE Hungary Section, 2013, pp. 83–87.

[490] A Szeles, D A Drexler, J Sápi, I Harmati, Z Sápi, and L Kovács. "Model-based Angiogenic Inhibition of Tumor Growth using Feedback Linearization". In: *Proceedings of the 52nd IEEE Conference on Decision and Control*. Ed. by Parisini T and Tempo R. Piscataway (NJ): IEEE, 2013, pp. 2054–2059.

[491] Tamas Ferenci and Levente Kovacs. "Effects of paediatric obesity: a multivariate analysis of laboratory parameters". In: *Mathematical and Statistical Methods in Food Science and Technology*. Ed. by Daniel Granato and Gastón Ares. Chichester: John Wiley and Sons, Inc., 2014, pp. 303–320.

[492] Árpád Takács, Sándor Jordán, Radu-Emil Precup, Levente Kovács, József Tar, Imre Rudas, and Tamás Haidegger. "Review of Tool–Tissue Interaction Models for Robotic Surgery Applications". In: *Proceedings of the IEEE 12th International Symposium on Applied Machine Intelligence and Informatics (SAMI 2014)*. Ed. by Liberios Vokorokos, Ladislav Hluchý, and János Fodor. Budapest: IEEE Hungary Section, 2014, pp. 339–344.

[493] J Klespitz and L Kovács. "Peristaltic pumps – a review on working and control possibilities". In: *Proceedings of the IEEE 12th International Symposium on Applied Machine Intelligence and Informatics (SAMI 2014)*. Ed. by Liberios Vokorokos, Ladislav Hluchý, and János Fodor. Budapest: IEEE Hungary Section, 2014, pp. 191–194.

[494] L Kovács, M Kozlovszky, P Szalay, Gy Eigner, I P Sas, Zs Almássy, E Felszeghy, Gy Kocsis, J Fövényi, A Körner, L Kautzky, H Soós, A Orbán, T Niederland, A Juhászné Tuifel, T Tóthné Sebestyén, M Hocsi, A Soós, A Török, and L Barkai. "Newest results of the Hungarian artificial pancreas project". In: *7th International Conference on Advanced Technologies and Treatment for Diabetes*. Ed. by Moshe Phillip and Tadej Battelino. Wien: Mary Ann Liebert, 2014, A–149.

[495] Levente Kovács, Annamária Szeles, Johanna Sápi, Dániel A Drexler, Imre Rudas, István Harmati, and Zoltán Sápi. "Model-based angiogenic inhibition of tumor growth using modern robust control method". In: *COMPUTER METHODS AND PROGRAMS IN BIOMEDICINE* 114 (2014), pp. 98–110.

[496] M Kozlovszky, D Mészáros, G Bognár, B A Jókay, N Pálos, and L Kovács. "Protocol based intervention plan analyser". In: 2014, pp. 1–4.

[497] Levente Kovács. "Model-Based Disease Treatment. A Control Engineering Approach". In: *Advances in Soft Computing, Intelligent Robotics and Control*. Ed. by János Fodor and Robert Fullér. Heidelberg; London; New York: Springer, 2014, pp. 55–68.

[498] Annamária Szeles, Dániel András Drexler, Johanna Sápi, István Harmati, and Levente Kovács. "Model-based Angiogenic Inhibition of Tumor Growth using Adaptive Fuzzy Techniques". In: *PERIODICA POLYTECHNICA-ELECTRICAL ENGINEERING AND COMPUTER SCIENCE* 58.1 (2014), pp. 29–36.

[499] L Kovács, M Kozlovszky, P Szalay, Gy Eigner, P Sas, T Ferenci, Zs Almássy, E Felszeghy, G Kocsis, J Fövényi, K Wudi, A Körner, L Kautzky, H Soós, A Orbán, T Niederland, A Juhászné Tuifel, T Tóthné Sebestyén, M Hocsi, A Soós, A Török, and L Barkai. "Magyar mesterséges hasnyálmirigy projekt. Eredmények és távlatok". In: *DIABETOLOGIA HUNGARICA* XXII (2014), pp. 73–76.

[500] K Lukács, T Ferenci, L Kovács, M Balogh, K H Nagy, Zs Karádi, H Soós, L Madácsy, and N Hosszúfalusi. "Glykaemiás variabilitás és anyagcsere-kontroll vizsgálatok 1-es típusú diabetesben". In: *DIABETOLOGIA HUNGARICA* XXII (2014), pp. 101–102.

[501] P Gyuk, I Szabó, I Vassányi, I Kósa, and L Kovács. "Modell alapú diabetes életmód-támogatás". In: *DIABETOLOGIA HUNGARICA* XXII (2014), pp. 41–43.

[502] P Gyuk, I Szabó, I Vassányi, I Kósa, L Kovács, and L Stoicu-Tivadar et al. "Combined Model for Diabetes Lifestyle Support". In: *European Federation for Medical Informatics (EFMI) Special Topic Conference*. Budapest: IOS Press, 2014, pp. 77–81.

[503] Gy Eigner, P I Sas, and L Kovács. "Continuous glucose monitoring systems in the service of artificial pancreas". In: *9th IEEE International Symposium on Applied Computational Intelligence and Informatics ; SACI 2014*. Ed. by Anikó Szakál. Timisoara: IEEE Hungary Section, 2014, pp. 117–122.

[504] L Kovács, J Sápi, Gy Eigner, T Ferenci, P Szalay, J Klespitz, B Kurtán, M Kozlovszky, D A Drexler, P Pausits, I Harmati, Z Sápi, and I Rudas. "Model-based healthcare applications at Obuda University". In: *9th IEEE International Symposium on Applied Computational Intelligence and Informatics ; SACI 2014*. Ed. by Anikó Szakál. Timisoara: IEEE Hungary Section, 2014, pp. 183–187.

[505] Sápi Johanna, Drexler Dániel, Harmati István, Sápi Zoltán, and Kovács Levente. "Linear state-feedback control synthesis of tumor growth control in antiangiogenic therapy". In: *IEEE 10th Jubilee International Symposium on Applied Machine Intelligence and Informatics, SAMI 2012: Proceedings*. Ed. by IEEE. Budapest: IEEE Hungary Section, 2012, pp. 143–148.

[506] Benyó Balázs, Kovács Levente, Illyés Attila, Havas Attila, Szabó Némedi Noémi, and J Geoffrey Chase. "INTENZÍV ÁPOLÁS SORÁN HATÉKONYAN ALKALMAZHATÓ PROTOKOLLOK A VÉRCUKORSZINT SZABÁLYOZÁSÁRA". In: *ANESZTEZIOLÓGIA ÉS INTENZÍV TERÁPIA* 42 (Suppl. 1 2012), p. 11.

[507] Illyés Attila, Havas Attila, Szabó Némedi Noémi, Benyó Balázs, Kovács Levente, and J Geoffrey Chase. "SPRINT, STAR: KÉT HATÉKONY KEZELÉSI PROTOKOLL AZ INTENZÍV OSZTÁLYON KEZELT BETEGEK VÉRCUKORSZINTJÉNEK NORMOGLIKÉMIÁS TARTOMÁNYBAN TARTÁSÁHOZ". In: *ANESZTEZIOLÓGIA ÉS INTENZÍV TERÁPIA* 42 (Suppl. 1 2012), p. 25.

[508] Szalay Péter and Kovács Levente. "Applicability of Asymptotic Tracking in Case of Type 1 Diabetes". In: *Applied Computational Intelligence in Engineering and Information Technology: Revised and Selected Papers from the 6th IEEE International Symposium on Applied Computational Intelligence and Informatics SACI 2011*. Ed. by Radu-Emil Precup, Stefan Preitl, Szilveszter Kovács, and Emil M Petriu. Berlin; Heidelberg: Springer-Verlag, 2012, pp. 249–260.

[509] Benyó Balázs, Kovács Levente, Illyés Attila, Havas Attila, Szabó Némedi Noémi, Sophie Penning, Thomas Desaive, Paul Massion, Aaron Le Compte, Cristopher Pretty, Geoffrey M. Shaw, Geoffrey J. Chase, and Katherine T. Moorhead. "Vércukor szabályozás intenzív ápolásra szoruló betegeknél: A SPRINT és a STAR protokolok". In: *DIABETOLOGIA HUNGARICA* XX (Suppl.1 2012), pp. 43–45.

[510] Illyés Attila, Havas Attila, Szabó Némedi Noémi, Benyó Balázs, Kovács Levente, Aaron Le Compte, Geoffrey M. Shaw, and Geoffrey J. Chase. "Initial ICU clinical results using SPRINT to guide insulin infusions in a Hungarian medical ICU". In: *JOURNAL OF DIABETES SCIENCE AND TECHNOLOGY* 6.2 (2012), A68–A69.

[511] Haidegger Tamás, Sirokai Beáta, Fenyvesi Gábor, Kovács Levente, Benyó Zoltán, and Benyó Balázs. “Repeatable Assessment Protocol for Electromagnetic Trackers”. In: *PROCEEDINGS OF SPIE - THE INTERNATIONAL SOCIETY FOR OPTICAL ENGINEERING* 8316 (2012).

[512] Haidegger Tamás, Benyó Balázs, and Kovács Levente. “Methods to extend the cognitive horizon for more effective telepresence”. In: 2012, pp. 1–8.

[513] Sirokai Beáta, Kiss Máté, Kovács Levente, Benyó Balázs, Benyó Zoltán, and Haidegger Tamás. “Best Practices in Electromagnetic Tracking System Assessment”. In: *II SCATh Joint Workshop on New Technologies for Computer/Robot Assisted Surgery*. Ed. by Holzapfel, Pierce, Sloten, and Sette. Madrid: Katholieke Universiteit Leuven, 2012, pp. 1–4.

[514] R -E Precup, T Haidegger, S Preitl, Z Benyó, A S Paul, and L Kovács. “Fuzzy Control Solution for Telesurgical Applications”. In: *APPLIED AND COMPUTATIONAL MATHEMATICS* 11.3 (2012), pp. 378–397.

[515] Tamas Haidegger, Levente Kovacs, Radu-Emil Precup, Balazs Benyo, Zoltan Benyo, and Stefan Preitl. “Simulation and control for telerobots in space medicine”. In: *ACTA ASTRONAUTICA* 81 (2012), pp. 390–402.

[516] Szalay Péter, Sas Péter István, Barkai László, and Kovács Levente. “Nonlinear analysis of Type 1 Diabetes Models by Differential Geometric Approach”. In: *Proceedings of 8th IFAC Symposium on Biological and Medical Systems*. Ed. by Balazs Benyo, David Feng, J Geoffrey Chase, Steen Andreassen, Ewart Carson, and Levente Kovacs. New York: Curran, 2012, pp. 55–60.

[517] Kovács Adalbert, Precup Radu-Emil, Paláncz Béla, and Kovács Levente, eds. *Modern numerical methods in engineering*. Timisoara: Editura Politehnica, 2012.

[518] Tar JK, Haidegger T, Kovács L, Kósi K, Botka B, and Rudas IJ. “Nonlinear Order-Reduced Adaptive Controller for a DC Motor Driven Electric Cart”. In: *18th International Conference on Intelligent Engineering Systems - INES 2014*. Ed. by Szakál A. Piscataway (NJ): Institute of Electrical and Electronics Engineers (IEEE), 2014, pp. 73–78.

[519] Kozlovszky M, Hegedus K, Windisch G, Kovács L, and Pintér G. “Image classification optimization of high resolution tissue images”. In: *LECTURE NOTES IN COMPUTER SCIENCE* 8353 (2014), pp. 532–539.

[520] A Szeles, D A Drexler, J Sápi, I Harmati, and L Kovács. “Study of Modern Control Methodologies Applied to Tumor Growth under Angiogenic Inhibition”. In: *Proceedings of the 19th IFAC World Congress, 2014*. Ed. by Boje E and Xia X. New York: IFAC, 2014, pp. 9271–9276.

[521] P Szalay, Gy Eigner, and L Kovács. “Linear Matrix Inequality-based Robust Controller design for Type-1 Diabetes Model”. In: *Proceedings of the 19th IFAC World Congress, 2014*. Ed. by Boje E and Xia X. New York: IFAC, 2014, pp. 9247–9252.

[522] J Klespitz, M Takács, and L Kovács. “Application of fuzzy logic in hemodialysis equipment”. In: *18th International Conference on Intelligent Engineering Systems - INES 2014*. Ed. by Szakál A. Piscataway (NJ): Institute of Electrical and Electronics Engineers (IEEE), 2014, pp. 169–173.

[523] T Ferenci and L Kovács. “Using Total Correlation to Discover Related Clusters of Clinical Chemistry Parameters”. In: *SISY 2014: IEEE 12th International Symposium on Intelligent Systems and Informatics*. Ed. by Anikó Szakál. Subotica: IEEE Hungary Section, 2014, pp. 49–54.

[524] L Szilágyi, G Dénesi, L Kovács, and S M Szilágyi. “Comparison of Various Improved-Partition Fuzzy c-Means Clustering Algorithms in Fast Color Reduction”. In: *SISY 2014: IEEE 12th International Symposium on Intelligent Systems and Informatics*. Ed. by Anikó Szakál. Subotica: IEEE Hungary Section, 2014, pp. 197–202.

[525] József Tar, Levente Kovács, Árpád Takács, Bence Takács, Péter Zentay, Tamás Haidegger, and Imre J Rudas. “Novel Design of a Model Reference Adaptive Controller for Soft Tissue Operations”. In: 2014.

[526] Jozsef Tar, I J Rudas, L Kovács, T Haidegger, and B Kurtán. “Observation-Based Data Driven Adaptive Control of an Electromechanical Device”. In: *2014 IEEE Multi-Conference on Systems and Control*. Ed. by Dominique Sauter. Piscataway (NJ): IEEE, 2014, pp. 1895–1900.

[527] M Kozlovszky, L Kovacs, and K Karoczkai. “Cardiovascular and diabetes focused remote patient monitoring”. In: *IFMBE Proceedings : 6th Latin American Congress on Biomedical Engineering, CLAIB 2014*. Ed. by Braidot A and Hadad A. New York: Springer-Verlag Wien, 2015, pp. 568–571.

[528] S Panunzi, A Borri, P Palumbo, L Kovács, and A De Gaetano. “Simulation of insulin regimen and glucose profiles in Type 1 Diabetic Patient”. In: *2014 IEEE International Conference on Systems, Man and Cybernetics (SMC)*. Ed. by W A Gruver. Piscataway (NJ): IEEE, 2014, pp. 2464–2469.

[529] P Szalay, L Szilágyi, Z Benyó, and L Kovács. “Sensor Drift Compensation Using Fuzzy Interference System and Sparse-Grid Quadrature Filter in Blood Glucose Control”. In: *LECTURE NOTES IN COMPUTER SCIENCE* 8835 (2014), pp. 445–453. ISSN: 0302-9743.

[530] L Szilágyi, L Kovács, and S M Szilágyi. “Synthetic Test Data Generation for Hierarchical Graph Clustering Methods”. In: *LECTURE NOTES IN COMPUTER SCIENCE* 8835 (2014), pp. 303–310.

[531] J Sápi, D A Drexler, Z Sápi, and L Kovács. “Identification of C38 colon adenocarcinoma growth under bevacizumab therapy and without therapy”. In: *CINTI 2014 - 15th IEEE International Symposium on Computational Intelligence and Informatics*. Ed. by IEEE. Budapest: IEEE Hungary Section, 2014, pp. 443–448.

[532] J Klespitz, M Takács, I Rudas, and L Kovács. “Adaptive soft computing methods for control of hemodialysis machines”. In: *iFuzzy2014 – 2014 International Conference on Fuzzy Theory and Its Applications*. Ed. by J H Chou, S J Lee, C W Tao, and L S L Wang. Kaohsiung: IEEE Systems, Man and Cybernetics Society, 2014, pp. 109–112.

[533] R E Precup, T Haidegger, and L Kovács. “Stable Hybrid Fuzzy Controller-based Architecture for Robotic Telesurgery Systems”. In: *INTERNATIONAL JOURNAL OF COMPUTATIONAL INTELLIGENCE AND PATTERN RECOGNITION* 1.1 (2014), pp. 61–76.

[534] T Ferenci, A Körner, and L Kovács. “The interrelationship of HbA1c and real-time continuous glucose monitoring in children with type 1 diabetes”. In: *DIABETES RESEARCH AND CLINICAL PRACTICE* 108.1 (2015), pp. 38–44.

[535] Gy Eigner, B Kurtán, I Rudas, C K Chui, and L Kovács. “Examination of a novel double diabetes model”. In: *SAMI 2015 • IEEE 13th International Symposium on Applied Machine Intelligence and Informatics*. Ed. by Anikó Szakál. Herlany: IEEE Hungary Section, 2015, pp. 41–46.

[536] M Kozlovszky, J Fodor, R Ősz, I Rudas, and L Kovács. “Multimodal remote biosignal acquisition and processing at Obuda University”. In: *Computer Aided Systems Theory - EUROCAST 2015: 15th International Conference, Las Palmas*

de Gran Canaria, Spain. Ed. by Roberto Moreno-Díaz, Franz Pichler, and Alexis Quesada-Arencibia. Las Palmas: Springer-Verlag, 2015, pp. 129–130.

[537] L Kovács, J Fodor, R Ősz, I Rudas, and M Kozlovszky. "Physiological Control Researches at Obuda University". In: *Computer Aided Systems Theory - EUROCAST 2015: 15th International Conference, Las Palmas de Gran Canaria, Spain*. Ed. by Roberto Moreno-Díaz, Franz Pichler, and Alexis Quesada-Arencibia. Las Palmas: Springer-Verlag, 2015, pp. 127–128.

[538] Gy Eigner and L Kovács. "Realization methods of continuous glucose monitoring systems". In: *BULETINUL STIINTIFIC AL UNIVERSITATII POLITEHNICA DIN TIMISOARA ROMANIA SERIA AUTOMATICA SI CALCULATORAE* 59.73 (2014), pp. 175–182.

[539] T Ferenci, A Körner, and L Kovács. "Association of autoantibody levels with the hazard of autoimmune comorbidities in children with type 1 diabetes". In: *First European Biomedical Engineering Conference for Young Investigators: ENCY 2015*. Ed. by Ákos Jobbágy. Singapore: Springer, 2015, pp. 110–113.

[540] L Kovács. "Modeling and Control of Physiological Systems". In: *First European Biomedical Engineering Conference for Young Investigators: ENCY 2015*. Ed. by Ákos Jobbágy. Singapore: Springer, 2015, pp. 7–10.

[541] E Kolossváry, T Ferenci, T Kováts, L Kovács, Z Járai, G Menyhei, and K Farkas. "Trends in major lower limb amputations related to peripheral arterial disease in Hungary. A nationwide study (2004-2012)". In: *EUROPEAN JOURNAL OF VASCULAR AND ENDOVASCULAR SURGERY* 50.1 (2015), pp. 78–85.

[542] Á Lehotsky, L Szilágyi, T Ferenci, L Kovács, R Pethes, G Wéber, and T Haidegger. "Quantitative impact of direct, personal feedback on hand hygiene technique". In: *JOURNAL OF HOSPITAL INFECTION* 91.1 (2015), pp. 81–84.

[543] J Klespitz, M Takács, I Rudas, and L Kovács. "Performance of soft computing controllers in hemodialysis machines". In: *INTERNATIONAL JOURNAL OF FUZZY SYSTEMS* 17.3 (2015), pp. 414–422.

[544] L Kovács, B Kurtán, Gy Eigner, I Rudas, and C K Chui. "Analyzing of a Novel Time Delay Diabetes Model". In: *ECC 2015 - 14th Annual European Control Conference*. Ed. by [S n]. Linz: European Control Association (EUCA), 2015, pp. 13–18.

[545] P Latafat, P Palumbo, P Pepe, L Kovács, S Panunzi, and A de Gaetano. “An LMI-Based Controller for the Glucose-Insulin System”. In: *ECC 2015 - 14th Annual European Control Conference*. Ed. by [S n]. Linz: European Control Association (EUCA), 2015, pp. 7–12.

[546] Gy Eigner, Jozsef Tar, and L Kovács. “Adaptive Control Solution for T1DM Control”. In: *10th Jubilee IEEE International Symposium on Applied Computational Intelligence and Informatics (SACI 2015)*. Ed. by Szakál Anikó. Budapest: Óbudai Egyetem, 2015, pp. 215–220.

[547] L Kovács, T Ferenci, J Sápi, Gy Eigner, J Klespitz, P Szalay, M Kozlovszky, and I Rudas. “Physiological Modeling and Control at Obuda University”. In: *10th Jubilee IEEE International Symposium on Applied Computational Intelligence and Informatics (SACI 2015)*. Ed. by Szakál Anikó. Budapest: Óbudai Egyetem, 2015, pp. 21–25.

[548] Z Garaguly, M Kozlovszky, and L Kovács. “High resolution digital holographic microscope and image reconstruction”. In: *19th IEEE International Conference on Intelligent Engineering Systems: INES 2015*. Ed. by Szakál A. Bratislava: IEEE, 2015, pp. 179–184.

[549] C M Ionescu, T F Mendonca, and L Kovacs. “Critically Safe General Anaesthesia in Closed Loop: Availability and Challenges”. In: *9th IFAC Symposium on Biological and Medical Systems (IFAC BMS 2015)*. Ed. by Berno Misgeld, Thomas Schauer, and Olaf Simanski. Berlin: Elsevier; IFAC, 2015, pp. 551–556.

[550] Sápi Johanna, Drexler Dániel András, and Kovács Levente. “Comparison of mathematical tumor growth models”. In: *SISY 2015 : IEEE 13th nternational Symposium on Intelligent Systems and Informatics: Proceedings*. Ed. by Anikó Szakál. New York: IEEE, 2015, pp. 323–328.

[551] Kiss Gábor, Cseri Orsolya Eszter, Altsach Ádám, Bándi I I, Kovács L, and Kozlovszky M. “High resolution digital tissue image processing using texture image databases”. In: *Technological Innovation for Cloud-Based Engineering Systems. 6th IFIP WG 5.5/SOCOLNET Doctoral Conference on Computing, Electrical and Industrial Systems, DoCEIS 2015, Costa de Caparica, Portugal, April 13-15, 2015, Proceedings*. Ed. by Camarinha-Matos L M, Baldissera T A, Di Orio G, and Marques F. Cham (Németország): Springer, 2015, pp. 239–247.

[552] Johanna Sápi, Tamás Ferenci, Dániel András Drexler, and Levente Kovács. “Tumor model identification and statistical analysis”. In: *IEEE International Conference*

on Systems, Man, and Cybernetics 2015: IEEE SMC 2015. Ed. by Kwong S and Yeung D. Hong Kong: IEEE, 2015, pp. 2481–2486.

[553] Johanna Sápi, Levente Kovács, Dániel András Drexler, Pál Kocsis, Dávid Gajári, and Zoltán Sápi. "Tumor Volume Estimation and Quasi- Continuous Administration for Most Effective Bevacizumab Therapy". In: *PLOS ONE* 10.11 (2015).

[554] Gy Eigner, P Horváth, Jozsef Tar, I Rudas, and L Kovács. "Application of Robust Fixed Point control in case of T1DM". In: *IEEE International Conference on Systems, Man, and Cybernetics 2015: IEEE SMC 2015*. Ed. by Kwong S and Yeung D. Hong Kong: IEEE, 2016, pp. 2459–2464.

[555] Z Garaguly, M Kozlovszky, and L Kovács. "Nagyfelbontású holografikus mikroszkóp és képrekonstrukció". In: *Új alapokon az egészségügyi informatika: A XXVIII. Neumann Kollokvium konferencia-kiadványa*. Ed. by Kósa István and Vassányi István. Veszprém: Neumann János Számítógép-tudományi Társaság (NJSZT), 2015, pp. 38–42.

[556] T Haidegger, V Varga, A Lehotsky, P Rona, R Pethes, P Szerémy, L. Szilágyi, T Ferenci, and L Kovács. "Information Technology Tools Employed in Infection Control". In: *16th IEEE International Symposium on Computational Intelligence and Informatics, CINTI 2015*. Ed. by Szakál Anikó. Budapest: IEEE, 2015, pp. 339–344.

[557] J Klespitz, M Biró, and L Kovács. "Aspects of improvement of software development lifecycle management". In: *16th IEEE International Symposium on Computational Intelligence and Informatics, CINTI 2015*. Ed. by Szakál Anikó. Budapest: IEEE, 2015, pp. 323–327.

[558] Gy Eigner, Jozsef Tar, and L Kovács. "Novel Error Interpretation in case of Linear Parameter Varying Systems". In: *16th IEEE International Symposium on Computational Intelligence and Informatics, CINTI 2015*. Ed. by Szakál Anikó. Budapest: IEEE, 2015, pp. 243–248.

[559] L Kovács and P Szalay. "Uncertainties and Modelling Errors of Type 1 Diabetes Models". In: *Prediction Methods for Blood Glucose Concentration*. Ed. by H Kirchsteiger, J B Jorgensen, E Renard, and L del Re. Zürich: Springer International Publishing, 2016, pp. 211–225.

[560] Árpád Takács, Levente Kovács, Imre J Rudas, Radu-Emil Precup, and Tamás Haidegger. "Models for Force Control in Telesurgical Robot Systems". In: *ACTA POLYTECHNICA HUNGARICA* 12.8 (2015), pp. 95–114.

[561] Eigner Gy, Tar J K, Rudas I J, and Kovács L. “LPV-based quality interpretations on modeling and control of diabetes”. In: *ACTA POLYTECHNICA HUNGARICA* 13.1 (2016), pp. 171–190.

[562] Z Garaguly, M Kozlovszky, and L Kovács. “The optimization of medical X-ray images”. In: *SAMI 2016 : IEEE 14th International Symposium on Applied Machine Intelligence and Informatics*. Ed. by Szakál Anikó. New York: IEEE, 2016, pp. 147–152.

[563] Johanna Sápi, Dániel A Drexler, István Harmati, Zoltán Sápi, and Levente Kovács. “Qualitative analysis of tumor growth model under antiangiogenic therapy: choosing the effective operating point and design parameters for controller design”. In: *OPTIMAL CONTROL APPLICATIONS & METHODS* 37.5 (2016), pp. 848–866.

[564] Árpád Takács, György Eigner, Levente Kovács, Imre Rudas, and Tamás Haidegger. “Teacher’s Kit : Development, Usability and Communities of Modular Robotic Kits for Classroom Education”. In: *IEEE ROBOTICS & AUTOMATION MAGAZINE* 23.2 (2016), pp. 30–39.

[565] Kolossváry Endre, Ferenci Tamás, Kováts Tamás, Kovács Levente, Járai Zoltán, and Farkas Katalin. “Kritikus alsó végtagi iszkémiás események szezonalitása a teljes magyar népesség adatainak elemzésével”. In: *CARDIOLOGIA HUNGARICA* 46 (Supplementum F 2016), F90.

[566] I Rudas, Gy Eigner, and L Kovács. “SMC 2016 and SMC Junior 2016”. In: *IEEE SYSTEMS MAN AND CYBERNETICS MAGAZINE* 2.1 (2016), pp. 41–44.

[567] J Klespitz, M Biro, and L Kovacs. “Evaluation criteria for application life cycle management systems in practice”. In: *Proceedings of the11th IEEE International Symposium on Applied Computational Intelligence and Informatics SACI 2016*. Ed. by Szakál Anikó. Budapest: IEEE, 2016, pp. 469–472.

[568] Miklós Biró, József Klespitz, Johannes Gmeiner, Christa Illibauer, and Levente Kovács. “Towards Automated Traceability Assessment through Augmented Lifecycle Space”. In: *COMMUNICATIONS IN COMPUTER AND INFORMATION SCIENCE* 633 (2016), pp. 94–105.

[569] J Klespitz, M Biró, and L Kovács. “Enhanced traceability and consistency with Augmented Lifecycle Space”. In: *20th IEEE Jubilee International Conference on Intelligent Engineering Systems: INES 2016*. Ed. by Szakál Anikó. Budapest: IEEE Hungary Section, 2016, pp. 207–212.

[570] György Eigner, Péter Pausits, and Levente Kovács. “A novel completed LPV controller and observer scheme in order to control nonlinear compartmental systems”. In: *IEEE 14th International Symposium on Intelligent Systems and Informatics: SISY 2016*. Ed. by Szakál A. Budapest: IEEE Hungary Section, 2016, pp. 85–92.

[571] József Klespitz, Miklós Bíró, and Levente Kovács. “Cross-Tool Interoperability in Heterogeneous Application Lifecycle Management Systems”. In: *New Trends in Software Methodologies, Tools and Techniques*. Ed. by Hamido Fujita and George Angelos Papadopoulos. Amsterdam: IOS Press, 2016, pp. 213–220.

[572] L Kovács, Gy Eigner, l Miclea, and I Stoian. “Clinical decision support systems for personalized healthcare”. In: *AQTR 2016 – International Conference on Automation, Quality and Testing, Robotics*. Ed. by I Stefan and O Ghiran. Cluj-Napoca: IEEE Computer Society, 2016, pp. 6–12.

[573] I R Birs, C Muresan, S Folea, O Prodan, L Kovács, l Miclea, and I Stoian. “Vibration suppression with fractional-order PID controller”. In: *AQTR 2016 – International Conference on Automation, Quality and Testing, Robotics*. Ed. by I Stefan and O Ghiran. Cluj-Napoca: IEEE Computer Society, 2016, pp. 1–6.

[574] L Kovács. “Physiological control systems for high-quality interdisciplinary researches”. In: *Proceedings of the11th IEEE International Symposium on Applied Computational Intelligence and Informatics SACI 2016*. Ed. by Szakál Anikó. Budapest: IEEE, 2016, pp. 11–12.

[575] J Sápi, D A Drexler, and L Kovács. “Discrete time state feedback with setpoint control, actual state observer and load estimation for a tumor growth model”. In: *Proceedings of the11th IEEE International Symposium on Applied Computational Intelligence and Informatics SACI 2016*. Ed. by Szakál Anikó. Budapest: IEEE, 2016, pp. 111–118.

[576] Garaguly Zoltán, Kozlovszky Miklós, and Kovács Levente. “Holografikus képrekonstrukció alkalmazása folyadékvizsgálat során”. In: *Orvosi Informatika 2016. A XXIX. Neumann Kollokvium konferencia-kiadványa*. Ed. by Bari Ferenc and Almási László. Szeged: Neumann János Számítógép-tudományi Társaság (NJSZT), 2016, pp. 79–83.

[577] Z Garaguly, M Kozlovszky, and L Kovács. “Platform independent telepathology system for pathologists”. In: *17th IEEE International Symposium on Computational Intelligence and Informatics (CINTI 2016)*. Ed. by Szakál Anikó. Budapest: IEEE Hungary Section, 2016, pp. 135–138.

[578] Péter Szalay, Zoltán Benyó, and Levente Kovács. “Long-Term Prediction for T1DM Model During State-Feedback Control”. In: *12th IEEE International Conference on Control and Automation, ICCA 2016*. Ed. by IEEE. New York: IEEE, 2016, pp. 311–316.

[579] Levente Kovács. “Control engineering approaches at Obuda University for physiological problems: Plenary talk”. In: *20th IEEE Jubilee International Conference on Intelligent Engineering Systems: INES 2016*. Ed. by Szakál Anikó. Budapest: IEEE Hungary Section, 2016, pp. 19–20.

[580] Gy Eigner and L Kovács. “Novel complementary LPV controller and observer structure for nonlinear control”. In: *Proceedings of 7th IEEE Conference on Cognitive Infocommunications*. Ed. by Baranyi Péter. Budapest: IEEE Hungary Section, 2016.

[581] J Sápi, D A Drexler, and L Kovács. “Comparison of protocol based cancer therapies and discrete controller based treatments in the case of endostatin administration”. In: *2016 IEEE International Conference on Systems, Man, and Cybernetics Conference Proceedings: SMC 2016*. Ed. by Szakál A. Budapest: IEEE, 2016, pp. 3830–3835.

[582] T Ferenci, J Sápi, and L Kovács. “Modelling xenograft tumor growth under antiangiogenic inhibitation with mixed-effects models”. In: *2016 IEEE International Conference on Systems, Man, and Cybernetics Conference Proceedings: SMC 2016*. Ed. by Szakál A. Budapest: IEEE, 2016, pp. 3912–3917.

[583] R Pethes, T Ferenci, and L Kovács. “Infectious Hospital Agents: an individual-based simulation framework”. In: *2016 IEEE International Conference on Systems, Man, and Cybernetics Conference Proceedings: SMC 2016*. Ed. by Szakál A. Budapest: IEEE, 2016, pp. 3434–3439.

[584] D A Drexler and L Kovács. “Second-order and implicit methods in numerical integration improve tracking performance of the closed-loop inverse kinematics algorithm”. In: *2016 IEEE International Conference on Systems, Man, and Cybernetics Conference Proceedings: SMC 2016*. Ed. by Szakál A. Budapest: IEEE, 2016, pp. 3362–3367.

[585] D Copot, R de Keyser, L Kovács, C Ionescu, and A Aitouche. “Towards a cyber-medical system for drug assisting devices”. In: *13th European Workshop on Advanced Control and Diagnosis*. London: IOP Publishing, 2016, pp. 1–9.

[586] József Klespitz, Miklós Biró, and Levente Kovács. “Augmented lifecycle space for traceability and consistency enhancement”. In: *2016 IEEE International Conference on Systems, Man, and Cybernetics Conference Proceedings: SMC 2016*. Ed. by Szakál A. Budapest: IEEE, 2016, pp. 3973–3977.

[587] M Kozlovszky, L Kovács, K Batbayar, and Z Garaguly. “Automatic Protocol Based Intervention Plan Analysis in Healthcare”. In: *39th International Convention on Information and Communication Technology, Electronics and Microelectronics (MIPRO 2016)*. Ed. by Biljanovic P. Opatija: Croatian Society for Information, Communication Technology Electronics, and Microelectronics (MIPRO), 2016, pp. 269–273.

[588] P Piros, R Fleiner, and L Kovács. “Linked Data Generation for Courses and Events at Obuda University”. In: *SAMI 2017 : IEEE 15th International Symposium on Applied Machine Intelligence and Informatics*. Ed. by Szakál A. Budapest: IEEE, 2017, pp. 253–258.

[589] D A Drexler, J Sápi, and L Kovács. “A minimal model of tumor growth with angiogenic inhibition using bevacizumab”. In: *SAMI 2017 : IEEE 15th International Symposium on Applied Machine Intelligence and Informatics*. Ed. by Szakál A. Budapest: IEEE, 2017, pp. 185–190.

[590] Gy Eigner, I Böjthe, P Pausits, and L Kovács. “Investigation of the TP modeling possibilities of the Hovorka T1DM model”. In: *SAMI 2017 : IEEE 15th International Symposium on Applied Machine Intelligence and Informatics*. Ed. by Szakál A. Budapest: IEEE, 2017, pp. 259–264.

[591] Eigner György, Kovács Levente, and Némethy Krisztina. “The 2016 IEEE Systems, Man, and Cybernetics Conference: Conference Reports”. In: *IEEE SYSTEMS MAN AND CYBERNETICS MAGAZINE* 3.2 (2017), pp. 43–51.

[592] Tamás Ferenci, Johanna Sápi, and Levente Kovács. “Modelling Tumor Growth Under Angiogenesis Inhibition with Mixed-effects Models”. In: *ACTA POLYTECHNICA HUNGARICA* 14.1 (2017), pp. 221–234.

[593] Kovács Levente, Eigner György, and Rudas Imre. “Inzulinpumpa prototípus fejlesztése”. In: Erdélyi Magyar Műszaki Tudományos Társaság (EMT), 2017, pp. 235–238.

[594] Endre Kolossváry, Tamás Ferenci, Tamás Kováts, Levente Kovács, Zoltán Járai, and Katalin Farkas. “Mortality following lower limb vascular amputation”. In: 3 (2017).

[595] Sápi Johanna, Drexler Dániel András, and Kovács Levente. “Potential Benefits of Discrete-Time Controllerbased Treatments over Protocol-based Cancer Therapies”. In: *ACTA POLYTECHNICA HUNGARICA* 14.1 (2017), pp. 11–23.

[596] Pethes R, Ferenci T, and Kovács L. “Infectious hospital agents: A HAI spreading simulation framework”. In: *ACTA POLYTECHNICA HUNGARICA* 14.1 (2017), pp. 95–110.

[597] Levente Kovács. “Preface”. In: *ACTA POLYTECHNICA HUNGARICA* 14.1 (2017), pp. 7–9.

[598] Levente Kovács, Zoltán Sápi, Dániel A. Drexler, and Johanna Sápi. “Taming Cancer: Is it Possible?” In: (2017).

[599] Ferenci Tamás and Kovács Levente. “Predicting body fat percentage from anthropometric and laboratory measurements using artificial neural networks”. In: *APPLIED SOFT COMPUTING* & (2017).

[600] Miklós Biró, Felix Kossak, József Klespitz, and Levente Kovács. “Graceful Integration of Process Capability Improvement, Formal Modeling and Web Technology for Traceability”. In: *COMMUNICATIONS IN COMPUTER AND INFORMATION SCIENCE* 748 (2017), pp. 381–398.

[601] Ferenci Tamás and Kovács Levente. “Experiences with Using Bayes Factors for Regression Analysis in Biostatistical Setting”. In: *PERIODICA POLYTECHNICA-ELECTRICAL ENGINEERING AND COMPUTER SCIENCE* 61.3 (2017), pp. 246–252.

[602] Piros P, Fleiner R, Ferenci T, Andréka P, Fujita H, Ofner P, Kovács L, and Jánosi A. “An overview of myocardial infarction registries and results from the hungarian myocardial infarction registry”. In: *FRONTIERS IN ARTIFICIAL INTELLIGENCE AND APPLICATIONS* 297 (2017), pp. 312–320.

[603] György Eigner, Árpád Varga, Miklós Mezei, and Levente Kovács. “LPV-based control of nonlinear compartmental model with input uncertainty”. In: *IEEE 15th International Symposium on Intelligent Systems and Informatics : SISY 2017*. Ed. by Szakál Anikó. New York: IEEE, 2017, pp. 17–22.

[604] Zsolt Fézer and Levente Kovács. “The Economic Impact of Diabetes”. In: *IEEE 15th International Symposium on Intelligent Systems and Informatics : SISY 2017*. Ed. by Szakál Anikó. New York: IEEE, 2017, pp. 77–82.

[605] Árpád Varga, György Eigner, Levente Kovács, Imre Felde, and Miklós Mezei. "Overview of taxi database from viewpoint of usability for traffic model development: a case study for Budapest". In: *IEEE 15th International Symposium on Intelligent Systems and Informatics : SISY 2017*. Ed. by Szakál Anikó. New York: IEEE, 2017, pp. 105–110.

[606] György Eigner, Katalin Koppány, Péter Pausitsz, and Levente Kovács. "Nonlinear Identification of Glucose Absorption Related to Diabetes Mellitus". In: *INES 2017, IEEE 21st International Conference on Intelligent Engineering Systems: Proceedings*. Ed. by IEEE. Larnaca: IEEE, 2017, pp. 265–270.

[607] Zoltán Garaguly, Miklós Kozlovszky, and Levente Kovács. "Comparison of numerical image reconstruction methods in holography". In: *IEEE 30th Jubilee Neumann Colloquium : Neumann Colloquium 2017*. Ed. by Szakál Anikó. Budapest: Óbudai Egyetem, 2017, pp. 65–70.

[608] Dániel A Drexler, Johanna Sápi, Levente Kovács, W Xie, and C Hu. "Positive control of a minimal model of tumor growth with bevacizumab treatment". In: *12th IEEE Conference on Industrial Electronics and Applications (ICIEA 2017)*. Ed. by L Jiang. Singapore: IEEE Industrial Electronics Society, 2017, pp. 2081–2084.

[609] György Eigner, Dániel A Drexler, Levente Kovács, W Xie, and C Hu. "Control of nolinear physiological systems via LPV framework". In: *12th IEEE Conference on Industrial Electronics and Applications (ICIEA 2017)*. Ed. by L Jiang. Singapore: IEEE Industrial Electronics Society, 2017, pp. 2085–2090.

[610] Daniel A Drexler, Johanna Sapi, and Levente Kovacs. "Positive nonlinear control of tumor growth using angiogenic inhibition". In: *Preprints of the 20th World Congress The International Federation of Automatic Control: 20th IFAC World Congress*. Ed. by IFAC. Toulouse: IFAC, 2017, pp. 15633–15638.

[611] Daniel A Drexler, Johanna Sapi, and Levente Kovacs. "Optimal discrete time control of antiangiogenic tumor therapy". In: *Preprints of the 20th World Congress The International Federation of Automatic Control: 20th IFAC World Congress*. Ed. by IFAC. Toulouse: IFAC, 2017, pp. 14046–14051.

[612] Dávid Csercsik, Johanna Sápi, and Levente Kovács. "A bicompartmental dynamic tumor growth model". In: *Preprints of the 20th World Congress The International Federation of Automatic Control: 20th IFAC World Congress*. Ed. by IFAC. Toulouse: IFAC, 2017, pp. 12727–12732.

[613] Kovács Levente, Sima Dezső, and Molnár András. “Mesterképzés másként: duális angol mérnökinformatikus MSc képzés az Óbudai Egyetemen”. In: *Informatika a felsőoktatásban 2017 konferencia kiadványa*. Ed. by Aradi Bernadett, Bujdosó Gyöngyi, Horváth Géza, and Szokol Patrícia. Debrecen: Debreceni Egyetem Informatikai Kar, 2017, pp. 181–182.

[614] Levente Kovács. “Cyber-Medical Systems: Challenges and Possibilities”. In: *IEEE 15th International Symposium on Intelligent Systems and Informatics : SISY 2017*. Ed. by Szakál Anikó. New York: IEEE, 2017, pp. 15–16.

[615] György Eigner, Gábor Szögi, Péter Pausits, Imre Rudas, and Levente Kovács. “Nonlinear identification of a tumor growth model for validating cancer treatments”. In: *2017 IEEE International Conference on Systems, Man and Cybernetics*. Ed. by Li Deng. New York: IEEE Systems, Man and Cybernetics Society, 2017, pp. 3159–3163.

[616] Levente Kovács. “Cyber-Medical Systems: the Digitalized Healthcare Approach and Its Trends”. In: 2017, pp. 1–2.

[617] Kovács Levente, Eigner György, Barkai László, Barkai László, Kempler Péter, and Várkonyi Tamás. “Closing the loop 2.0 – A mesterséges hasnyálmirigy szabályozásának legújabb eredményei”. In: 2017, pp. 13–14.

[618] Z Garaguly, M Kozlovszky, and L Kovács. “The application of holographic image reconstruction in the examination of liquids”. In: *SAMI 2018: IEEE 16th World Symposium on Applied Machine Intelligence and Informatics : Dedicated to the Memory of Pioneer of Robotics Antal (Tony) K. Bejczy : proceedings*. Ed. by Anikó Szakál and Iveta Zamecnikova. Seattle (WA): IEEE, 2018, pp. 125–130.

[619] József Klespitz, Miklós Bíró, and Levente Kovács. “Demonstration of Augmented Lifecycle Space in Heterogeneous Environment”. In: *SAMI 2018: IEEE 16th World Symposium on Applied Machine Intelligence and Informatics : Dedicated to the Memory of Pioneer of Robotics Antal (Tony) K. Bejczy : proceedings*. Ed. by Anikó Szakál and Iveta Zamecnikova. Seattle (WA): IEEE, 2018, pp. 167–172.

[620] Kovács Levente. “Merre tovább ...? II.” In: (XXII. Dunántúli Diabetes Hétvége 2018). Műhelyszekció - Inzulinpumpa munkacsoport, p. 1.

[621] Kovács Levente. “Mérnökinformatikus képzés új megközelítésben: Ipar 4.0”. In: (Legyél Te is Informatikus! - Informatikai Oktatási Konferencia 2018 2018). Informatikai felsőoktatás szekció.

[622] Hamza Khan, József K Tar, Imre Rudas, Levente Kovács, and György Eigner. "Receding Horizon Control of Type 1 Diabetes Mellitus by Using Nonlinear Programming". In: *COMPLEXITY* 2018 (2018).

[623] Kinan Moranix, György Eigner, Tamás Ferenci, Levente Kovács, and Seref Naci Engin. "Prediction of the Survival of Patients with Cardiac Failure by using Soft Computing Techniques". In: *IEEE 12th International Symposium on Applied Computational Intelligence and Informatics (SACI 2018)*. Ed. by Szakál Anikó. Temesvár: IEEE Hungary Section; IEEE Romania Section, 2018, pp. 201–206.

[624] József Klespitz and Levente Kovács. "Multivariable control structures of hemodialysis machines for patient fluid balance maintenance". In: *IEEE 12th International Symposium on Applied Computational Intelligence and Informatics (SACI 2018)*. Ed. by Szakál Anikó. Temesvár: IEEE Hungary Section; IEEE Romania Section, 2018, pp. 415–418.

Own Publications Pertaining to Theses

[56] Bence Czakó, Johanna Sápi, and Levente Kovács. "Model-based Optimal Control Method for Cancer Treatment Using Model Predictive Control and Robust Fixed Point Method". In: *INES 2017, IEEE 21st International Conference on Intelligent Engineering Systems: Proceedings*. Ed. by IEEE. Larnaca: IEEE, 2017, pp. 271–276.

[138] L. Kovács, Gy. Eigner, J.K. Tar, and I. Rudas. "Robust Fixed Point Transformation based Proportional-Derivative Control of Angiogenic Tumor Growth". In: *3rd IFAC Conference on Advances in Proportional- Integral-Derivative Control*. bibtex*[eventdate=2018-05-09/2018-05-11;venue=Ghent, Belgium]. IFAC, 2018, pp. 894–899.

[431] Kovács L, Szalay P, Sas PI, Benyó B, Benyó Z, Almássy Zs, Felszeghy E, Kocsis Gy, Fövényi J, Wudi K, Madarász E, Kerényi Zs, Körner A, Kautzky L, Grósz A, Soós H, Orbán A, Soós A, Török A, and Barkai L. "Closing the Loop – Mesterséges hasnyálmirigy szabályozási algoritmusának in silico validációja 1-es típusú magyar diabetesesek adatain". In: *DIABETOLOGIA HUNGARICA* 20.1 (2012), 98A.

[432] "Validation results of a Hungarian artificial pancreas algorithm". In: ed. by M Phillip and T Battelino. 2012, p. 1.

[433] Levente Kovács, Csaba Maszlag, Miklós Mezei, and György Eigner. "Robust Nonlinear Model Predictive Control of Diabetes Mellitus". In: *SAMI 2017 : IEEE 15th International Symposium on Applied Machine Intelligence and Informatics*. Ed. by Szakál A. Budapest: IEEE, 2017, pp. 55–60.

[434] L Kovács and Gy Eigner. "System Engineering Approach of Diabetes Treatment". In: *International Journal of Diabetes & Clinical Diagnosis* 3.116 (2016), pp. 1–6.

[435] P Szalay, Gy Eigner, Z Benyó, I Rudas, and L Kovács. "Comparison of sigma-point filters for state estimation of diabetes models". In: *2014 IEEE International Conference on Systems, Man and Cybernetics (SMC)*. Ed. by W A Gruver. Piscataway (NJ): IEEE, 2014, pp. 2476–2481.

[436] Kovács L and Szalay P. "H_∞ robust control of a T1DM model". In: *Proceedings of 8th IFAC Symposium on Biological and Medical Systems*. Ed. by Balazs Benyo, David Feng, J Geoffrey Chase, Steen Andreassen, Ewart Carson, and Levente Kovacs. New York: Curran, 2012, pp. 61–66.

[437] L. Kovács. "A robust fixed point transformation-based approach for type 1 diabetes control". In: *Nonlinear Dynamics* 89.4 (2017). bibtex*[publisher=Springer], pp. 2481–2493.

[438] Hamza Khan, József K Tar, Imre J Rudas, György Eigner, and Kovács Levente. "Adaptive Model Predictive Control Based on Fixed Point Iteration". In: *WSEAS TRANSACTIONS ON SYSTEMS AND CONTROL* 12 (2017), pp. 347–354.

[439] Gy Eigner and L Kovács. "Robust Fixed Point Transformation-based control of Type 1 Diabetes Mellitus". In: *Proceedings of 7th IEEE Conference on Cognitive Infocommunications*. Ed. by Baranyi Péter. Budapest: IEEE Hungary Section, 2016.

[440] Jozsef Tar, L Kovács, Á Takács, B Takács, P Zentay, T Haidegger, and I J Rudas. "Novel Design of a Model Reference Adaptive Controller for Soft Tissue Operations". In: *2014 IEEE International Conference on Systems, Man and Cybernetics (SMC)*. Ed. by W A Gruver. Piscataway (NJ): IEEE, 2014, pp. 2446–2451.

[441] Jozsef Tar, T A Várkonyi, L Kovács, I J Rudas, T Haidegger, K Lynch, and L Parker. "Robust Fixed Point Transformation Based Design for Model Reference Adaptive Control of a Modified TORA System". In: *IROS 2014 – 2014 IEEE/RSJ International Conference on Intelligent Robots and Systems*. Piscataway (NJ): Institute of Electrical and Electronics Engineers (IEEE), 2014, pp. 123–128.

[442] L. Kovács and Gy. Eigner. “Tensor Product Model Transformation based Parallel Distributed Control of Tumor Growth”. In: *ACTA Pol Hung* 15.3 (2018), pp. 101–123.

[443] Gy. Eigner and L. Kovács. “Tumor Growth Control by TP-LPV-LMI based Controller”. In: *IEEE International Conference on Systems, Man, and Cybernetics 2018: IEEE SMC 2018*. Accepted for publication bibtex*[eventdate=2018-10-07/2018-10-10;venue=Miyazaki, Japan]. IEEE SMC, 2018.

[444] Kovács Levente, Eigner György, and Barkai László. “Tensor Product-based Robust Control of Diabetes”. In: *DIABETES TECHNOLOGY AND THERAPEUTICS* 20.1 (2018), A–57.

[445] Dávid Csercsik, Johanna Sápi, Gönczy Tamás, and Levente Kovács. “Bi-compartmental modelling of tumor and supporting vasculature growth dynamics for cancer treatment optimization purpose”. In: *2017 IEEE 56th Annual Conference on Decision and Control, CDC 2017*. Ed. by IEEE. Piscataway (NJ): IEEE, 2017, pp. 4698–4702.

[446] György Eigner, Dániel Drexler, and Levente Kovács. “Control of Nonlinear Physiological Systems via LPV Framework”. In: (Conference Proceedings of the 12th IEEE Conference on Industrial Electronics and Applications 2017). Siem Reap, Kambodzsa, pp. 1–6.

[447] Dániel András Drexler, Johanna Sápi, and Levente Kovács. “Modeling of Tumor Growth Incorporating the Effects of Necrosis and the Effect of Bevacizumab”. In: *COMPLEXITY* 2017 (2017).

[448] György Eigner, Imre Rudas, Anikó Szakál, and Levente Kovács. “Tensor Product based modeling of Tumor Growth”. In: *2017 IEEE International Conference on Systems, Man and Cybernetics*. Ed. by Li Deng. New York: IEEE Systems, Man and Cybernetics Society, 2017, pp. 900–905.

[449] György Eigner and Levente Kovács. “Linear Matrix Inequality based Control of Tumor Growth”. In: *2017 IEEE International Conference on Systems, Man and Cybernetics*. Ed. by Li Deng. New York: IEEE Systems, Man and Cybernetics Society, 2017, pp. 1734–1739.

[450] Levente Kovács. “Linear parameter varying (LPV) based robust control of type-I diabetes driven for real patient data”. In: *KNOWLEDGE-BASED SYSTEMS* 122 (2017), pp. 199–213.

[451] Gy Eigner, P Pausits, and L Kovács. “Control of T1DM via Tensor Product-based framework”. In: *17th IEEE International Symposium on Computational Intelligence and Informatics (CINTI 2016)*. Ed. by Szakál Anikó. Budapest: IEEE Hungary Section, 2016, pp. 55–60.

[452] L Kovács and Gy Eigner. “Convex Polytopic Modeling of Diabetes Mellitus: A Tensor Product based approach”. In: *2016 IEEE International Conference on Systems, Man, and Cybernetics Conference Proceedings: SMC 2016*. Ed. by Szakál A. Budapest: IEEE, 2016, pp. 3393–3398.

[453] Gy Eigner, I Rudas, and L Kovács. “Investigation of the TP-based modeling possibility of a nonlinear ICU diabetes model”. In: *2016 IEEE International Conference on Systems, Man, and Cybernetics Conference Proceedings: SMC 2016*. Ed. by Szakál A. Budapest: IEEE, 2016, pp. 3405–3410.

[454] Gy Eigner and L Kovács. “Modeling of Diabetes Mellitus via Tensor Product framework”. In: *Proceedings of 7th IEEE Conference on Cognitive Infocommunications*. Ed. by Baranyi Péter. Budapest: IEEE Hungary Section, 2016.

[455] J Klespitz, I Rudas, and L Kovács. “LMI-based feedback regulator design via TP transformation for fluid volume control in blood purification therapies”. In: *IEEE International Conference on Systems, Man, and Cybernetics 2015: IEEE SMC 2015*. Ed. by Kwong S and Yeung D. Hong Kong: IEEE, 2015, pp. 2615–2619.

Own Publications Not Pertaining to Theses

[456] P. Sas, L. Lukács, A. Kovács, E. Borbléy, and L. Kovács. “Monitoring drivers’ vital parameters”. In: *4th IEEE International Symposium on Logistics and Industrial Informatics: LINDI 2012*. Ed. by Anikó Szakál. Smolenice: IEEE, 2012, pp. 255–259.

[457] P. Patrícia, L. Vajda, and L. Kovács. “Developing a decision support system to determine carbohydrate intake of diabetic patients”. In: *IEEE 10th Jubilee International Symposium on Applied Machine Intelligence and Informatics, SAMI 2012: Proceedings*. Ed. by IEEE. Budapest: IEEE Hungary Section, 2012, pp. 427–430.

[458] Drexler Dániel András, Sápi Johanna, Szeles Annamária, Harmati István, Kovács Adalbert, and Kovács Levente. “Flat control of tumor growth with angiogenic inhibition”. In: *Proceedings of the 7th IEEE International Symposium on Applied*

Computational Intelligence and Informatics (SACI), 2012. Ed. by Szakál Anikó. New York: IEEE, 2012, pp. 179–183.

[459] Kovács Levente, Szalay Péter, Ferenci Tamás, Sápi Johanna, Sas Péter István, Drexler Dániel, Harmati István, Benyó Balázs, and Kovács Adalbert. "Model-based control algorithms for optimal therapy of high-impact public health diseases". In: *Proceedings of the IEEE 16th International Conference on Intelligent Engineering Systems 2012*. Ed. by Szakál Anikó. Lisszabon: Institute of Electrical and Electronics Engineers (IEEE), 2012, pp. 531–536.

[460] Kovács Levente, Ferenci Tamás, Sápi Johanna, and Szalay Péter. "Népegészségügyi problémák számítógépes modellezése". In: *IME: INTERDISZCIPLINÁRIS MAGYAR EGÉSZSÉGÜGY / INFORMATIKA ÉS MENEDZSMENT AZ EGÉSZSÉGÜGYBEN* XI.8 (2012), pp. 49–55. ISSN: 1588-6387.

[461] Kovács Levente, Szalay Péter, Sas Péter István, Eigner György, Almássy Zsuzsa, Felszeghy Enikő, Soós Hajnalka, Orbán Andrea, Körner Anna, Niederland Tamás, Juhászné Tuifel Andrea, Tóthné Sebestyén Tímea, Soós Andrea, Török András, and Barkai László. "Magyar mesterséges hasnyálmirigy algoritmusának előzetes modell-független eredményei". In: ed. by Felszeghy Enikő. 2012, pp. 21–22.

[462] L Kovács, T Haidegger, and I Rudas. "Surgery from a Distance—Application of Intelligent Control for Telemedicine". In: *Proceedings of the IEEE 11th International Symposium on Applied Machine Intelligence and Informatics (SAMI 2013)*. Ed. by Anikó Szakál. Budapest: IEEE Hungary Section, 2013, pp. 125–129.

[463] L Kovács. "Modern Robust Control in Patophysiology: From Theory to Application: (Plenary Talk)". In: *Proceedings of the IEEE 11th International Symposium on Applied Machine Intelligence and Informatics (SAMI 2013)*. Ed. by Anikó Szakál. Budapest: IEEE Hungary Section, 2013, pp. 13–14.

[464] L Kovács, P Szalay, P I Sas, Gy Eigner, Zs Almássy, E Felszeghy, Gy Kocsis, J Fövényi, A Körner, L Kautzky, H Soós, A Orbán, T Niederland, A Juhászné Tuifel, T Tóthné Sebestyén, A Soós, A Török, and L Barkai. "Preliminary model-free results of a Hungarian robust artificial pancreas algorithm: Abstracts of 6th International Conference on Advanced Technologies & Treatment for Diabetes, Paris, France". In: *DIABETES TECHNOLOGY AND THERAPEUTICS* 15 (Suppl1 2013), A–96.

[465] D A Drexler, J Sápi, A Szeles, I Harmati, and L Kovács. "Comparison of Path Tracking Flat Control and Working Point Linearization Based Set Point Control of Tumor Growth with Angiogenic Inhibition". In: *BULETINUL STIINTIFIC*

AL UNIVERSITATII POLITEHNICA DIN TIMISOARA ROMANIA SERIA AUTOMATICA SI CALCULATORAE 57 (71).2 (2012), pp. 113–120.

[466] T Ferenci, B Benyó, L Kovács, L Fisk, G M Shaw, and G J Chase. "Daily Evolution of Insulin Sensitivity Variability with Respect to Diagnosis in the Critically Ill". In: *PLOS ONE* 8.2 (2013).

[467] Laura Kovács, Béla Paláncz, and Levente Kovács. "Solving Robust Glucose-Insulin Control by Dixon Resultant Computations". In: *Symbolic and Numeric Algorithms for Scientific Computing (SYNASC), 2012 14th International Symposium on*. Ed. by Andrei Voronkov, Viorel Negru, Tetsuo Ida, Tudor Jebelean, Dana Petcu, Stephen Watt, and Daniela Zaharie. Seattle (WA): IEEE, 2012, pp. 53–61.

[468] Ferenci Tamás, Kovács Levente, Benyó Balázs, and Kovács Adalbert. "Using Support Vector Machines to Recognize Changes Characteristic to Obesity in Laboratory Results". In: *Proceedings of the 5th European Conference of the International Federation for Medical and Biological Engineering*. Ed. by Jobbágy Á. Berlin; Heidelberg: Springer Verlag, 2012, pp. 215–218.

[469] Ferenci Tamás, Kovács Levente, Benyó Balázs, Aaron Le Compte, Geoffrey M. Shaw, and Geoffrey J. Chase. "Effect of Diagnosis on Variability of ICU Patients in Insulin Sensitivity". In: *Proceedings of 8th IFAC Symposium on Biological and Medical Systems*. Ed. by Balazs Benyo, David Feng, J Geoffrey Chase, Steen Andreassen, Ewart Carson, and Levente Kovacs. New York: Curran, 2012, pp. 462–466.

[470] Kovács L, Szalay P, Benyó B, and Chase JG. "Optimal tight glycaemic control supported by differential geometric methodsa". In: *Proceedings of the 5th European Conference of the International Federation for Medical and Biological Engineering*. Ed. by Jobbágy Á. Berlin; Heidelberg: Springer Verlag, 2012, pp. 351–354.

[471] Szeles Annamária, Sápi Johanna, Drexler Dániel, Harmati István, Sápi Zoltán, and Kovács Levente. "Model-based Angiogenic Inhibition of Tumor Growth using Modern Robust Control Method". In: *Proceedings of 8th IFAC Symposium on Biological and Medical Systems*. Ed. by Balazs Benyo, David Feng, J Geoffrey Chase, Steen Andreassen, Ewart Carson, and Levente Kovacs. New York: Curran, 2012, pp. 113–118.

[472] A Kovács, L Kovács, and L Kovács. "The boundary element method in the study of the fluid's non-stationary motion through network profiles". In: ed. by Ioan Cuculescu, Jovo Jaric, Pasc Gavruta, Ioan Golet, and Liviu Cadariu. Editura Politehnica, 2012, pp. 241–248.

[473] L Kovács, T Ferenci, B Benyó, A Kovács, and J G Chase. “Short- and long-term evolution of insulin sensitivity variability in critically ill patients”. In: ed. by Ioan Cuculescu, Jovo Jaric, Pasc Gavruta, Ioan Golet, and Liviu Cadariu. Editura Politehnica, 2012, pp. 329–334.

[474] L Kovács, P Szalay, Zs Almássy, and L Barkai. “Applicability Results of a Nonlinear Model-Based Robust Blood Glucose Control Algorithm”. In: *JOURNAL OF DIABETES SCIENCE AND TECHNOLOGY* 7.3 (2013), pp. 708–716.

[475] J Sápi, D A Drexler, I Harmati, A Szeles, B Kiss, Z Sápi, and L Kovács. “Tumor growth model identification and analysis in case of C38 colon adenocarcinoma and B16 melanoma”. In: *IEEE 8th International Symposium on Applied Computational Intelligence and Informatics: SACI 2013*. Ed. by Szakál Anikó. New York: IEEE, 2013, pp. 303–308.

[476] T Ferenci, A Körner, and L Kovács. “Correlation investigations between HbA1c and blood glucose indicators on type 1 diabetic Hungarian children”. In: *IEEE 8th International Symposium on Applied Computational Intelligence and Informatics: SACI 2013*. Ed. by Szakál Anikó. New York: IEEE, 2013, pp. 443–447.

[477] M Kozlovszky, L Kovács, M Törőcsik, G Windisch, S Ács, D Prém, Gy Eigner, P I Sas, T Schubert, and V Póserné. “Cloud security monitoring and vulnerability management”. In: *IEEE 17th International Conference on Intelligent Engineering Systems (INES), 2013*. Ed. by IEEE. Piscataway (NJ): IEEE, 2013, pp. 265–269.

[478] M Kozlovszky, K Hegedűs, S Szénási, G Kiszler, B Wichmann, I Bándi, Gy Eigner, P I Sas, L Kovács, Z Garaguly, V Jónás, G Kiss, G Valcz, and B Molnár. “Parameter assisted HE colored tissue image classification”. In: *IEEE 17th International Conference on Intelligent Engineering Systems (INES), 2013*. Ed. by IEEE. Piscataway (NJ): IEEE, 2013, pp. 203–207.

[479] L Kovács, J Sápi, T Ferenci, P Szalay, D Drexler, Gy Eigner, P I Sas, I Harmati, M Kozlovszky, and Z Sápi. “Model-based optimal therapy for high-impact diseases”. In: *IEEE 17th International Conference on Intelligent Engineering Systems (INES), 2013*. Ed. by IEEE. Piscataway (NJ): IEEE, 2013, pp. 209–214.

[480] Gyorgy Eigner, Peter Istvan Sas, and Levente Kovács. “Insulin pump testing platform for robust controller”. In: *ICCC 2013, Proceedings of IEEE 9th International Conference on Computational Cybernetics*. Ed. by Anikó Szakál. Tihany: IEEE Hungary Section, 2013, pp. 201–205.

[481] S Jordán, T Haidegger, L Kovács, I Felde, and I Rudas. “The Rising Prospects of Cloud Robotic Applications”. In: *ICCC 2013, Proceedings of IEEE 9th International Conference on Computational Cybernetics*. Ed. by Anikó Szakál. Tihany: IEEE Hungary Section, 2013, pp. 327–332.

[482] P Szalay, Gy Eigner, M Kozlovszky, I Rudas, and L Kovács. “The significance of LPV modeling of a widely used T1DM model”. In: *EMBC 2013 – 35th Annual International Conference of the IEEE Engineering in Medicine and Biology Society*. Ed. by K Sunagawa. Seattle (WA): IEEE, 2013, pp. 3531–3534.

[483] Balazs Benyo, David Feng, J Geoffrey Chase, Steen Andreassen, Ewart Carson, and Levente Kovacs, eds. *Proceedings of 8th IFAC Symposium on Biological and Medical Systems*. New York: Curran, 2012.

[484] Benyo B, Illyés A, Némedi NS, Le Compte AJ, Havas A, Kovacs L, Fisk L, Shaw GM, and Chase JG. “Pilot study of the SPRINT glycemic control protocol in a Hungarian medical intensive care unit.” In: *JOURNAL OF DIABETES SCIENCE AND TECHNOLOGY* 6.6 (2012), pp. 1464–1477.

[485] T Ferenci, L Kovács, and A Körner. “Az életkor, diabetestartam, HBA1C és a vércukorszint alakulásának jellemzői közti összefüggések CGM adatok alapján”. In: ed. by Soós Hajnalka and Nagyné Orbán Andrea. Magyar Diabetes Társaság, 2013, pp. 18–19.

[486] L Kovács, M Kozlovszky, P Szalay, Gy Eigner, P I Sas, Zs Almássy, E Felszeghy, H Soós, A Orbán, A Körner, T Niederland, A Juhászné Tuifel, T Tóthné Sebestyén, A Soós, A Török, and L Barkai. “A magyar mesterséges hasnyálmirigy projekt legújabb eredményei”. In: ed. by Soós Hajnalka and Nagyné Orbán Andrea. Magyar Diabetes Társaság, 2013, pp. 16–17.

[488] J Sápi, D A Drexler, and L Kovács. “Parameter optimization of H_∞ controller designed for tumor growth in the light of physiological aspects”. In: *CINTI 2013 : Proceeding of the 14th IEEE International Symposium on Computational Intelligence and Informatics*. Ed. by Anikó Szakál. Budapest: IEEE Hungary Section, 2013, pp. 19–24.

[489] J Klespitz and L Kovács. “Identification and control of peristaltic pumps in hemodialysis machines”. In: *CINTI 2013 : Proceeding of the 14th IEEE International Symposium on Computational Intelligence and Informatics*. Ed. by Anikó Szakál. Budapest: IEEE Hungary Section, 2013, pp. 83–87.

[490] A Szeles, D A Drexler, J Sápi, I Harmati, Z Sápi, and L Kovács. "Model-based Angiogenic Inhibition of Tumor Growth using Feedback Linearization". In: *Proceedings of the 52nd IEEE Conference on Decision and Control*. Ed. by Parisini T and Tempo R. Piscataway (NJ): IEEE, 2013, pp. 2054–2059.

[491] Tamas Ferenci and Levente Kovacs. "Effects of paediatric obesity: a multivariate analysis of laboratory parameters". In: *Mathematical and Statistical Methods in Food Science and Technology*. Ed. by Daniel Granato and Gastón Ares. Chichester: John Wiley and Sons, Inc., 2014, pp. 303–320.

[492] Árpád Takács, Sándor Jordán, Radu-Emil Precup, Levente Kovács, József Tar, Imre Rudas, and Tamás Haidegger. "Review of Tool–Tissue Interaction Models for Robotic Surgery Applications". In: *Proceedings of the IEEE 12th International Symposium on Applied Machine Intelligence and Informatics (SAMI 2014)*. Ed. by Liberios Vokorokos, Ladislav Hluchý, and János Fodor. Budapest: IEEE Hungary Section, 2014, pp. 339–344.

[493] J Klespitz and L Kovács. "Peristaltic pumps – a review on working and control possibilities". In: *Proceedings of the IEEE 12th International Symposium on Applied Machine Intelligence and Informatics (SAMI 2014)*. Ed. by Liberios Vokorokos, Ladislav Hluchý, and János Fodor. Budapest: IEEE Hungary Section, 2014, pp. 191–194.

[494] L Kovács, M Kozlovszky, P Szalay, Gy Eigner, I P Sas, Zs Almássy, E Felszeghy, Gy Kocsis, J Fövényi, A Körner, L Kautzky, H Soós, A Orbán, T Niederland, A Juhászné Tuifel, T Tóthné Sebestyén, M Hocsi, A Soós, A Török, and L Barkai. "Newest results of the Hungarian artificial pancreas project". In: *7th International Conference on Advanced Technologies and Treatment for Diabetes*. Ed. by Moshe Phillip and Tadej Battelino. Wien: Mary Ann Liebert, 2014, A–149.

[495] Levente Kovács, Annamária Szeles, Johanna Sápi, Dániel A Drexler, Imre Rudas, István Harmati, and Zoltán Sápi. "Model-based angiogenic inhibition of tumor growth using modern robust control method". In: *COMPUTER METHODS AND PROGRAMS IN BIOMEDICINE* 114 (2014), pp. 98–110.

[496] M Kozlovszky, D Mészáros, G Bognár, B A Jókay, N Pálos, and L Kovács. "Protocol based intervention plan analyser". In: 2014, pp. 1–4.

[497] Levente Kovács. "Model-Based Disease Treatment. A Control Engineering Approach". In: *Advances in Soft Computing, Intelligent Robotics and Control*. Ed. by János Fodor and Robert Fullér. Heidelberg; London; New York: Springer, 2014, pp. 55–68.

[498] Annamária Szeles, Dániel András Drexler, Johanna Sápi, István Harmati, and Levente Kovács. "Model-based Angiogenic Inhibition of Tumor Growth using Adaptive Fuzzy Techniques". In: *PERIODICA POLYTECHNICA-ELECTRICAL ENGINEERING AND COMPUTER SCIENCE* 58.1 (2014), pp. 29–36.

[499] L Kovács, M Kozlovszky, P Szalay, Gy Eigner, P Sas, T Ferenci, Zs Almássy, E Felszeghy, G Kocsis, J Fövényi, K Wudi, A Körner, L Kautzky, H Soós, A Orbán, T Niederland, A Juhászné Tuifel, T Tóthné Sebestyén, M Hocsi, A Soós, A Török, and L Barkai. "Magyar mesterséges hasnyálmirigy projekt. Eredmények és távlatok". In: *DIABETOLOGIA HUNGARICA* XXII (2014), pp. 73–76.

[500] K Lukács, T Ferenci, L Kovács, M Balogh, K H Nagy, Zs Karádi, H Soós, L Madácsy, and N Hosszúfalusi. "Glykaemiás variabilitás és anyagcsere-kontroll vizsgálatok 1-es típusú diabetesben". In: *DIABETOLOGIA HUNGARICA* XXII (2014), pp. 101–102.

[501] P Gyuk, I Szabó, I Vassányi, I Kósa, and L Kovács. "Modell alapú diabetes életmód-támogatás". In: *DIABETOLOGIA HUNGARICA* XXII (2014), pp. 41–43.

[502] P Gyuk, I Szabó, I Vassányi, I Kósa, L Kovács, and L Stoicu-Tivadar et al. "Combined Model for Diabetes Lifestyle Support". In: *European Federation for Medical Informatics (EFMI) Special Topic Conference*. Budapest: IOS Press, 2014, pp. 77–81.

[503] Gy Eigner, P I Sas, and L Kovács. "Continuous glucose monitoring systems in the service of artificial pancreas". In: *9th IEEE International Symposium on Applied Computational Intelligence and Informatics ; SACI 2014*. Ed. by Anikó Szakál. Timisoara: IEEE Hungary Section, 2014, pp. 117–122.

[504] L Kovács, J Sápi, Gy Eigner, T Ferenci, P Szalay, J Klespitz, B Kurtán, M Kozlovszky, D A Drexler, P Pausits, I Harmati, Z Sápi, and I Rudas. "Model-based healthcare applications at Obuda University". In: *9th IEEE International Symposium on Applied Computational Intelligence and Informatics ; SACI 2014*. Ed. by Anikó Szakál. Timisoara: IEEE Hungary Section, 2014, pp. 183–187.

[505] Sápi Johanna, Drexler Dániel, Harmati István, Sápi Zoltán, and Kovács Levente. "Linear state-feedback control synthesis of tumor growth control in antiangiogenic therapy". In: *IEEE 10th Jubilee International Symposium on Applied Machine Intelligence and Informatics, SAMI 2012: Proceedings*. Ed. by IEEE. Budapest: IEEE Hungary Section, 2012, pp. 143–148.

[506] Benyó Balázs, Kovács Levente, Illyés Attila, Havas Attila, Szabó Némedi Noémi, and J Geoffrey Chase. “INTENZÍV ÁPOLÁS SORÁN HATÉKONYAN ALKALMAZHATÓ PROTOKOLLOK A VÉRCUKORSZINT SZABÁLYOZÁSÁRA”. In: *ANESZTEZIOLÓGIA ÉS INTENZÍV TERÁPIA* 42 (Suppl. 1 2012), p. 11.

[507] Illyés Attila, Havas Attila, Szabó Némedi Noémi, Benyó Balázs, Kovács Levente, and J Geoffrey Chase. “SPRINT, STAR: KÉT HATÉKONY KEZELÉSI PROTOKOLL AZ INTENZÍV OSZTÁLYON KEZELT BETEGEK VÉRCUKORSZINTJÉNEK NORMOGLIKÉMIÁS TARTOMÁNYBAN TARTÁSÁHOZ”. In: *ANESZTEZIOLÓGIA ÉS INTENZÍV TERÁPIA* 42 (Suppl. 1 2012), p. 25.

[508] Szalay Péter and Kovács Levente. “Applicability of Asymptotic Tracking in Case of Type 1 Diabetes”. In: *Applied Computational Intelligence in Engineering and Information Technology: Revised and Selected Papers from the 6th IEEE International Symposium on Applied Computational Intelligence and Informatics SACI 2011*. Ed. by Radu-Emil Precup, Stefan Preitl, Szilveszter Kovács, and Emil M Petriu. Berlin; Heidelberg: Springer-Verlag, 2012, pp. 249–260.

[509] Benyó Balázs, Kovács Levente, Illyés Attila, Havas Attila, Szabó Némedi Noémi, Sophie Penning, Thomas Desaive, Paul Massion, Aaron Le Compte, Cristopher Pretty, Geoffrey M. Shaw, Geoffrey J. Chase, and Katherine T. Moorhead. “Vércukor szabályozás intenzív ápolásra szoruló betegeknél: A SPRINT és a STAR protokolok”. In: *DIABETOLOGIA HUNGARICA* XX (Suppl.1 2012), pp. 43–45.

[510] Illyés Attila, Havas Attila, Szabó Némedi Noémi, Benyó Balázs, Kovács Levente, Aaron Le Compte, Geoffrey M. Shaw, and Geoffrey J. Chase. “Initial ICU clinical results using SPRINT to guide insulin infusions in a Hungarian medical ICU”. In: *JOURNAL OF DIABETES SCIENCE AND TECHNOLOGY* 6.2 (2012), A68–A69.

[511] Haidegger Tamás, Sirokai Beáta, Fenyvesi Gábor, Kovács Levente, Benyó Zoltán, and Benyó Balázs. “Repeatable Assessment Protocol for Electromagnetic Trackers”. In: *PROCEEDINGS OF SPIE - THE INTERNATIONAL SOCIETY FOR OPTICAL ENGINEERING* 8316 (2012).

[512] Haidegger Tamás, Benyó Balázs, and Kovács Levente. “Methods to extend the cognitive horizon for more effective telepresence”. In: 2012, pp. 1–8.

[513] Sirokai Beáta, Kiss Máté, Kovács Levente, Benyó Balázs, Benyó Zoltán, and Haidegger Tamás. “Best Practices in Electromagnetic Tracking System Assessment”. In: *II SCATh Joint Workshop on New Technologies for Computer/Robot*

Assisted Surgery. Ed. by Holzapfel, Pierce, Sloten, and Sette. Madrid: Katholieke Universiteit Leuven, 2012, pp. 1–4.

[514] R -E Precup, T Haidegger, S Preitl, Z Benyó, A S Paul, and L Kovács. "Fuzzy Control Solution for Telesurgical Applications". In: *APPLIED AND COMPUTATIONAL MATHEMATICS* 11.3 (2012), pp. 378–397.

[515] Tamas Haidegger, Levente Kovacs, Radu-Emil Precup, Balazs Benyo, Zoltan Benyo, and Stefan Preitl. "Simulation and control for telerobots in space medicine". In: *ACTA ASTRONAUTICA* 81 (2012), pp. 390–402.

[516] Szalay Péter, Sas Péter István, Barkai László, and Kovács Levente. "Nonlinear analysis of Type 1 Diabetes Models by Differential Geometric Approach". In: *Proceedings of 8th IFAC Symposium on Biological and Medical Systems*. Ed. by Balazs Benyo, David Feng, J Geoffrey Chase, Steen Andreassen, Ewart Carson, and Levente Kovacs. New York: Curran, 2012, pp. 55–60.

[517] Kovács Adalbert, Precup Radu-Emil, Paláncz Béla, and Kovács Levente, eds. *Modern numerical methods in engineering*. Timisoara: Editura Politehnica, 2012.

[518] Tar JK, Haidegger T, Kovács L, Kósi K, Botka B, and Rudas IJ. "Nonlinear Order-Reduced Adaptive Controller for a DC Motor Driven Electric Cart". In: *18th International Conference on Intelligent Engineering Systems - INES 2014*. Ed. by Szakál A. Piscataway (NJ): Institute of Electrical and Electronics Engineers (IEEE), 2014, pp. 73–78.

[520] A Szeles, D A Drexler, J Sápi, I Harmati, and L Kovács. "Study of Modern Control Methodologies Applied to Tumor Growth under Angiogenic Inhibition". In: *Proceedings of the 19th IFAC World Congress, 2014*. Ed. by Boje E and Xia X. New York: IFAC, 2014, pp. 9271–9276.

[521] P Szalay, Gy Eigner, and L Kovács. "Linear Matrix Inequality-based Robust Controller design for Type-1 Diabetes Model". In: *Proceedings of the 19th IFAC World Congress, 2014*. Ed. by Boje E and Xia X. New York: IFAC, 2014, pp. 9247–9252.

[522] J Klespitz, M Takács, and L Kovács. "Application of fuzzy logic in hemodialysis equipment". In: *18th International Conference on Intelligent Engineering Systems - INES 2014*. Ed. by Szakál A. Piscataway (NJ): Institute of Electrical and Electronics Engineers (IEEE), 2014, pp. 169–173.

[523] T Ferenci and L Kovács. “Using Total Correlation to Discover Related Clusters of Clinical Chemistry Parameters”. In: *SISY 2014: IEEE 12th International Symposium on Intelligent Systems and Informatics*. Ed. by Anikó Szakál. Subotica: IEEE Hungary Section, 2014, pp. 49–54.

[524] L Szilágyi, G Dénesi, L Kovács, and S M Szilágyi. “Comparison of Various Improved-Partition Fuzzy c-Means Clustering Algorithms in Fast Color Reduction”. In: *SISY 2014: IEEE 12th International Symposium on Intelligent Systems and Informatics*. Ed. by Anikó Szakál. Subotica: IEEE Hungary Section, 2014, pp. 197–202.

[525] József Tar, Levente Kovács, Árpád Takács, Bence Takács, Péter Zentay, Tamás Haidegger, and Imre J Rudas. “Novel Design of a Model Reference Adaptive Controller for Soft Tissue Operations”. In: 2014.

[526] Jozsef Tar, I J Rudas, L Kovács, T Haidegger, and B Kurtán. “Observation-Based Data Driven Adaptive Control of an Electromechanical Device”. In: *2014 IEEE Multi-Conference on Systems and Control*. Ed. by Dominique Sauter. Piscataway (NJ): IEEE, 2014, pp. 1895–1900.

[527] M Kozlovszky, L Kovacs, and K Karoczkai. “Cardiovascular and diabetes focused remote patient monitoring”. In: *IFMBE Proceedings : 6th Latin American Congress on Biomedical Engineering, CLAIB 2014*. Ed. by Braidot A and Hadad A. New York: Springer-Verlag Wien, 2015, pp. 568–571.

[528] S Panunzi, A Borri, P Palumbo, L Kovács, and A De Gaetano. “Simulation of insulin regimen and glucose profiles in Type 1 Diabetic Patient”. In: *2014 IEEE International Conference on Systems, Man and Cybernetics (SMC)*. Ed. by W A Gruver. Piscataway (NJ): IEEE, 2014, pp. 2464–2469.

[529] P Szalay, L Szilágyi, Z Benyó, and L Kovács. “Sensor Drift Compensation Using Fuzzy Interference System and Sparse-Grid Quadrature Filter in Blood Glucose Control”. In: *LECTURE NOTES IN COMPUTER SCIENCE* 8835 (2014), pp. 445–453. ISSN: 0302-9743.

[530] L Szilágyi, L Kovács, and S M Szilágyi. “Synthetic Test Data Generation for Hierarchical Graph Clustering Methods”. In: *LECTURE NOTES IN COMPUTER SCIENCE* 8835 (2014), pp. 303–310.

[531] J Sápi, D A Drexler, Z Sápi, and L Kovács. “Identification of C38 colon adenocarcinoma growth under bevacizumab therapy and without therapy”. In: *CINTI*

2014 - 15th IEEE International Symposium on Computational Intelligence and Informatics. Ed. by IEEE. Budapest: IEEE Hungary Section, 2014, pp. 443–448.

[532] J Klespitz, M Takács, I Rudas, and L Kovács. "Adaptive soft computing methods for control of hemodialysis machines". In: *iFuzzy2014 – 2014 International Conference on Fuzzy Theory and Its Applications*. Ed. by J H Chou, S J Lee, C W Tao, and L S L Wang. Kaohsiung: IEEE Systems, Man and Cybernetics Society, 2014, pp. 109–112.

[533] R E Precup, T Haidegger, and L Kovács. "Stable Hybrid Fuzzy Controller-based Architecture for Robotic Telesurgery Systems". In: *INTERNATIONAL JOURNAL OF COMPUTATIONAL INTELLIGENCE AND PATTERN RECOGNITION* 1.1 (2014), pp. 61–76.

[534] T Ferenci, A Körner, and L Kovács. "The interrelationship of HbA1c and real-time continuous glucose monitoring in children with type 1 diabetes". In: *DIABETES RESEARCH AND CLINICAL PRACTICE* 108.1 (2015), pp. 38–44.

[535] Gy Eigner, B Kurtán, I Rudas, C K Chui, and L Kovács. "Examination of a novel double diabetes model". In: *SAMI 2015 • IEEE 13th International Symposium on Applied Machine Intelligence and Informatics*. Ed. by Anikó Szakál. Herlany: IEEE Hungary Section, 2015, pp. 41–46.

[536] M Kozlovszky, J Fodor, R Ősz, I Rudas, and L Kovács. "Multimodal remote biosignal acquisition and processing at Obuda University". In: *Computer Aided Systems Theory - EUROCAST 2015: 15th International Conference, Las Palmas de Gran Canaria, Spain*. Ed. by Roberto Moreno-Díaz, Franz Pichler, and Alexis Quesada-Arencibia. Las Palmas: Springer-Verlag, 2015, pp. 129–130.

[537] L Kovács, J Fodor, R Ősz, I Rudas, and M Kozlovszky. "Physiological Control Researches at Obuda University". In: *Computer Aided Systems Theory - EUROCAST 2015: 15th International Conference, Las Palmas de Gran Canaria, Spain*. Ed. by Roberto Moreno-Díaz, Franz Pichler, and Alexis Quesada-Arencibia. Las Palmas: Springer-Verlag, 2015, pp. 127–128.

[538] Gy Eigner and L Kovács. "Realization methods of continuous glucose monitoring systems". In: *BULETINUL STIINTIFIC AL UNIVERSITATII POLITEHNICA DIN TIMISOARA ROMANIA SERIA AUTOMATICA SI CALCULATORAE* 59.73 (2014), pp. 175–182.

[539] T Ferenci, A Körner, and L Kovács. “Association of autoantibody levels with the hazard of autoimmune comorbidities in children with type 1 diabetes”. In: *First European Biomedical Engineering Conference for Young Investigators: ENCY 2015*. Ed. by Ákos Jobbágy. Singapore: Springer, 2015, pp. 110–113.

[540] L Kovács. “Modeling and Control of Physiological Systems”. In: *First European Biomedical Engineering Conference for Young Investigators: ENCY 2015*. Ed. by Ákos Jobbágy. Singapore: Springer, 2015, pp. 7–10.

[541] E Kolossváry, T Ferenci, T Kováts, L Kovács, Z Járai, G Menyhei, and K Farkas. “Trends in major lower limb amputations related to peripheral arterial disease in Hungary. A nationwide study (2004-2012)”. In: *EUROPEAN JOURNAL OF VASCULAR AND ENDOVASCULAR SURGERY* 50.1 (2015), pp. 78–85.

[542] Á Lehotsky, L Szilágyi, T Ferenci, L Kovács, R Pethes, G Wéber, and T Haidegger. “Quantitative impact of direct, personal feedback on hand hygiene technique”. In: *JOURNAL OF HOSPITAL INFECTION* 91.1 (2015), pp. 81–84.

[543] J Klespitz, M Takács, I Rudas, and L Kovács. “Performance of soft computing controllers in hemodialysis machines”. In: *INTERNATIONAL JOURNAL OF FUZZY SYSTEMS* 17.3 (2015), pp. 414–422.

[544] L Kovács, B Kurtán, Gy Eigner, I Rudas, and C K Chui. “Analyzing of a Novel Time Delay Diabetes Model”. In: *ECC 2015 - 14th Annual European Control Conference*. Ed. by [S n]. Linz: European Control Association (EUCA), 2015, pp. 13–18.

[545] P Latafat, P Palumbo, P Pepe, L Kovács, S Panunzi, and A de Gaetano. “An LMI-Based Controller for the Glucose-Insulin System”. In: *ECC 2015 - 14th Annual European Control Conference*. Ed. by [S n]. Linz: European Control Association (EUCA), 2015, pp. 7–12.

[546] Gy Eigner, Jozsef Tar, and L Kovács. “Adaptive Control Solution for T1DM Control”. In: *10th Jubilee IEEE International Symposium on Applied Computational Intelligence and Informatics (SACI 2015)*. Ed. by Szakál Anikó. Budapest: Óbudai Egyetem, 2015, pp. 215–220.

[547] L Kovács, T Ferenci, J Sápi, Gy Eigner, J Klespitz, P Szalay, M Kozlovszky, and I Rudas. “Physiological Modeling and Control at Obuda University”. In: *10th Jubilee IEEE International Symposium on Applied Computational Intelligence and Informatics (SACI 2015)*. Ed. by Szakál Anikó. Budapest: Óbudai Egyetem, 2015, pp. 21–25.

[548] Z Garaguly, M Kozlovszky, and L Kovács. “High resolution digital holographic microscope and image reconstruction”. In: *19th IEEE International Conference on Intelligent Engineering Systems: INES 2015*. Ed. by Szakál A. Bratislava: IEEE, 2015, pp. 179–184.

[549] C M Ionescu, T F Mendonca, and L Kovacs. “Critically Safe General Anaesthesia in Closed Loop: Availability and Challenges”. In: *9th IFAC Symposium on Biological and Medical Systems (IFAC BMS 2015)*. Ed. by Berno Misgeld, Thomas Schauer, and Olaf Simanski. Berlin: Elsevier; IFAC, 2015, pp. 551–556.

[550] Sápi Johanna, Drexler Dániel András, and Kovács Levente. “Comparison of mathematical tumor growth models”. In: *SISY 2015 : IEEE 13th nternational Symposium on Intelligent Systems and Informatics: Proceedings*. Ed. by Anikó Szakál. New York: IEEE, 2015, pp. 323–328.

[551] Kiss Gábor, Cseri Orsolya Eszter, Altsach Ádám, Bándi I I, Kovács L, and Kozlovszky M. “High resolution digital tissue image processing using texture image databases”. In: *Technological Innovation for Cloud-Based Engineering Systems. 6th IFIP WG 5.5/SOCOLNET Doctoral Conference on Computing, Electrical and Industrial Systems, DoCEIS 2015, Costa de Caparica, Portugal, April 13-15, 2015, Proceedings*. Ed. by Camarinha-Matos L M, Baldissera T A, Di Orio G, and Marques F. Cham (Németország): Springer, 2015, pp. 239–247.

[552] Johanna Sápi, Tamás Ferenci, Dániel András Drexler, and Levente Kovács. “Tumor model identification and statistical analysis”. In: *IEEE International Conference on Systems, Man, and Cybernetics 2015: IEEE SMC 2015*. Ed. by Kwong S and Yeung D. Hong Kong: IEEE, 2015, pp. 2481–2486.

[553] Johanna Sápi, Levente Kovács, Dániel András Drexler, Pál Kocsis, Dávid Gajári, and Zoltán Sápi. “Tumor Volume Estimation and Quasi- Continuous Administration for Most Effective Bevacizumab Therapy”. In: *PLOS ONE* 10.11 (2015).

[554] Gy Eigner, P Horváth, Jozsef Tar, I Rudas, and L Kovács. “Application of Robust Fixed Point control in case of T1DM”. In: *IEEE International Conference on Systems, Man, and Cybernetics 2015: IEEE SMC 2015*. Ed. by Kwong S and Yeung D. Hong Kong: IEEE, 2016, pp. 2459–2464.

[555] Z Garaguly, M Kozlovszky, and L Kovács. “Nagyfelbontású holografikus mikroszkóp és képrekonstrukció”. In: *Új alapokon az egészségügyi informatika: A XXVIII. Neumann Kollokvium konferencia-kiadványa*. Ed. by Kósa István and Vassányi István. Veszprém: Neumann János Számítógép-tudományi Társaság (NJSZT), 2015, pp. 38–42.

[556] T Haidegger, V Varga, A Lehotsky, P Rona, R Pethes, P Szerémy, L. Szilágyi, T Ferenci, and L Kovács. "Information Technology Tools Employed in Infection Control". In: *16th IEEE International Symposium on Computational Intelligence and Informatics, CINTI 2015*. Ed. by Szakál Anikó. Budapest: IEEE, 2015, pp. 339–344.

[557] J Klespitz, M Biró, and L Kovács. "Aspects of improvement of software development lifecycle management". In: *16th IEEE International Symposium on Computational Intelligence and Informatics, CINTI 2015*. Ed. by Szakál Anikó. Budapest: IEEE, 2015, pp. 323–327.

[558] Gy Eigner, Jozsef Tar, and L Kovács. "Novel Error Interpretation in case of Linear Parameter Varying Systems". In: *16th IEEE International Symposium on Computational Intelligence and Informatics, CINTI 2015*. Ed. by Szakál Anikó. Budapest: IEEE, 2015, pp. 243–248.

[559] L Kovács and P Szalay. "Uncertainties and Modelling Errors of Type 1 Diabetes Models". In: *Prediction Methods for Blood Glucose Concentration*. Ed. by H Kirchsteiger, J B Jorgensen, E Renard, and L del Re. Zürich: Springer International Publishing, 2016, pp. 211–225.

[560] Árpád Takács, Levente Kovács, Imre J Rudas, Radu-Emil Precup, and Tamás Haidegger. "Models for Force Control in Telesurgical Robot Systems". In: *ACTA POLYTECHNICA HUNGARICA* 12.8 (2015), pp. 95–114.

[561] Eigner Gy, Tar J K, Rudas I J, and Kovács L. "LPV-based quality interpretations on modeling and control of diabetes". In: *ACTA POLYTECHNICA HUNGARICA* 13.1 (2016), pp. 171–190.

[562] Z Garaguly, M Kozlovszky, and L Kovács. "The optimization of medical X-ray images". In: *SAMI 2016 : IEEE 14th International Symposium on Applied Machine Intelligence and Informatics*. Ed. by Szakál Anikó. New York: IEEE, 2016, pp. 147–152.

[563] Johanna Sápi, Dániel A Drexler, István Harmati, Zoltán Sápi, and Levente Kovács. "Qualitative analysis of tumor growth model under antiangiogenic therapy: choosing the effective operating point and design parameters for controller design". In: *OPTIMAL CONTROL APPLICATIONS & METHODS* 37.5 (2016), pp. 848–866.

[564] Árpád Takács, György Eigner, Levente Kovács, Imre Rudas, and Tamás Haidegger. "Teacher's Kit : Development, Usability and Communities of Modular Robotic Kits

for Classroom Education". In: *IEEE ROBOTICS & AUTOMATION MAGAZINE* 23.2 (2016), pp. 30–39.

[565] Kolossváry Endre, Ferenci Tamás, Kováts Tamás, Kovács Levente, Járai Zoltán, and Farkas Katalin. "Kritikus alsó végtagi iszkémiás események szezonalitása a teljes magyar népesség adatainak elemzésével". In: *CARDIOLOGIA HUNGARICA* 46 (Supplementum F 2016), F90.

[566] I Rudas, Gy Eigner, and L Kovács. "SMC 2016 and SMC Junior 2016". In: *IEEE SYSTEMS MAN AND CYBERNETICS MAGAZINE* 2.1 (2016), pp. 41–44.

[567] J Klespitz, M Biro, and L Kovacs. "Evaluation criteria for application life cycle management systems in practice". In: *Proceedings of the11th IEEE International Symposium on Applied Computational Intelligence and Informatics SACI 2016*. Ed. by Szakál Anikó. Budapest: IEEE, 2016, pp. 469–472.

[568] Miklós Biró, József Klespitz, Johannes Gmeiner, Christa Illibauer, and Levente Kovács. "Towards Automated Traceability Assessment through Augmented Lifecycle Space". In: *COMMUNICATIONS IN COMPUTER AND INFORMATION SCIENCE* 633 (2016), pp. 94–105.

[569] J Klespitz, M Biró, and L Kovács. "Enhanced traceability and consistency with Augmented Lifecycle Space". In: *20th IEEE Jubilee International Conference on Intelligent Engineering Systems: INES 2016*. Ed. by Szakál Anikó. Budapest: IEEE Hungary Section, 2016, pp. 207–212.

[570] György Eigner, Péter Pausits, and Levente Kovács. "A novel completed LPV controller and observer scheme in order to control nonlinear compartmental systems". In: *IEEE 14th International Symposium on Intelligent Systems and Informatics: SISY 2016*. Ed. by Szakál A. Budapest: IEEE Hungary Section, 2016, pp. 85–92.

[571] József Klespitz, Miklós Bíró, and Levente Kovács. "Cross-Tool Interoperability in Heterogeneous Application Lifecycle Management Systems". In: *New Trends in Software Methodologies, Tools and Techniques*. Ed. by Hamido Fujita and George Angelos Papadopoulos. Amsterdam: IOS Press, 2016, pp. 213–220.

[572] L Kovács, Gy Eigner, l Miclea, and I Stoian. "Clinical decision support systems for personalized healthcare". In: *AQTR 2016 – International Conference on Automation, Quality and Testing, Robotics*. Ed. by I Stefan and O Ghiran. Cluj-Napoca: IEEE Computer Society, 2016, pp. 6–12.

[573] I R Birs, C Muresan, S Folea, O Prodan, L Kovács, l Miclea, and I Stoian. "Vibration suppression with fractional-order PID controller". In: *AQTR 2016 – International Conference on Automation, Quality and Testing, Robotics*. Ed. by I Stefan and O Ghiran. Cluj-Napoca: IEEE Computer Society, 2016, pp. 1–6.

[574] L Kovács. "Physiological control systems for high-quality interdisciplinary researches". In: *Proceedings of the11th IEEE International Symposium on Applied Computational Intelligence and Informatics SACI 2016*. Ed. by Szakál Anikó. Budapest: IEEE, 2016, pp. 11–12.

[575] J Sápi, D A Drexler, and L Kovács. "Discrete time state feedback with setpoint control, actual state observer and load estimation for a tumor growth model". In: *Proceedings of the11th IEEE International Symposium on Applied Computational Intelligence and Informatics SACI 2016*. Ed. by Szakál Anikó. Budapest: IEEE, 2016, pp. 111–118.

[576] Garaguly Zoltán, Kozlovszky Miklós, and Kovács Levente. "Holografikus képrekonstrukció alkalmazása folyadékvizsgálat során". In: *Orvosi Informatika 2016. A XXIX. Neumann Kollokvium konferencia-kiadványa*. Ed. by Bari Ferenc and Almási László. Szeged: Neumann János Számítógép-tudományi Társaság (NJSZT), 2016, pp. 79–83.

[577] Z Garaguly, M Kozlovszky, and L Kovács. "Platform independent telepathology system for pathologists". In: *17th IEEE International Symposium on Computational Intelligence and Informatics (CINTI 2016)*. Ed. by Szakál Anikó. Budapest: IEEE Hungary Section, 2016, pp. 135–138.

[578] Péter Szalay, Zoltán Benyó, and Levente Kovács. "Long-Term Prediction for T1DM Model During State-Feedback Control". In: *12th IEEE International Conference on Control and Automation, ICCA 2016*. Ed. by IEEE. New York: IEEE, 2016, pp. 311–316.

[579] Levente Kovács. "Control engineering approaches at Obuda University for physiological problems: Plenary talk". In: *20th IEEE Jubilee International Conference on Intelligent Engineering Systems: INES 2016*. Ed. by Szakál Anikó. Budapest: IEEE Hungary Section, 2016, pp. 19–20.

[580] Gy Eigner and L Kovács. "Novel complementary LPV controller and observer structure for nonlinear control". In: *Proceedings of 7th IEEE Conference on Cognitive Infocommunications*. Ed. by Baranyi Péter. Budapest: IEEE Hungary Section, 2016.

[581] J Sápi, D A Drexler, and L Kovács. “Comparison of protocol based cancer therapies and discrete controller based treatments in the case of endostatin administration”. In: *2016 IEEE International Conference on Systems, Man, and Cybernetics Conference Proceedings: SMC 2016*. Ed. by Szakál A. Budapest: IEEE, 2016, pp. 3830–3835.

[582] T Ferenci, J Sápi, and L Kovács. “Modelling xenograft tumor growth under antiangiogenic inhibitation with mixed-effects models”. In: *2016 IEEE International Conference on Systems, Man, and Cybernetics Conference Proceedings: SMC 2016*. Ed. by Szakál A. Budapest: IEEE, 2016, pp. 3912–3917.

[583] R Pethes, T Ferenci, and L Kovács. “Infectious Hospital Agents: an individual-based simulation framework”. In: *2016 IEEE International Conference on Systems, Man, and Cybernetics Conference Proceedings: SMC 2016*. Ed. by Szakál A. Budapest: IEEE, 2016, pp. 3434–3439.

[584] D A Drexler and L Kovács. “Second-order and implicit methods in numerical integration improve tracking performance of the closed-loop inverse kinematics algorithm”. In: *2016 IEEE International Conference on Systems, Man, and Cybernetics Conference Proceedings: SMC 2016*. Ed. by Szakál A. Budapest: IEEE, 2016, pp. 3362–3367.

[585] D Copot, R de Keyser, L Kovács, C Ionescu, and A Aitouche. “Towards a cyber-medical system for drug assisting devices”. In: *13th European Workshop on Advanced Control and Diagnosis*. London: IOP Publishing, 2016, pp. 1–9.

[586] József Klespitz, Miklós Biró, and Levente Kovács. “Augmented lifecycle space for traceability and consistency enhancement”. In: *2016 IEEE International Conference on Systems, Man, and Cybernetics Conference Proceedings: SMC 2016*. Ed. by Szakál A. Budapest: IEEE, 2016, pp. 3973–3977.

[587] M Kozlovszky, L Kovács, K Batbayar, and Z Garaguly. “Automatic Protocol Based Intervention Plan Analysis in Healthcare”. In: *39th International Convention on Information and Communication Technology, Electronics and Microelectronics (MIPRO 2016)*. Ed. by Biljanovic P. Opatija: Croatian Society for Information, Communication Technology Electronics, and Microelectronics (MIPRO), 2016, pp. 269–273.

[588] P Piros, R Fleiner, and L Kovács. “Linked Data Generation for Courses and Events at Obuda University”. In: *SAMI 2017 : IEEE 15th International Symposium on Applied Machine Intelligence and Informatics*. Ed. by Szakál A. Budapest: IEEE, 2017, pp. 253–258.

[589] D A Drexler, J Sápi, and L Kovács. “A minimal model of tumor growth with angiogenic inhibition using bevacizumab”. In: *SAMI 2017 : IEEE 15th International Symposium on Applied Machine Intelligence and Informatics*. Ed. by Szakál A. Budapest: IEEE, 2017, pp. 185–190.

[590] Gy Eigner, I Böjthe, P Pausits, and L Kovács. “Investigation of the TP modeling possibilities of the Hovorka T1DM model”. In: *SAMI 2017 : IEEE 15th International Symposium on Applied Machine Intelligence and Informatics*. Ed. by Szakál A. Budapest: IEEE, 2017, pp. 259–264.

[591] Eigner György, Kovács Levente, and Némethy Krisztina. “The 2016 IEEE Systems, Man, and Cybernetics Conference: Conference Reports”. In: *IEEE SYSTEMS MAN AND CYBERNETICS MAGAZINE* 3.2 (2017), pp. 43–51.

[592] Tamás Ferenci, Johanna Sápi, and Levente Kovács. “Modelling Tumor Growth Under Angiogenesis Inhibition with Mixed-effects Models”. In: *ACTA POLYTECHNICA HUNGARICA* 14.1 (2017), pp. 221–234.

[593] Kovács Levente, Eigner György, and Rudas Imre. “Inzulinpumpa prototípus fejlesztése”. In: Erdélyi Magyar Műszaki Tudományos Társaság (EMT), 2017, pp. 235–238.

[594] Endre Kolossváry, Tamás Ferenci, Tamás Kováts, Levente Kovács, Zoltán Járai, and Katalin Farkas. “Mortality following lower limb vascular amputation”. In: 3 (2017).

[595] Sápi Johanna, Drexler Dániel András, and Kovács Levente. “Potential Benefits of Discrete-Time Controllerbased Treatments over Protocol-based Cancer Therapies”. In: *ACTA POLYTECHNICA HUNGARICA* 14.1 (2017), pp. 11–23.

[596] Pethes R, Ferenci T, and Kovács L. “Infectious hospital agents: A HAI spreading simulation framework”. In: *ACTA POLYTECHNICA HUNGARICA* 14.1 (2017), pp. 95–110.

[597] Levente Kovács. “Preface”. In: *ACTA POLYTECHNICA HUNGARICA* 14.1 (2017), pp. 7–9.

[598] Levente Kovács, Zoltán Sápi, Dániel A. Drexler, and Johanna Sápi. “Taming Cancer: Is it Possible?” In: (2017).

[599] Ferenci Tamás and Kovács Levente. “Predicting body fat percentage from anthropometric and laboratory measurements using artificial neural networks”. In: *APPLIED SOFT COMPUTING* & (2017).

[600] Miklós Biró, Felix Kossak, József Klespitz, and Levente Kovács. “Graceful Integration of Process Capability Improvement, Formal Modeling and Web Technology for Traceability”. In: *COMMUNICATIONS IN COMPUTER AND INFORMATION SCIENCE* 748 (2017), pp. 381–398.

[601] Ferenci Tamás and Kovács Levente. “Experiences with Using Bayes Factors for Regression Analysis in Biostatistical Setting”. In: *PERIODICA POLYTECHNICA-ELECTRICAL ENGINEERING AND COMPUTER SCIENCE* 61.3 (2017), pp. 246–252.

[602] Piros P, Fleiner R, Ferenci T, Andréka P, Fujita H, Ofner P, Kovács L, and Jánosi A. “An overview of myocardial infarction registries and results from the hungarian myocardial infarction registry”. In: *FRONTIERS IN ARTIFICIAL INTELLIGENCE AND APPLICATIONS* 297 (2017), pp. 312–320.

[603] György Eigner, Árpád Varga, Miklós Mezei, and Levente Kovács. “LPV-based control of nonlinear compartmental model with input uncertainty”. In: *IEEE 15th International Symposium on Intelligent Systems and Informatics : SISY 2017*. Ed. by Szakál Anikó. New York: IEEE, 2017, pp. 17–22.

[604] Zsolt Fézer and Levente Kovács. “The Economic Impact of Diabetes”. In: *IEEE 15th International Symposium on Intelligent Systems and Informatics : SISY 2017*. Ed. by Szakál Anikó. New York: IEEE, 2017, pp. 77–82.

[605] Árpád Varga, György Eigner, Levente Kovács, Imre Felde, and Miklós Mezei. “Overview of taxi database from viewpoint of usability for traffic model development: a case study for Budapest”. In: *IEEE 15th International Symposium on Intelligent Systems and Informatics : SISY 2017*. Ed. by Szakál Anikó. New York: IEEE, 2017, pp. 105–110.

[606] György Eigner, Katalin Koppány, Péter Pausitsz, and Levente Kovács. “Nonlinear Identification of Glucose Absorption Related to Diabetes Mellitus”. In: *INES 2017, IEEE 21st International Conference on Intelligent Engineering Systems: Proceedings*. Ed. by IEEE. Larnaca: IEEE, 2017, pp. 265–270.

[607] Zoltán Garaguly, Miklós Kozlovszky, and Levente Kovács. “Comparison of numerical image reconstruction methods in holography”. In: *IEEE 30th Jubilee Neumann Colloquium : Neumann Colloquium 2017*. Ed. by Szakál Anikó. Budapest: Óbudai Egyetem, 2017, pp. 65–70.

[608] Dániel A Drexler, Johanna Sápi, Levente Kovács, W Xie, and C Hu. "Positive control of a minimal model of tumor growth with bevacizumab treatment". In: *12th IEEE Conference on Industrial Electronics and Applications (ICIEA 2017)*. Ed. by L Jiang. Singapore: IEEE Industrial Electronics Society, 2017, pp. 2081–2084.

[609] György Eigner, Dániel A Drexler, Levente Kovács, W Xie, and C Hu. "Control of nolinear physiological systems via LPV framework". In: *12th IEEE Conference on Industrial Electronics and Applications (ICIEA 2017)*. Ed. by L Jiang. Singapore: IEEE Industrial Electronics Society, 2017, pp. 2085–2090.

[610] Daniel A Drexler, Johanna Sapi, and Levente Kovacs. "Positive nonlinear control of tumor growth using angiogenic inhibition". In: *Preprints of the 20th World Congress The International Federation of Automatic Control: 20th IFAC World Congress*. Ed. by IFAC. Toulouse: IFAC, 2017, pp. 15633–15638.

[611] Daniel A Drexler, Johanna Sapi, and Levente Kovacs. "Optimal discrete time control of antiangiogenic tumor therapy". In: *Preprints of the 20th World Congress The International Federation of Automatic Control: 20th IFAC World Congress*. Ed. by IFAC. Toulouse: IFAC, 2017, pp. 14046–14051.

[612] Dávid Csercsik, Johanna Sápi, and Levente Kovács. "A bicompartmental dynamic tumor growth model". In: *Preprints of the 20th World Congress The International Federation of Automatic Control: 20th IFAC World Congress*. Ed. by IFAC. Toulouse: IFAC, 2017, pp. 12727–12732.

[613] Kovács Levente, Sima Dezső, and Molnár András. "Mesterképzés másként: duális angol mérnökinformatikus MSc képzés az Óbudai Egyetemen". In: *Informatika a felsőoktatásban 2017 konferencia kiadványa*. Ed. by Aradi Bernadett, Bujdosó Gyöngyi, Horváth Géza, and Szokol Patrícia. Debrecen: Debreceni Egyetem Informatikai Kar, 2017, pp. 181–182.

[614] Levente Kovács. "Cyber-Medical Systems: Challenges and Possibilities". In: *IEEE 15th International Symposium on Intelligent Systems and Informatics : SISY 2017*. Ed. by Szakál Anikó. New York: IEEE, 2017, pp. 15–16.

[615] György Eigner, Gábor Szögi, Péter Pausits, Imre Rudas, and Levente Kovács. "Nonlinear identification of a tumor growth model for validating cancer treatments". In: *2017 IEEE International Conference on Systems, Man and Cybernetics*. Ed. by Li Deng. New York: IEEE Systems, Man and Cybernetics Society, 2017, pp. 3159–3163.

[616] Levente Kovács. “Cyber-Medical Systems: the Digitalized Healthcare Approach and Its Trends”. In: 2017, pp. 1–2.

[617] Kovács Levente, Eigner György, Barkai László, Barkai László, Kempler Péter, and Várkonyi Tamás. “Closing the loop 2.0 – A mesterséges hasnyálmirigy szabályozásának legújabb eredményei”. In: 2017, pp. 13–14.

[618] Z Garaguly, M Kozlovszky, and L Kovács. “The application of holographic image reconstruction in the examination of liquids”. In: *SAMI 2018: IEEE 16th World Symposium on Applied Machine Intelligence and Informatics : Dedicated to the Memory of Pioneer of Robotics Antal (Tony) K. Bejczy : proceedings*. Ed. by Anikó Szakál and Iveta Zamecnikova. Seattle (WA): IEEE, 2018, pp. 125–130.

[619] József Klespitz, Miklós Bíró, and Levente Kovács. “Demonstration of Augmented Lifecycle Space in Heterogeneous Environment”. In: *SAMI 2018: IEEE 16th World Symposium on Applied Machine Intelligence and Informatics : Dedicated to the Memory of Pioneer of Robotics Antal (Tony) K. Bejczy : proceedings*. Ed. by Anikó Szakál and Iveta Zamecnikova. Seattle (WA): IEEE, 2018, pp. 167–172.

[620] Kovács Levente. “Merre tovább ...? II.” In: (XXII. Dunántúli Diabetes Hétvége 2018). Műhelyszekció - Inzulinpumpa munkacsoport, p. 1.

[621] Kovács Levente. “Mérnökinformatikus képzés új megközelítésben: Ipar 4.0”. In: (Legyél Te is Informatikus! - Informatikai Oktatási Konferencia 2018 2018). Informatikai felsőoktatás szekció.

[622] Hamza Khan, József K Tar, Imre Rudas, Levente Kovács, and György Eigner. “Receding Horizon Control of Type 1 Diabetes Mellitus by Using Nonlinear Programming”. In: *COMPLEXITY* 2018 (2018).

[623] Kinan Moranix, György Eigner, Tamás Ferenci, Levente Kovács, and Seref Naci Engin. “Prediction of the Survival of Patients with Cardiac Failure by using Soft Computing Techniques”. In: *IEEE 12th International Symposium on Applied Computational Intelligence and Informatics (SACI 2018)*. Ed. by Szakál Anikó. Temesvár: IEEE Hungary Section; IEEE Romania Section, 2018, pp. 201–206.

[624] József Klespitz and Levente Kovács. “Multivariable control structures of hemodialysis machines for patient fluid balance maintenance”. In: *IEEE 12th International Symposium on Applied Computational Intelligence and Informatics (SACI 2018)*. Ed. by Szakál Anikó. Temesvár: IEEE Hungary Section; IEEE Romania Section, 2018, pp. 415–418.

A. Physiological background

In this Appendix, I summarize the relevant physiological background to the scrutinized problems in the thesis. I also show the current technologies related to the possible physical implementation of the designed controllers described in the main part of the text.

A.1. Diabetes Mellitus

A.1.1. The role of glucose in the human body

The primary energy source of the human body is glucose ($C_6H_{12}O_6$) [139], and the body can utilize glucose in $\alpha - D$ structure only. Glucose (CHO) enters the body through the gastrointestinal system by eating. First, the consumed food degrades into smaller parts including complex sugars, which through different enzymatic reactions are broken down into simple sugars. The monosaccharides (glucose, galactose, fructose) are absorbed in the small intestines through sodium-dependent glucose cotransporters. The glucose is absorbed by the glucose-consuming cells (muscle-, fatty-, brain-cells and others) via glucose transporter (GLUT) gates formed by membrane proteins. These gates are driven by different reactions or in the case of muscle cells the physical activity can catalyze the opening of specific GLUT gate [139–141]. The reaction can be seen in Fig. A.1.

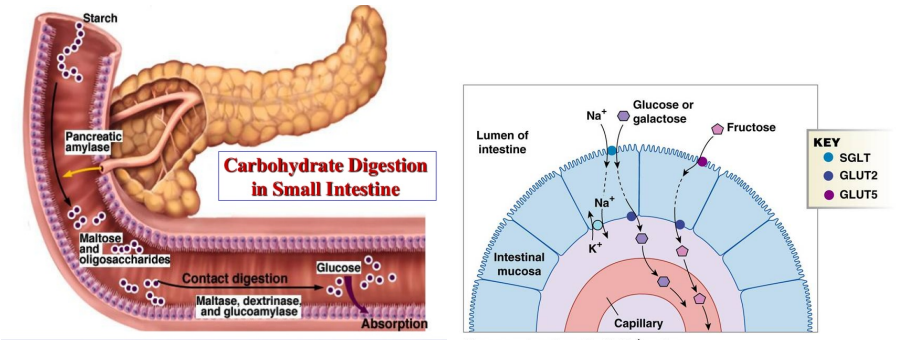


Figure A.1.: Digestion and glucose absorption processes ([142, 143])

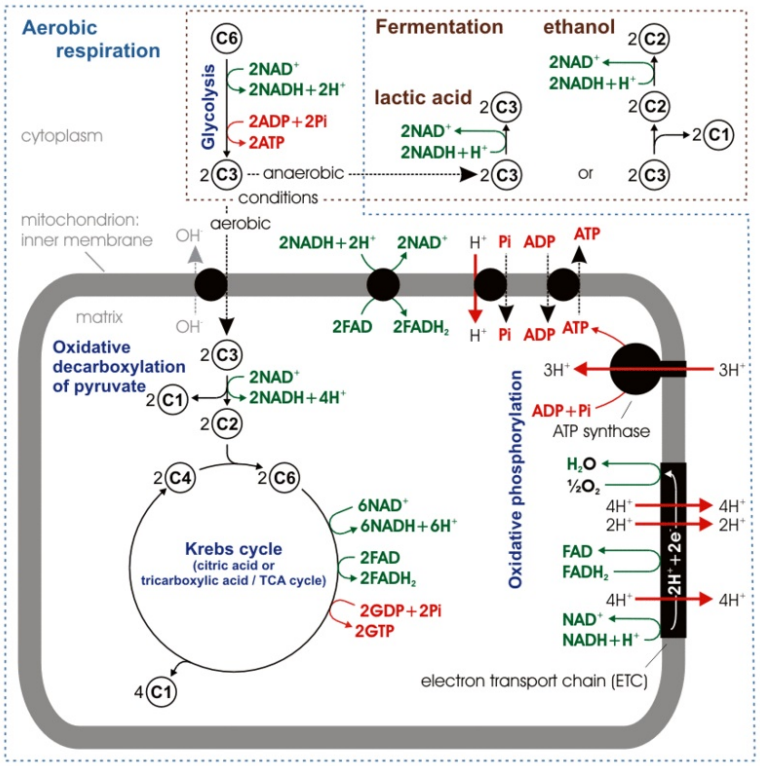


Figure A.2.: Energetic reactions on the atomic level at eucaryotic cell, Credit: Darekk2 [144]

The energy stored in glucose is processed through anaerobic and aerobic chemical reactions. This energy is applied to supplement the adenosine diphosphate (ADP) molecules with an extra phosphor atom to transform into adenosine triphosphate (ATP), which is the most important energy storage molecule in the body. ATPs are responsible for driving the electron transport reactions, protein pumps, etc. A graphical depiction can be seen in Fig. A.2, which presents these reactions for eukaryotic cells. The glycolysis is the first step of the catabolic reaction through which one molecule glucose is oxidised into two molecules of pyruvate ($C_6H_{12}O_6 + 2\,NAD^+ 2\,ADP + 2\,Pi \rightarrow 2\,C_3H_4O_3 + 2\,NADH + 2\,H^+ + 2\,ATP + 2\,H_2O$), with the release of ATP [141]. The primary energy-producing unit in eukaryotic cells is the mitochondria, operating as a separated unit with its micro-environment and internal DNA. The pyruvate molecules enter the mitochondria where, through the Szentgyörgyi-Krebs cycle, they are oxidized. The oxygen which is taken via the respiratory system is utilized mostly at this point. The result of the cycle is carbon dioxide (CO_2) and water (H_2O) (see Fig. A.2).

By understanding the natural glucose regulation processes, one can get a better picture

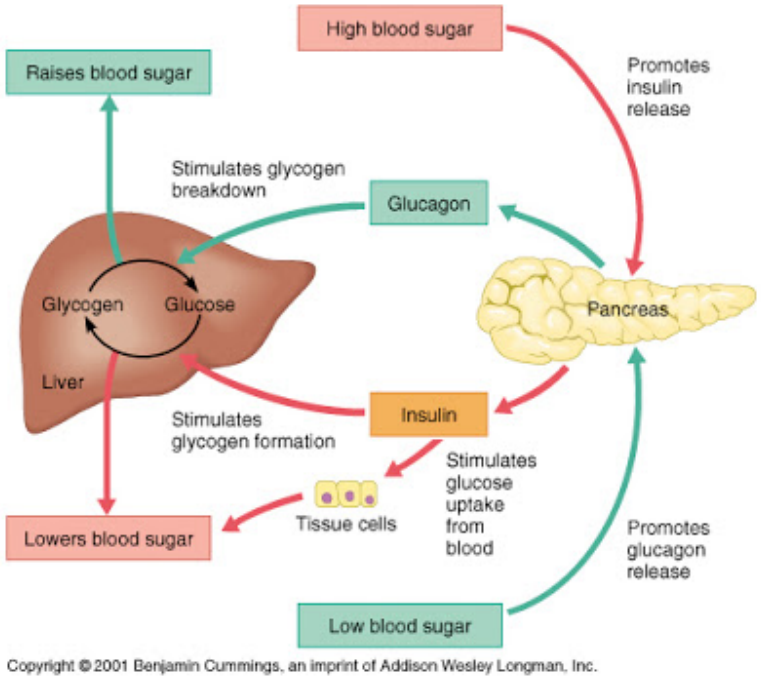


Figure A.3.: The regulation of the glucose household, Credit: Benjamin Cummings [145]

of diabetes mellitus (DM) as well. The main regulatory system of the glucose household (and other physiological processes) is operated by two pancreatic hormones, insulin and glucagon. The regulatory system can be seen in Fig. A.3.

When many glucose molecules can be found in the blood, the pancreatic Langerhans-islets release insulin hormones into the blood. The presence of insulin drives many processes at the same time. Insulin opens the insulin-dependent GLUT gates (e.g. GLUT-4) which facilitates the entering of glucose into the cells; it stimulates the glycogen synthesis, it fosters esterification (when the glucose becomes glycerol (i.e. fat)) and it coerces the production and secretion of glucagon. The result of these processes is low blood sugar levels. The counter-reaction becomes active when the blood glucose (BG) level is low, which drives the production and secretion of glucagon. The increasing level of glucagon facilitates glycogenolysis (the degradation of glycogen to glucose and the glucose secretion of the liver cells) and it inhibits insulin production and secretion, besides other processes [139, 146]. The liver is a central organ of the glucose household due to its ability to store and mobilize massive amounts of glucose in different forms and if it is required, release 500 [g] glucose per day [141]. Other important body parts are the muscle cells which can produce and store a small amount of glycogen for local usage in

case of extra need. An important aspect is that adrenaline (epinephrine) can facilitate the glucose secretion of the liver to handle stress reactions. In case of stress, glucose is needed to react to the source immediately and continuously. The glucose household is highly influenced by the brain and the nervous system. The brain does not require insulin for efficient glucose uptake due to that cells of the brain use insulin-independent GLUT transporters. The brain itself consumes approximately 25% glucose from the daily intake. The storing capabilities of the brain cells are very limited, thus it needs continuous glucose supply at the expense of other parts of the body. Continuous low blood sugar level leads to cumbersome decision making, dizziness, fainting, metabolic collapse, and finally coma or even death [146]. Kidneys play a key role in the glucose household due to they reabsorb the glucose molecules and other vital nutrients from the primer filtrate. Kidneys consume glucose to maintain their activities, although there is a limit to their effectiveness regarding glucose reabsorption. If the blood glucose level is persistently high, the tubular transporters may be saturated which leads to glucose loss through the urine. The DM got its name after this phenomenon when the kidney is not able to stop the loss of glucose which makes the urine sweet (while diabetes means passing through, the mellitus means sweet as the honey). As a consequence, the first indicator of the disease is the sweet urine suggesting that a given patient suffers from DM [6, 146].

A.1.2. The role of insulin hormone

The insulin peptide hormone is produced by the β-cells in the Langerhans islets of the pancreas. The most important catalyst for the production and secretion of the hormone is the low blood sugar level. The production and secretion of insulin can be seen in Fig. A.4. The β-cell uptakes the glucose via the GLUT2 gate. Increasing glucose level drives the ADP to ATP reactions, i.e. the energetic level of the cell increases. The high ATP level does inhibit the $Na - K$ channels. The consequence is the increasing level in K which facilitates the depolarization of the cell membrane and leads to Ca inflow. The increasing Ca level drives the secretion of insulin, which is stored in small granules. These are merged with the cell membrane [147].

Although the most important driver of insulin secretion is the high blood glucose level, other physiological processes may affect the phenomena (e.g. nervous activity, adrenaline, other hormones, and proteins). By increasing the BG level, the frequency of secretion also increases [6].

Insulin secretion oscillates with a period of 3 – 6 minutes [149, 150], which can be seen in Fig. A.5. The insulin is secreted into the bloodstream (near to the portal vein) and

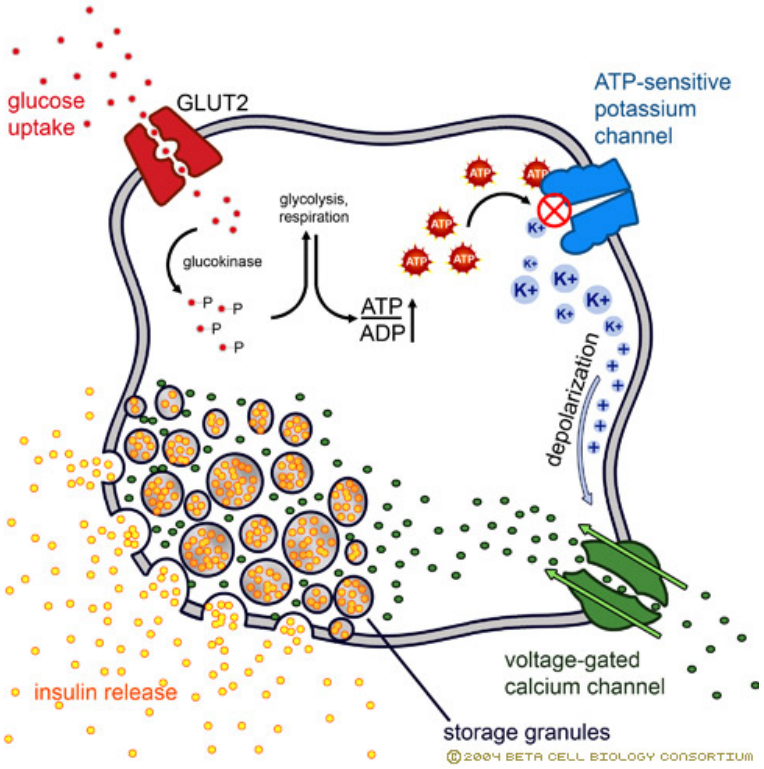


Figure A.4.: Production and secretion of insulin. Credit: Beta Cell Biology Consortium [148]

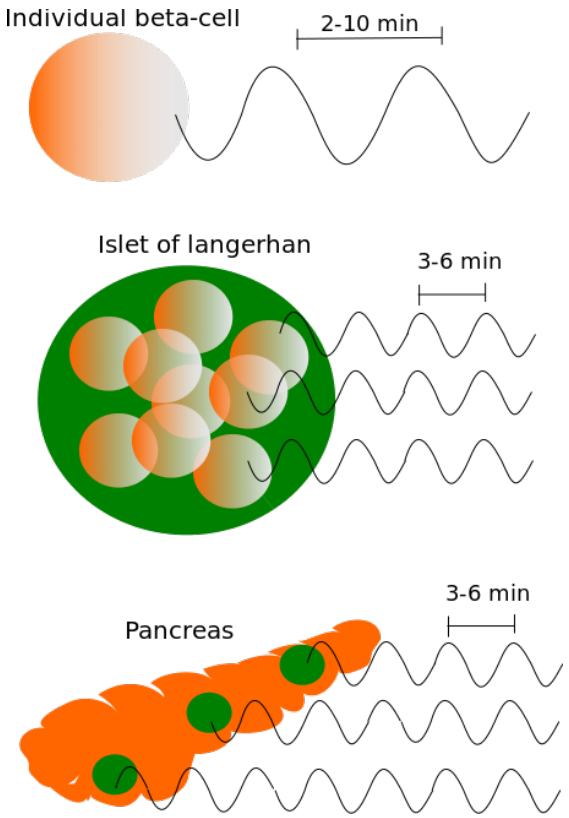


Figure A.5.: Insulin secretion [151]

spreads out through the veins.

Last, but not least, it is important to show how works insulin concretely. Fig. A.6 shows the operation of the hormone in the case of a liver cell. Insulin binds to the receptor which leads to the release of chemical messenger molecules. These facilitate glycogen production, the opening of the GLUT4 gate beside others.

A.1.3. Types of diabetes mellitus

Type 1 DM

Type 1 DM (T1DM) is the most dangerous DM condition which is lethal without treatment. It is caused by an autoimmune reaction in which the body's immune system burns out the β-cells of the pancreas. That results in insulin deficiency because the internal insulin production is practically ceased. Without insulin, the glucose-consuming cells with insulin-dependent GLUT gates are not able to uptake the insulin from the blood which leads to high blood glucose levels and the starvation of these cells at the

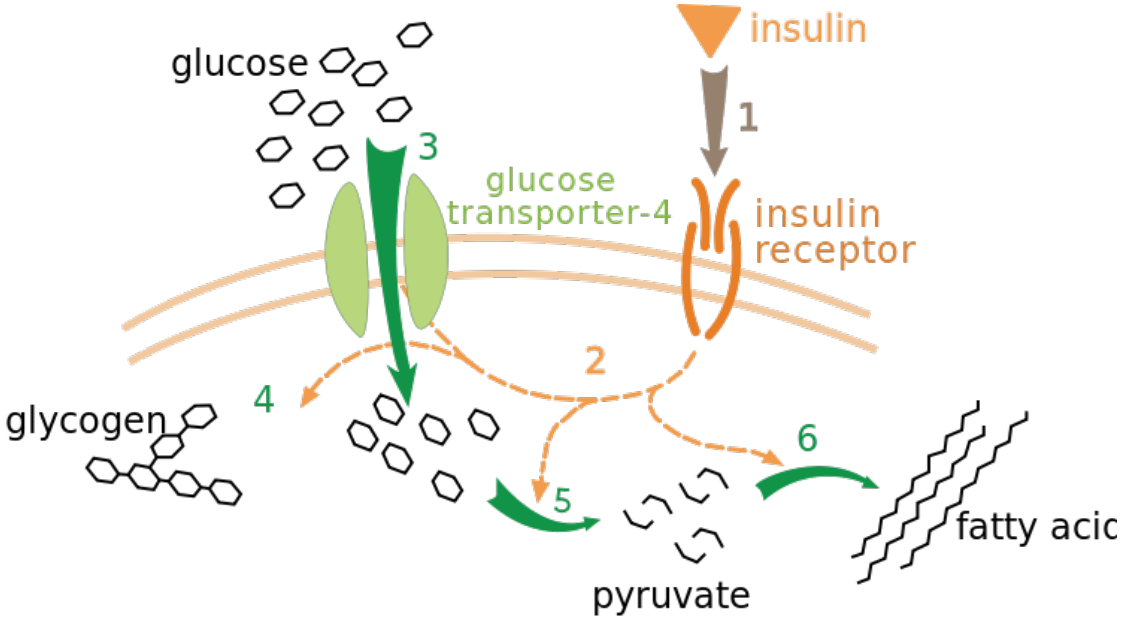


Figure A.6.: Effect of insulin in case of hepatic cell. Credit: XcepticZP [152]

same time. Usually, the disease emerges at a young age, and the symptoms (e.g. thirst and dry mouth, frequent urination, lack of energy, tiredness, constant hunger, sudden weight loss, blurred vision, dizziness, confusion) occur suddenly without any previous indication. Patients with T1DM form approximately 10 % of the diabetic population [5].

Type 2 DM

The most common type of DM is Type 2 DM (T2DM), and approximately 90 % of the diabetic population suffers from this variant. T2DM mostly occurs in mid-aged adults, but in recent years the prevalence is increasing in the younger population as well which is caused by the modern lifestyle [5]. In the case of T2DM, the body needs to face two equally harmful processes, which are the decreasing insulin sensitivity and the slow overload of the β-cells. The first stage of T2DM starts with high blood glucose variance caused by the consumed processed food and drinks which are usually loaded with CHO possessing a high glycemic index. Due to the appearing high BG levels, the body reacts with high insulin levels to maintain the diabetic state. Over time, this significant load leads to insufficient insulin production which causes permanently high BG levels. The high BG level demands continuous insulin production which is another source of stress. Besides, the permanently high BG level causes the saturation of the glucose-consuming cells as well. To protect themselves, the cells become increasingly

resistant to insulin which leads that an elevated amount of glucose remains in the blood. Due to the continuous load, the β-cells are not able to keep up with the insulin level This process leads to the burn-out of β-cells over time, and at this point, the T2DM turns into T1DM. Moreover, in this case, the symptoms are worse since the established insulin resistance requires different insulin treatments usually with high insulin dosages. Compared to T1DM patients, T2DM patients do not need external insulin intake in the first stage of the illness. Their condition can be maintained by changing their lifestyle and (if necessary) taking medication. In the second stage, they may need external insulin intake to help their internal production and decrease their load. In the third stage the insulin administration, similarly to T1DM patients, becomes necessary [5, 6, 147].

Other types of DMs

One of the frequently occurring diabetic states is the gestational DM (GDM) obtained during pregnancy, and caused by the increased BG level needed to provide enough energy for both the woman and the fetus. In most cases, GDM disappears after pregnancy, although, in some cases, occasional GDM turns into T2DM [5]. Another type is Double DM (DDM) which is characterized by increasing insulin resistance and decaying insulin production [3]. There are other rare types of DMs as well, but their occurrence is very mild and most of them are caused by genetic disorders [5, 146].

A.1.4. Possible means of treatment

Prevention

The easiest solution is the avoidance of the diabetic state in the case of T2DM. The risk of having T2DM can be highly reduced by establishing an appropriate lifestyle. This means doing physical activities, eating appropriate food may prevent the occurrence of T2DM in people with a genetic predisposition. It is not questionable that the person diagnosed with DM has to change his/her lifestyle. Doing physical activities is crucial because there are GLUT gates on the muscle cells that are catalyzed by physical activity. In this way, the BG level can be decreased without other drugs or insulin. Usually, these people are obese which could make DM worse, so that the weight also needed to be reduced. Consumption of food with a high glycemic index should also be avoided at all.

Medication by drugs

Medication by drugs is a common therapy both in the pre-diabetic state and in the early stage of T2DM. Several drugs are available with different physiological effects. The drugs

can be categorized according to their effect mechanism [153, 154]:

- Biguanides: Inhibiting the glucose production of the liver (e.g. Metformin);
- α-glucosidase inhibitors: Facilitating the break down of complex sugars (e.g. Acarbose);
- Dopamin agonist: Helping to avoid the establishment of insulin resistance;
- DPP-4 inhibitors: Facilitating the insulin production (e.g. Linagliptin);
- Incretin mimetics, glucagon analogs: Slowing down the emptying of the stomach and maintaining the glucagon usage (e.g. Albiglutide);
- Meglitinides: Facilitating the insulin release (e.g. Nateglinide);
- Sodium-glucose transporter (SGLT) 2 inhibitors: Facilitating the glucose excretion to the urine (e.g. Dapaglifozin);
- Sulfonylureas: Increasing the activity of β-cells (e.g. Glimepirid);
- Thiazolidinediones: Decreasing the glucose level in the liver by increasing the uptake and use of glucose in the fatty tissues (e.g. Rosiglitazone).

Intensive Conservative Therapy (ICT)

ICT is a combination of the use of external insulin intake, medication, changing lifestyle, and continuous education. In the case of ICT, diabetic patients use short- and long-term insulins complying with the prescribed glycemic goals and use different medications to prevent the side effects (e.g. Aspirin) and to decrease the load on their body. ICT can provide a longer and healthier life for diabetic patients. However, ICT can be done only in a strong collaboration between the medical staff and the patient.

Insulin administration by insulin pen

External insulin administration is the most common way of treatment. By using an insulin pen, the insulin can be injected into the subcutaneous level immediately. A pen consists of an insulin reservoir, dispenser, and needle. The dispenser can be used for precise insulin administration. A schematic insulin pen can be seen in Fig. A.7.

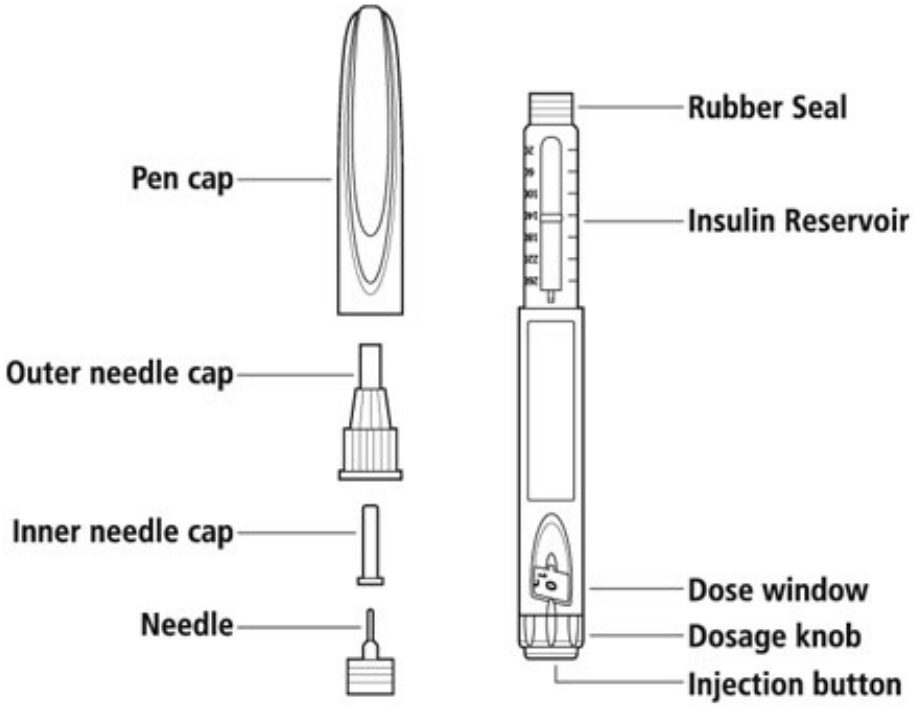


Figure A.7.: A regular insulin pen, Credit: UPMC [155]

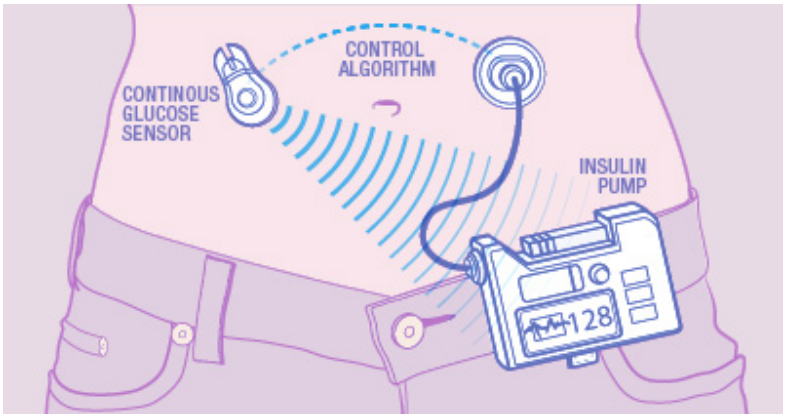


Figure A.8.: Insulin pump, Credit: Mayo Clinic [156]

Insulin administration by insulin pump

Insulin pumps were developed almost 20 years ago. In this thesis, these devices provide a central element in the realization of the control algorithms, since the actuation of continuous insulin administration can only be performed by using these devices. Figure A.8 shows a regular insulin pump and its components.

A.2. Tumor Growth

A.2.1. Physiological background of tumor growth

Cancer is a group of diseases that are characterized by abnormal cell mechanisms. The tumor consists of a cell concourse (tumor or cancer concourse) which is not regulated (or cannot be regulated) by the cell-regulatory mechanisms. The biggest problem besides the unregulated growing and spreading of these cells is that they consume nutrients from normal cells. They also create masses that affect the normal operation of organs, nerves, and vessels, and produce cell materials that are toxic to the body [157]. Two main groups of tumors can be distinguished which are benign and malignant. Benign tumors (usually) do not produce metastasis and do not invade surrounding tissues and organs. On the contrary, malignant tumors do provide metastasis and the general outlook for the patient is far worse. The most usual behavior of malignant tumors can be easily described. First, the cells are growing, dividing, and proliferating with no respect to the presence of regulatory signals. After that, they avoid programmed cell death (apoptosis) such that the number of cell divisions is limitless. At last, they promote blood vessels construction to uptake more nutrients. They also create metastases with which they

invade an increased number of tissues and organs [158].

The presence of cancer may cause different symptoms. Unfortunately, it is generally true that these symptoms more or less appear at a developed stage of the tumor. Depending on the type of the tumor, unexplained weight loss, lump, abnormal bleeding, strange bowel movements, prolonged (maybe bloody) cough, frequent inflammations, unexpected movements, issues in nervous and hormone homeostasis could occur as a sign of the illness. In the case of humans one distinguishes between more than a hundred type of cancers [159].

The majority (90–95%) of cancers are due to genetic mutations caused by environmental causes, while the remaining 5–10% cases are stemming from genetic disorders [159]. Several artificial and natural environmental effects could cause cancer. Artificial causes often involve the use of tobacco and alcohol, poor diet and/or obesity, exposure to radiative environment, pollution and/or contact with polluting materials, high stress and absence of good quality rest, and lack of physical activity. In contrast, natural causes can be radiation from natural sources, toxic environment and contact with toxic elements, or infections [159, 160]. In males, the most common type of internal cancer is colorectal, prostate, stomach, and lung cancer. In women the most common types of internal cancers are colorectal cancer, breast cancer, lung cancer, and cervical cancer [161]. External cancer is called melanoma which is also a common type with increasing occurrence in the global population [159].

Regular treatments of cancer

The most conservative therapy is a surgical intervention in which the tumor is partially or completely removed by the surgeon. Surgical intervention is suggested if the tumor is well-localized [162], although, it can be applied only if the cancer is operable. Surgical oncology is commonly applied if the tumor is related to the esophagus, stomach, duodenum, colon, liver, and pancreas [163]. Radiotherapy is also regularly applied, especially, if the tumor is not-operable. This type of treatment utilizes the fast division of tumor cells by damaging their DNA [164]. Radiotherapy can be applied as monotherapy, but usually, it is combined with surgical intervention or chemotherapy [165]. In the case of radiation therapy, the targeted high-energy particles (electrons and photons) are used [166] to degrade the integrity of the DNA of the tumor cells. Nevertheless, this ionizing radiation damages the surrounding healthy tissues as well. Chemotherapy utilizes the fast division of tumor cells as well because its effect is much more dangerous. The chemical agents can destroy cancer cells by interfering with their ability to grow or multiply. The response of tumor cells for chemotherapy can be different, thus different types of chemical agents needed to be used

for different tumors, although, it may happen that a given tumor does not react to the therapy at all [167]. Chemotherapy could have serious side effects, for example damaging organs, especially the liver, loss of hair, urinary incontinence, and so on. Unfortunately, these chemical agents also disrupt the general behavior of healthy cells, leading to side effects in the vast majority.

Targeted Molecular Therapies

TMTs can inhibit the signaling pathways of tumors, i.e. the specific molecules which are produced by the tumor cells. These molecules can be found in the case of other cells as well, but their presence is much smaller than in tumors. At the early stage of TMT development there was a need to find antibodies that target only tumor cells [24]. As a consequence, most often targeted signaling pathways by TMTs are the EGFR/HER1 (epidermal growth factor receptor, human epidermal growth factor receptor), VEGF (vascular endothelial growth factor) and HER2. The most common inhibition types are [168]:

(i) binding and neutralizing ligands;

(ii) occupying receptor-binding sites;

(iii) blocking receptor signaling within the cancer cell;

(iv) interfering with downstream intra-cellular molecules.

Today, two common TMTs are used in medical practice, which are monoclonal antibodies and small molecule inhibitors. Monoclonal antibodies are large molecules with a protein structure and they target the *(i)* and *(ii)* pathways [169]. These drugs can be used intravenously to avoid their protein structure from denaturation which would happen in the gastrointestinal system. Small molecule inhibitors are smaller than the antibodies which allow them to enter the cells and target *(iii)* and *(iv)* pathways [170], typically the tyrosine kinase signaling (intracellular alter its components. Small molecule inhibitors are usually administered orally. One of the main differences between the two types of TMTs is that monoclonal antibodies do not undergo hepatic metabolism, but small molecule inhibitors do. Hence, by using TMTs, a more personalized treatment can be achieved focusing on the vital phenomena of the tumor and applying specific drugs according to [171]. The main benefits of TMTs are that they are less damaging to the normal cells, causing fewer side effects, improving the efficiency of regular therapies, and improving the quality of life of the patients [172]. Among the several types of TMTs, the most common

used ones are the apoptosis inducers [173], anti-hormone therapies [174], immune system facilitators [175, 176], gene expression inhibitors [177], signal transmission inhibitors [178] and anti-angiogenic therapies [171].

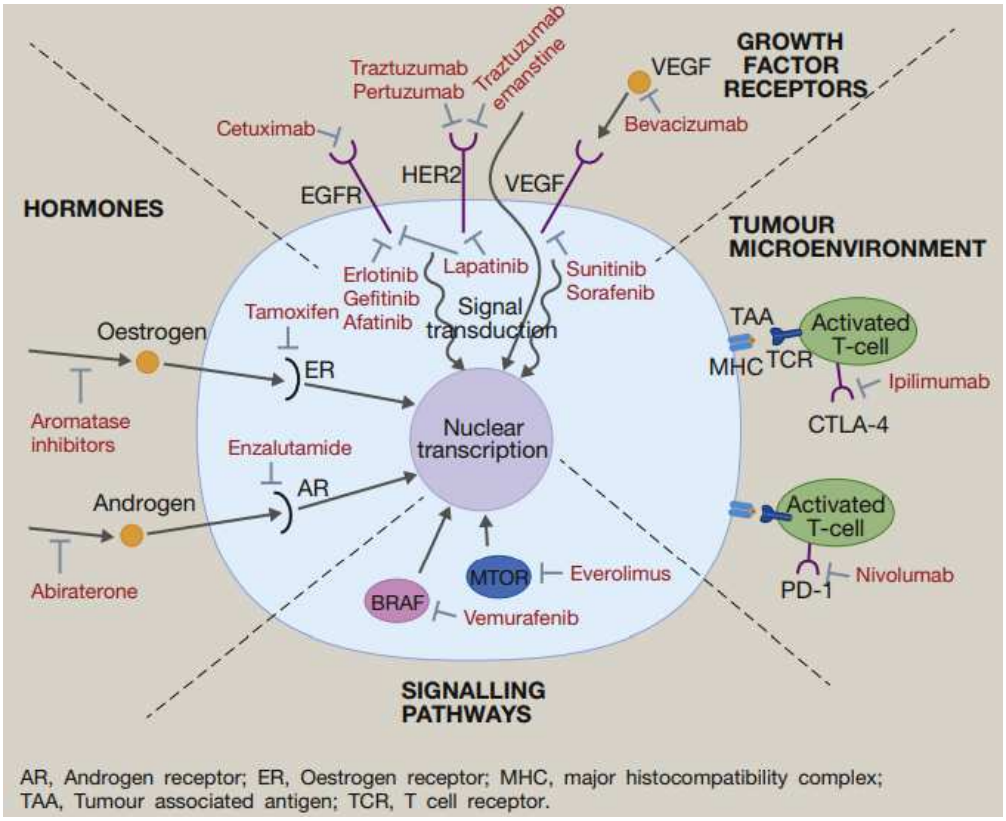


Figure A.9.: Targeted molecular therapies, Credit: Charlton et al. [178]

In the case of conventional therapies, the development of tumors might not be precisely required, because the goal is to eliminate the mass of the tumor (by removal or radiative of chemical degradation). The goal of TMTs is to eliminate not the tumor mass itself, but instead to eliminate the toxicity of the tumor and as a side effect degrading the tumor mass. In the case of TMTs, a proper tumor model must be derived to select the best therapeutic agent or to develop one. It is more important to act against the toxicity of the tumors because the life expectancies of patients are better with an inactive tumor mass than if they do not have a tumor for while with a higher chance of relapse [168].

A.2.2. Antiangiogenic Therapies

Tumor induced angiogenesis

Angiogenesis is a physiological process in which new blood vessels are formed by endothelial tissues. Angiogenesis occurs at specific times in the human body as a cardinal process (e.g. the embryogenesis). In the case of adults, angiogenesis is quite infrequent and mostly happens after injuries during recovery, when it is induced by external circumstances (e.g. low oxygen concentration) and for example, in the women's menstrual cycle [179]. Angiogenesis is also a very common phenomenon during the vascularization of tumors [157]. The development of tumors can be divided into two phases. In the first phase, the tumor is small and utilizes the oxygen and nutrients from its surroundings via diffusion, and in this phase, the tumor is growing slowly. This phase is called as "avascular" state of the tumor, which means it does not have its blood vessels for the oxygen uptake [157]. By using this source of energy, the tumor can grow only for a certain limited volume. This volume is different with every tumor (usually it is 100 to 200 μm) and it is limited by the so-called diffusion barrier.

After this certain volume, cancer requires more oxygen and nutrients to grow. The lack of oxygen induces the tumor cells to start the production of the Vascular Endothelial Growth Factor (VEGF). This stage is called the angiogenic switch. By signaling VEGF, the tumor stimulates the endothelial cells, which are responsible for the formation of new blood vessels. From these new vessels, the tumor can get all nutrients for further growth and to induce metastasis through these vessels from which invader colonies are created at other parts of the body. The tumor with its blood vessels is called a "vascularized" tumor [160]. The formation of new blood vessels induced by the tumor can be seen in Fig. A.10.

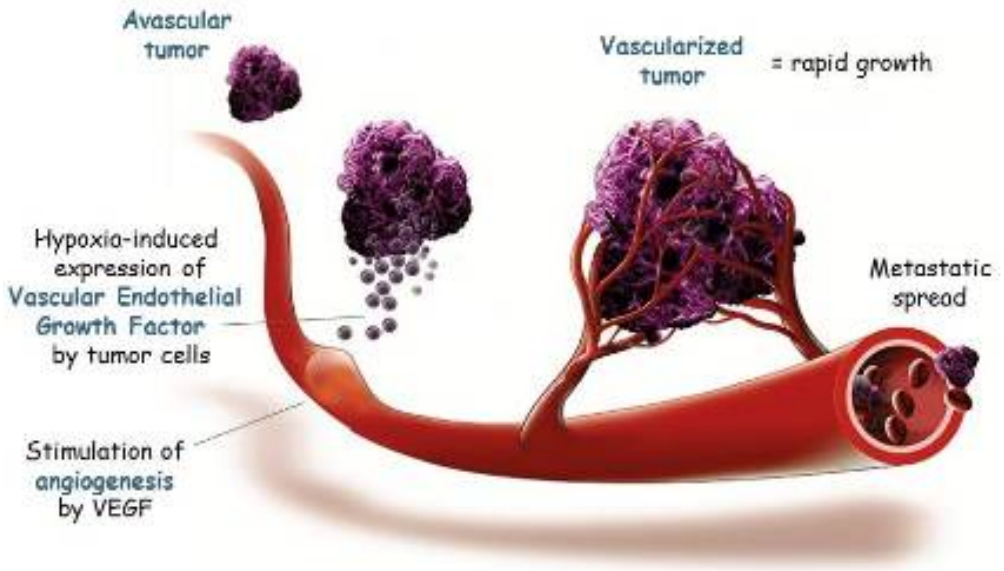


Figure A.10.: Development of tumor in general, Credit: Letellier et al. [180]

Antiangiogenic therapy

During tumor-induced angiogenesis, the new vessels change phenotype, which is called vascular remodeling. Thus the newly formed vessels become disease-specific. The endothelial cells undergo sprouting, proliferation, and regression in tumors, and they also become dependent on VEGF. VEGF is an important pro-angiogenic factor controlling tumor growth. By inhibiting VEGF signaling in tumors, the additional angiogenesis stops. The inhibition of VEGF leads to apoptosis only in the new vessels in tumors and does not harm vessels that already exist, which makes the blocking of this pathway a promising target [28]. The VEGF is continuously produced during the growth of tumors. The main difficulty to develop antiangiogenic therapies is the poor feedback about the efficiency of treatment because the decrease of tumor size is a slow process that is hard to monitor. However, changes in the hemodynamic parameters appear soon after the initiation of the therapy. These can be monitored for example by using perfusion MRI or CT or ultrasound devices [181]. As it was already mentioned, the aim of angiogenic inhibitors (and TMTs as well) is not to eliminate the tumor mass itself but eliminate the developing, growing, and spreading of tumor cells. If the tumor evolution can be kept in a dormant state and the cellular proliferation rate is balanced by the rate of apoptosis then the size of the tumor will be only a few millimeters and it will not be able to grow [25].

Compared to chemotherapy, this does not result in toxicity in the body which is one of

the most important aspects of TMTs. In the case of chemotherapy, a significant portion of people dies each year because of side effects and the toxicity caused by the drug [182]. Another drawback is that the tumors can develop resistance against chemotherapy due to the genetic instability, heterogeneity, and fast proliferation of tumor cells. However, endothelial cells are genetically stable and homogeneous with a low rate of mutation. Thus, a therapy that affects endothelial cells induces low or no resistance against drugs [183–185]. Antiangiogenic therapies can improve survival by increasing tolerance to the toxicity induced by chemotherapy as well [186].