Óbuda University

PhD Thesis

Closed-Loop Controller Design Possibilities for Nonlinear Physiological Systems

by

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Budapest, 2017

Contents

Acknowledgments

First of all, I would like to thank my doctoral supervisor, *Prof. Levente Kovács* – without his guidance and support from the beginning of my master studies this dissertation would not have been written. He believed in me when I was not and sometimes only his faith has been keeping my spirit up.

Next, I would like to special thank *Prof. József K. Tar*, from whom I have learnt a lot not just professionally but also humanly – his help was eternally in order to finish this work.

After, I would also like to say thank *Prof. Imre Rudas* – who has gave me extraordinary possibilities and embraced me.

I would like highlight my colleague *Dr. Tamás Ferenci*, who provided me practical advices while I was writing the dissertation.

Special thanks behoove the leaders of the Doctoral School *Prof. Aurél Galántai* and *Prof. László Horváth* for their support.

I want to say thanks to my family without they help this work would have been impossible – to my Mother-in-Law *Kati* and brother-in-law *Benji*; to *Dr. Bernadett Eigner and Aunt Mary* for their humanly and financial support; to my *Sis* for her kindness; to my *Grandma* who always supported me; to my *Dad* for his encouragement; to my *Mom* for her continuous love and support.

I would like to also thank to all of those who are not personally listed here – many of my colleagues and friends from whom I learned a lot.

Finally, I would like to say special thanks to my beloved fiancée *Barbi* for her endless patience and love – as she always says this work would have been shorter but more boring without her.

1 Background of the Research

The aim of this theses is to introduce such kind of modeling and controller design solutions which can be used in case of nonlinear biological systems. Each proposed methods are universal ones and can be used in case of arbitrary nonlinear processes, however, the application of them is unique in the current research field.

My main motivating goal was the use of the developments and applications in the research of Diabetes Mellitus (DM) from engineering point of view - in this spirit I always kept in the focus how the reached results will be useful to reach this goal. Namely, how can the proposed techniques be applied in case of DM.

Modeling and control is extremely important in the artificial regulation of physiological processes, especially where the good quality of external control is a must [1]. However, the given field is loaded by several challenges. Most of them are highly nonlinear, poorly described in full aspects due to the multiple and diverse connections between the physiological systems, deep investigations and measurements cannot be done or possible but with hard constraints, etc. [2]. Although these facts, the evolution and process of different types of DM became well described in the recent decades [3].

DM is a serious, chronic disease connected to the metabolic system of the human body. The disease occurs either when the amount of insulin produced by the pancreas is insufficient or when the body cannot effectively use the insulin it produces [4]. Insulin is the key hormone of the blood glucose regulation produced by the β-cells in the Langerhans-islets in the pancreas [5]. It makes possible the entering of the glucose into the glucose consuming body cells. Most of the cells feast glucose which is the major energy source in living organisms [6]. DM researches are hot topics on the biomedical engineering field due to the dramatically increasing number of diabetic patients. According to the newest estimations of the International Diabetes Federation (IDF) for the number of people who live with such form of diagnosed and undiagnosed DM is about 415 million worldwide in 2015 [3]. Furthermore, the short term prospects suggest that this number can be reached the 642 million, around 6.8% of the expected global population by 2040 [3, 4].

DM is classified into Type 1 DM (T1DM), Type 2 DM (T2DM), Gestational DM, Double DM, Genetic DM, Secondary DM, etc. [7, 3]. Despite the several different types of DM, the T1DM and T2DM are the most widespread. The T1DM is related to the insulin hormone, since during the emergence of the disorder, the insulin producer β-cells are burned out due to intense autoimmune reaction in which the patient's own immune cells destroy them. The occurrence of T1DM is around 10% in the diabetic population [7]. The most common type of DM is T2DM [3]. The incidence of it is around 90% in the diabetic population. The disease evolves over longer period in the patients body. However, the body is able to produce insulin internally, the body cells become resistant to the hormone and the effect of it becomes insufficient. Over long period persistent hyperglycemia and increasing insulin resistance can be observed [8, 5].

In most of the cases the patients with DM need external insulin intake in order to keep their glycemia in an appropriate, healthy range. The common therapy - beside prescription about the lifestyle (physical activities and diet) - is the external insulin administration. Insulin is delivered via subcutaneous injections. There are different devices with which the diabetic patients can manage the insulin delivery. Usually, it is done by insulin pen which is a small pen shape mechanical device which consists of dispenser, insulin reservoir, injection mechanics and thin needle parts. [9, 7]

An other solution for insulin administration is the semi-automatic or automatic insulin pump or Continuous Subcutaneous Insulin Infusion (CSII) devices, which can be used both DM cases as well, however, the indications of usage are different [10, 11, 12, 13, 14]. The pump or injection system contains insulin reservoir which connects to the subcutaneous regions via thin catheter. This electromechanical devices are able to delivery insulin boluses automatically based on predefined rules. The pumps using rapid acting insulin and the delivery protocols are varying as demands the patients need.

The long term goal of the research of DM from engineering point of view is to develop the so-called Artificial Pancreas (AP) concept. This development consist of three major part [15, 16, 17, 18, 19, 20, 21]:

- Continuous Glucose Monitoring System (CGMS) which provides the BG measurements at given time instances (regularly in every 5 minutes);
- Programmable electromechanical insulin pump device (and an other unit if necessary, e.g. a connected smartphone) – the softwares (including the control algorithms) run on this;
- Advanced control algorithms which are able to provide sophisticated control of the BG level.

Due to the fact that insulin pump therapies are used mostly in 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 in order to keep the blood glucose concentration in the normal glycemic range, i.e. 70-110 mg/dL (3.9-6 mmol/L) and relying if possible on the compliance of the patient. The ultimate goal is to avoid the dangerously low blood glucose levels (massive hypoglycemia) that could directly endanger the patients' life.

The soul of the AP concept is the usage of appropriate control algorithms. Over the last decades, most of the available control concepts have tested on this field. However, – more or less – almost all of the applied methods lie on Lyapunov's second or direct method about the stability of systems [22, 23].

The most important directions focus on model predictive control (MPC), fuzzy rule-based and other soft computing techniques, classical, robust and fractional PID control techniques; however, without having yet a general solution on the problem [15, 17, 20, 21, 24, 16].

Simplistically, every control algorithm considers similar principles; namely, the fulfillment of prescribed quality and quantity properties. The first attempts on this area were related to "Proportional-Integral-Derivative (PID)" control being still the most widely used classical control technique in the industry. Although the basic concept of PID control is not too sophisticated, highly advanced solutions like robust PID [25, 20] or switching PID [26, 27] have been applied for the AP concept. Fractional PID control is in the mainframe of the physiological related control tasks [28]. There is example regarding to the application of fractional PID in the research field, like [29], but the usage as a common technique is not usual in the research field, however.

The MPC based solutions are widely used successfully since almost thirty years ago in the control engineering [30, 31, 32, 33] and in physiological related context as well [34, 35, 36]. MPC techniques represent probably the mostly used advanced control method in the AP concept, but they suffers from intra- and inter-patient variabilities and external noises. MPC is a model based solution meaning that the controller tuning is based on the properties of a mathematical model (called nominal model). Nonetheless, MPC algorithms produce the best results in individual therapy with considering closely ideal conditions. Several, highly developed MPC based control solutions appeared in the recent years like Robust MPC (RMPC), Nonlinear MPC (NMPC), Robust, Nonlinear MPC (RNMPC), MPC with moving horizon [37, 38, 39, 40]. One of the most straightforward direction is the MPC design by using soft computing tuning tools [41]. The latter technique was successfully implemented on embedded systems which is a part of an artificial implementable AP [42].

Soft computing methodologies have been applied also several times in the AP concept, but only in the recent years have been investigated in clinical trials [43, 44, 45].

Modern robust control methods like $\mathcal{L}_2$- or $\mathcal{H}_\infty$-based ones were introduced in the AP researches in order to stave off the determinative uncertainties coming from inter- and intra-patient variability. Supplemented by LPV methodology (providing the opportunity to handle the original nonlinear system/model as a linear one; hence, to give access using the original nonlinear model for linear control methods enumerated above), modern robust control successfully deals with the quality and quantity requirements [46, 47, 48, 49]. Another useful direction in this domain proved to be the combination of LPV methodologies with LMI-based one [50, 49, 51].

2 Directions and Goals of the Research

The theoretical and practical developments provided by this thesis are fit into the above mentioned AP concept. The introduced methods can be used concerning to this research area.

2.1 Robust Fixed Point Transformation based solutions

The RFPT based methods have several benefits compared to other techniques (most important ones are detailed later). Previous researches shown that the RFPT based controllers are able to provide appropriate control action with high accuracy in case of highly nonlinear systems beside having only limited information about the internal states of the controlled system and using only the measured output as the basis of control [52, 53, 54, 55, 56]. Furthermore, these techniques proven their applicability in physiological related control tasks as well [57, 58].

My primary aim was the investigation of the application possibilities of the RFPT based controller design method regarding to T1DM control in order to prove that by using this method similar, satisfactory glycemia control can be achieved than the currently exists methods – as aforesaid, on a more flexible basis from controller design point of view. The introduction and use of this is novel on the given research field.

2.2 Linear Parameter Varying based tools

Most of the mathematical models which describe physiological processes have nonlinear attitude, where the nonlinearity comes from several sources (e.g. type of connections, communication between parts, enzyme kinetics, etc.) [1]. These models can be described with the LPV theorem without exception. The main motivation behind the use of LPV methods is to embed the nonlinearity causing, time varying and other unfavorable elements into a given ”scheduling variables” which form the so-called parameter vector. The parameter vector realizes the parameter space and – due to the mentioned reasons –

carry the fundamental properties of the LPV model. By using these methods, from the controller design point of view these disadvantageous terms can be hidden and linear designing theorems and tools can be used.

My primary aim was to exploit the aforesaid beneficial properties of the parameter space of LPV systems for control engineering purposes. Moreover, my goal was to the developed tools could be used in general sense and not just only apply for physiological processes.

2.3 Tensor Product Transformation based methods

In nonlinear physiological systems one crucial point is the effective handling of the nonlinearity from both modeling and control points of view. This is challenging even now, when several methods are available, because all of the processes and systems require unique approach. There is no general solution, yet. Although, the recently appeared TP transformation based modeling and controller design provide a general way regard to the issues concerning the control of such systems. The TP model transformation can be effectively combined with LPV techniques and LMI or Bilinear Matrix Inequality (BMI) based design methods [59, 60, 61, 62].

The first step of this path is to realize appropriate TP models through the TP model transformation which can be used later for controller design purposes. In this thesis my goal was to achieve this ”first step”, namely, to realize the TP models which can be used concerning to the LMI based controller design in my later research on the research field.

3 Materials and Methods of Investigation

3.1 T1DM control via RFPT framework

In contrast to the Lyapunov method or classical control, the RFPT-based controller design has many advantages. It focuses on the kinematics of the motion which may have more importance than the global asymptotic stability; it does not require precise model of the controlled process, just an approximate one may do well (may be as highly approximate that the state feedback may become unimportant); the parameter uncertainties are well tolerated; and finally, the realization of the method is easier alongside certain given steps [55, 56, 54].

In the first thesis described how are we able to apply the RPFT based controller designing method in case of general physiological processes. I provided deep analysis about the use of the process along which were built up the appropriate framework for my research.

I strived to provide the full picture about the T1DM related controls. In this manner, I proven the usability in case of three different T1DM model (Minimal Model [15], Cambridge Model [40], UVA/Padova Model [63]) – the differences between them reflected in their complexity, internal connections, sub-models (absorption, insulin dynamics, etc.) and other properties. However, both of them contained those highly nonlinear core structures which make the controller design challenging.

3.2 Completed LPV controller and observer scheme for LPV systems

In my second thesis I focused to a special form of LPV models which are the most frequent in physiological related control engineering tasks. It is generally true that in most of the cases, the nonlinearities are connected to the central model structure. That means that these nonlinearities occur in the state matrix $\mathbf{A}$ and the inputs and outputs of the models are not affected by them [64, 65]. Therefore, when the LPV form of them are constructed, only the state matrix will be parameter dependent: $\mathbf{A}(\mathbf{p}(t))$.

In case of LPV systems it is hard to find such universal tools of which the performance of the LPV based modeling and control can be measured and comparison can be done. In accordance with my aims, I wanted to find such general tool which is able serve in such a way. I used the special properties of the parameter space which is a real Euclidean vector space ($\mathbb{R}^q$) generated by the $\mathbf{p}(t) \in \mathbb{R}^q$ parameter vector which carries the fundamental properties of the investigated LPV model class. These special properties allow us to define Euclidean norm based difference on that space which can be used as the sought tool.

During the investigations I discovered that based on the special properties of the parameter space it is possible to design novel completed controller and observer structures – which efficiently exploit the afore mentioned properties and the matrix similarity theorems. By using these methods is it possible to use linear controller design methods on a state feedback basis and apply them on the original nonlinear model via the developed tools.

3.3 Usability of the TP model transformation for DM

The TP model transformation based approaches originate from the parameter dependent fuzzy system techniques [66]. The TP method was originally described in [67, 59]. The approach was summarized in [60] in case of qLPV based systems and controller design. Concisely summarized, the TP model transformation is able to transforms a given function into a determined TP function form regardless of the type of the original function, if the exact transformation is possible; otherwise, the TP model transformation provides a TP function form approximation with given accuracy.

The TP form complexity can be settled by sampling frequency on the given parameter domain which allows to determine the approximation accuracy of the original function by the TP function. Since most of the qLPV models can be described by qLPV functions, TP model based transformation can be used on them. Through this process, a TP transformation based TP model can be created which can approximate the original qLPV model. In other words, the resulting TP model can approximate the original qLPV model. This approximation can be a ”close-to-original” approximation (lower accuracy) or maybe a ”mimicry” (high accuracy) of the original model depending on the used simplifications (regarding to HOSVD and convex hull) during the transformation. TP transformation is an effective way for convex hull manipulation of polytopic structures and can be well combined with LMI-based techniques. These properties allow to reach less conservative, more optimal LMI-based controller design possibilities than the usual LMI-methods [60].

As I mentioned above my goal was to develop those DM related TP models, which can be used later during the TP based control.

4 New Scientific Results

Thesis Group 1: T1DM control via RFPT framework

Thesis 1

I have developed an RFPT-based controller design framework for physiological systems. The provided solutions allows the using of highly approximating (rough) model of the physiological system to be controlled.

Thesis 1.1

I have proven the usability of the developed framework in case of the low complexity T1DM model, the Minimal Model. The designed controller keeps the BG level in a narrow range and it is able to suppress high glucose variability as well.

Thesis 1.2
I have proven the usability of the RFPT-based controller design framework in case of highly complex T1DM models: the Cambridge model (so called Hovorva-model) and the Pavia-Padova model (so called Magni-model). The developed RFPT-based controllers provide fast adaptivity and they are able to keep the blood glucose level of the complex T1DM models inside a given selected range even under unfavorable glucose loads or soft blood sugar variability.

Relevant own publications pertaining to this thesis group: [68, 69, 70, 71, 72].

Thesis Group 2: Completed LPV controller and observer scheme for LPV systems.

Thesis 2
I have introduced mathematical tools for LPV related control tasks which successfully exploit the possibilities lied in the specific properties of the parameter space of LPV systems. By using these tools different quality markers can be defined and specific complementary LPV controller and observer structures can be designed.

Thesis 2.1
I have introduced a norm based ”difference” interpretation regarding the LPV systems, based on the properties of the LPV parameter space. I have defined how to use these interpretations as error and quality criteria during modeling and control and demonstrated my theoretical findings on a concrete example in diabetes modeling.

Thesis 2.2

I have developed an LPV based complementary controller structure in order to control nonlinear systems. The developed method requires the knowledge of classical state feedback theorems and less complex than the LMI-based methods, moreover it requires less computational capacity than the LMI-based techniques. I have demonstrated the usability of the developed tool in case of different nonlinear systems, with unfavorable circumstances demonstrating that the developed method provides stability and appropriate control action.

Thesis 2.3

I have developed an LPV based complementary observer structure which can estimate the actual values of the states in case of directly not measurable ones. I demonstrated the usability of the developed tools in case of a nonlinear system. I have proven that the complementary observer can accurately estimate the states of the given specific LPV systems.

Relevant own publications pertaining to this thesis group: [73, 74, 75, 76].

Thesis Group 3: Usability of the TP model transformation for DM

Thesis 3.1

I have realized a TP-based ICU model with small approximation error. I proved that in case of the given nonlinear ICU model better approximation error can be reached, if the operating equilibrium of glycemia (G_d) of the model was not equal to the model equilibrium of glycemia (G_E).

Thesis 3.2
I have investigated the robustization possibility of the blood glucose Minimal Model via TP framework. I have realized robust T1DM and T2DM TP-models, robust from parameter variation point of view. Regarding the LMI-based controller design, this property can be useful in guaranteeing the controller's robustness by the created robust TP models.

Thesis 3.3
I have proven the usability of TP-model transformation in case of highly complex T1DM model. I have demonstrated that several control oriented qLPV models can be derived from the original model approximating it with high accuracy.

Relevant own publications pertaining to this thesis group: [77, 78, 79].

5 Discussion and Practical Applicability of the Results

This dissertation presented three control engineering solutions which can be applied in case of physiological controls. Each of them can be divided smaller developments which are strengthen by case studies.

5.1 T1DM control via RFPT framework

The first thesis group investigated the usability of RFPT theorems in conjunction with T1DM control. I have examined three cases, which were different from the applied T1DM model, absorption submodel point of view, however, I used almost the same control strategies in each cases, namely, PID-kind control laws in the control block. I followed the general RFPT controller design steps, what I summarized at the beginning of the given chapter. The results showed that the RFPT-based controllers can be used in case of T1DM models with low and high complexity beside unfavorable disturbances (glucose loads). The developed controller were able to keep the BG level in the normal glycemic range; totally avoid hypoglycemia; however, short hyperglycemic periods occurred during the simulations. With this research I have proven that the RFPT-based controller design method can be used for controller design in case of T1DM models with high nonlinearities.

Although, the reached results were appropriate, I have found several opportunities for further improvements which are beyond this research. First, the velocity of convergence of the Cauchy-series – which is the key point of the RFPT method – depends on the measurements update. The currently used technology is capable to provide BG measurements at every 5 min, which makes the convergence slower and through the reaching of the desired BG levels become later. This can be faster, if an interim Kalman estimator or equivalent is used and the measurements can be completed by estimation. Since the estimation horizon is small (5 min) precise estimations can be done and via the convergence can be faster. Investigation of usability of pure input-output models based on real measurements can be done, as well. In this work, I have used the model equations to realize approximating inverse models. However, I used rough approximations this can be the next step, since the patient data reflects the glucose-insulin dynamics of the patient and more robust solutions can be reached by using this fact.

5.2 Completed LPV controller and observer scheme for LPV systems

The second thesis group introduces a two novel achievements in the field of LPV-based control. I have developed a norm based tool in which the norm (2-norm) is defined on the abstract parameter space of LPV systems and can be used as a metric between LTI systems. This tool can be used as error or difference metric and via quality requirements can be defined with it. The second achievement can be divided into two parts: I have developed a novel LPV completed controller scheme which can be used for control of LPV (and trough nonlinear) systems with given properties; moreover, I have developed a completed LPV controller-observer scheme in order to control given LPV systems. The novel controller design tools are a mixture of linear state-feedback theorem and the matrix similarity theorems. I have proven the usability of the methods via nonlinear physiological examples including DM control. I provided deep analysis of the methods.

This novel development has several further improvement possibilities. The first is the generalization - in order to use it in case of arbitrary nonlinear systems further research is needed. Moreover, it should be investigated how can be decreased the conservatism regarding the structures of the input/output matrices, which is currently a strict restriction. Furthermore, an interesting question can be the extension of the method for those cases, where the elements of the parameter vector cannot be directly measured and the only possibility is the model-based estimation. The examination of these questions are beyond this dissertation.

5.3 Usability of the TP model transformation for DM

The third thesis group investigates the TP modeling possibilities of different DM models – due to I want to use the developed TP models as subjects for TP-based controller design in the future. The first step of this direction was made during my research, namely, I have introduced control oriented LPV models via mathematical transformation from the existing DM models and I successfully developed the TP model form of them. I showed three possible direction during this part: it is possible to use TP model transformation and realize TP model in case of simple ICU kind DM model with high nonlinearities; it is possible to use TP model transformation and realize TP model in case of highly complex T1DM model with high nonlinearities and coupling; and I showed that how is it possible to increase the robustness of the TP model (from parameter point of view).

Further step regarding this thesis will be the usage of the developed TP models for TP-based controller design. Moreover, I would like to investigate the opportunity of robustization possibilities not just from model but controller design point of views, as well.

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