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ESTIMATION AND ROBUST CONTROL OF NONLINEAR DIABETES MODEL

NEMLINEÁRIS DIABÉTESZ MODELL BECSLÉSE ÉS ROBUSZTUS SZABÁLYOZÁSA

Summary of PhD thesis

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Motivation

Diabetes Mellitus is a collective term referring to several chronic metabolic diseases which have an increasing prevalence worldwide [1]. They are characterized by elevated glucose levels (hyperglycemia) over a prolonged period of time. In 2019, diabetes was the direct cause of 1.5 million deaths. In the case of type-1 Diabetes Mellitus (T1DM), the pancreas cannot produce insulin due to the loss of β-islet cells [2]. Insulin is a peptide hormone that plays a crucial role in glucose utilization, and thus in decreasing plasma glucose concentration. If left untreated, T1DM can lead to severe acute and long-term complications. Acute complications include diabetic ketoacidosis and hyperglycemic hyperosmolar state, both of which can be life-threatening in severe cases. Long-term complications include cardiovascular disease, kidney failure, nerve damage, visual impairment, and susceptibility to infection. The treatment of T1DM mainly consists of regular insulin injections, which poses significant challenges. Insufficient insulin does not decrease glucose levels enough to avoid long-term complications. On the other hand, administering too much insulin results in low glucose concentration (hypoglycemia), which can lead to seizure, coma, or death.

Recent decades saw extensive research in the automation of insulin delivery, commonly referred to as Artificial Pancreas (AP) [3]. Artificial Pancreas can potentially lessen both the severity and time spent in hyperglycemia while completely avoiding dangerous hypoglycemic episodes. Keeping a T1DM patient consistently in the normal range of blood glucose concentration decreases the chance of developing acute and long-term complications of diabetes.

From the hardware perspective, Artificial Pancreas is a portable medical device with two main components: Continuous Glucose Monitoring (CGM) system and a Continuous Subcutaneous Insulin Infusion (CSII) pump. The most common AP systems are insulin-only types, which achieve a target glucose level by automatically increasing or decreasing the amount of insulin infused based on the CGM values. However, their functionality is limited to decreasing glucose levels, with no means to increase them.

From the software perspective, AP consists of several key components, such as a control algorithm, state observer, parameter identification, event and fault detection, and predictor, among others.

Maintaining normal glucose concentration (normoglycemia) is a challenging control problem for several reasons. First, human metabolism is a highly complex and severely nonlinear dynamic system [4]. Furthermore, the dynamics tend to change significantly over time. The metabolic glucose process may also be affected by various factors that are difficult to measure, detect, or even quantify [5]. The most influental

of them, carbohydrate intake via meals, can raise glucose levels much faster than the subcutaneous insulin that serves as the control signal [6, 7]. Furthermore, hypoglycemia is a more severe acute complication than hyperglycemia [8], even though reducing the latter in severity and frequency is the main goal of AP. Finally, the commercially available continuous glucose monitoring (CGM) sensors have significant noise, and drift [9, 10].

A wide range of control algorithms is proposed in the literature to overcome these challenges [11, 12]. These methods include PID control, sliding mode control, adaptive controllers, model predictive control (MPC), robust control, linear parameter-varying (LPV) control, deep learning, and other soft computing methods. Although MPC has been one of the most widely accepted approaches, safety and robustness have been an increasing concern [13, 14, 15, 16, 17] as AP implementations entered clinical trials [18, 19].

AP control algorithms, especially model-based techniques, can significantly benefit from state and disturbance estimation. Due to the stochastic nature of the disturbances present, Kalman Filter (KF) is a popular choice [20]. Sigma point filters are an effective way to extend KF to nonlinear systems [SMM$^+$14] at the cost of computational power. Furthermore, sigma point filters can be used for long-term prediction of glucose concentration. Prediction can support AP in several ways. For example, prediction is the core concept behind MPC. Moreover, an overseer logic can assess the expected quality of the blood glucose control using predicted values and tune controller parameters accordingly. Furthermore, it is possible to intervene if the prediction warns for a potentially hazardous hypoglycemic episode. Finally, a significant deviation between predicted and measured behavior can indicate fault or an unannounced event (e.g., meal intake).

The motivation behind the dissertation is to address certain challenges of automated blood glucose regulation with AP. The focus is on insulin-only setup and only on the software level. Within the numerous features an AP can have, this work addresses three key areas: estimation, prediction, and control. It is possible to contribute to these areas even if one has no access to medical data due to the existence of validated models and simulation environments.

The first goal is to provide a control algorithm that has the following properties:

- A model-based approach that is adaptable to the most popular T1DM models. It shall address the nonlinearity of these models and the difference in dynamics between control signal and disturbances.

- The algorithm shall be able to deal with glucose increase due to

meal intake, as it is the most impactful disturbance from blood glucose control perspective.

- There should be no reliance on meal intake announcements.
- The controller shall be robust against the intra-patient variability and uncertainty of the human metabolism.
- The controlled system shall completely avoid hypoglycemia while reducing time in hyperglycemia as much as possible.

The second goal is to provide a state observer that can support the control algorithm with accurate estimations derived from the readings of a single continuous glucose sensor affected by measurement noise. Additionally, the proposed state observer should be extendable into a predictor. The chosen method is sigma point filters since they have good estimation capabilities for severely nonlinear models, can deal with stochastic noises and disturbances, and strike a good balance between accuracy and required computation power.

The third goal is to validate the proposed control and state observer methods in silico via simulations.

Summary of new scientific results

Thesis Group 1 (Chapter 3)

I provided a new state observer framework for estimating the state variables of nonlinear T1DM models and the glucose flux resulting from meal intake. The state observer considers the measurement noise of CGM sensors, the nonlinearity, uncertainty, and nonnegativity of the model, and the glucose utilization resulting from physical activity.

Square root sigma point filters can provide a satisfactory estimation of the state variables of T1DM models, combined with meal intake and uncertainty dynamics. The meal intake, physical activity, and the estimation error of state variables directly or indirectly affected by these disturbances should be modeled with lognormal distribution.

Publications related to the theses are: [SEK14, SMM$^+$14, SSBK14, KS16, SBK16, SDKew].

Thesis 1.1

I provided a method for a generic stochastic state estimation algorithm to consider the nonnegativity of the model and the most significant disturbances: meal intake and physical activity.

Let $\mathcal{T}_x$ denote the transformation of selected state variables to their natural logarithm: $\varkappa_{i,k} = \ln x_{i,k}$, where i is the index of a single state

variable in the state vector x and k indicates time. Let $\mathcal{T}_w$ denote the same transformation for disturbances. The transformed discrete time state space T1DM model used during the estimation is as follows:

$$\begin{aligned} \varkappa_k &= \mathcal{T}_x \mathrm{x}_k \\ \varkappa_{k+1} &= \mathcal{T}_x \mathrm{f}(\mathcal{T}_x^{-1}\varkappa_k, \mathcal{T}_w^{-1}\mathrm{w}_k, k) \\ \mathrm{y}_k &= \mathrm{h}(\mathcal{T}_x^{-1}\varkappa_k, \mathrm{z}_k, k). \end{aligned} \tag{1}$$

This approach is not limited to lognormal distribution. Other positive or nonnegative valued distributions may be applicable as well.

Publication related to this thesis: [SMM+14, SBK16, SDKew].

Thesis 1.2

I provided a new state observer framework that considers and estimates the additive and multiplicative output uncertainty of a T1DM model.

Extending the nominal T1DM model with uncertainty weighting functions driven by white noise can account for modeling uncertainties and intra-patient variability. Figure 1 presents a system that uses output uncertainty weighting functions.

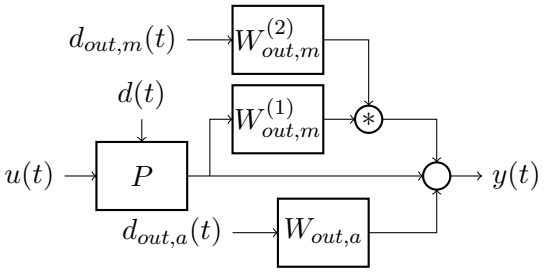

Figure 1: Model P extended with additive $W_{out,a}$ and multiplicative $W_{out,m}$ output uncertainty weighting functions for state estimation purposes.

Additionally, this approach enables robust state feedback control that relies on the same weighting functions.

Publications related to this thesis: [SEK14, KS16, SDKew].

Thesis 1.3

I provided a state observer framework that can estimate the glucose flux resulting from meal intake and ingestion.

Extending the nominal T1DM model with a dynamic meal ingestion subsystem, driven by white noise with lognormal distribution, can provide a reliable estimation of the glucose flux resulting from meal intake, especially if the state observer algorithm is a sigma point filter.

Publications related to this thesis: [SEK14, SMM$^+$14, SSBK14].

Thesis 1.4

I proposed a predictor algorithm that can provide a long-term prediction for a nonlinear and uncertain T1DM model using planned meal intake announcements.

Sigma point filters, just like the Kalman filter, can be used for model-based prediction. These state observer algorithms consist of two steps. First, an *Estimation* step, which is already a model-based prediction. Second, an *Update* step, which corrects the prediction with the difference between the predicted and measured output. Thus, a sigma point filter-based predictor merely needs to repeatedly perform the *Estimation* step. As an additional benefit, this kind of predictor can also assess its accuracy of state variable and output prediction.

However, in the case of closed loop control, the predictor should consider how future estimation errors can influence the system. Hence, the proposed algorithm combines the predictor with a simplified state observer that predicts future state estimation error covariance matrices.

The predicted distribution of the model output can be used to validate meal intake announcements, detect unannounced events, or early detection of potential hypoglycemic episodes.

Publication related to this thesis: [SBK16].

Thesis Group 2 (Chapter 4)

I provided a new robust nonlinear control algorithm for Artificial Pancreas. The controller addresses the nonlinearity, nonnegativity, and intra-patient variability of the glucose-insulin interaction in a T1DM patient.

The controller is realized via a quasi linear parameter-varying state feedback. The state observer proposed in Thesis 1 supplies the estimated state and scheduling variables. By extending the nominal model with appropriate weighting functions, the controller can be configured to meet robustness criteria, avoid severe hypoglycemia, and rely on a nonnegative control signal.

Publications related to the theses are: [KSZ11, KSF$^+$11, KTSS12, KS12, KSF$^+$12, KKSE13, SEK$^+$13, KSAB13, KSS$^+$13, KKS$^+$14, SEK14, KS16, SDKew].

Thesis 2.1

I provided a linear parameter varying approximation of the well-known Cambridge T1DM model, which enabled the synthesis of quasi linear

parameter-varying controllers via the solution of linear matrix inequalities.

The Cambridge model has the following nonlinearities that the quasi LPV model must address:

1. Remote effect of insulin on glucose distribution, represented by the product of two state variables.
2. Remote effect of insulin on glucose disposal, also represented by the product of two state variables.
3. Michelis-Menten function of non-insulin-dependent glucose flux.
4. Saturation of endogenous glucose production.
5. Saturation of renal extraction.

Nonlinearities 1-3 can be resolved by introducing scheduling variables. These scheduling variables are functions of state variables. Setting constraints on the control signal via a dynamic weighting function can avoid the saturation of endogenous glucose production. At the same time, the nonlinearity of the renal extraction is resolved by replacing it with a less conservative disturbance. The resulting model contains only matrix-valued affine functions of the scheduling variables, making it a linear parameter-varying representation.

Publications related to this thesis: [SEK+13, KSAB13, SEK14, KS16, SDKew].

Thesis 2.2

I provided a $\mathcal{H}_2/\mathcal{H}_\infty$ controller for Artificial Pancreas, which considers model uncertainties and intra-patient variability, as well as constraints on the control signal.

The controller synthesis is performed by solving appropriate linear matrix inequalities. Furthermore, the nominal T1DM model used for the controller synthesis is extended with weighting functions.

Publications related to this thesis: [KSZ11, KSF+11, KS12, KSF+12, KKSE13, KSS+13, KKS+14, SEK14, KS16, SDKew].

Thesis 2.3

I provided a method to automatically scale performance and multiplicative uncertainty outputs of a T1DM model so that robust stability constraints are ensured and nominal performance is optimized, as long as they are feasible.

I applied changes to particular well-known linear matrix inequalities commonly used for the synthesis of linear parameter-varying controllers. The changes enable automatic scaling for performance and uncertainty outputs for a state-feedback controller. However, only performance scaling is available for dynamic controller synthesis.

Publications related to this thesis: [SEK14, SDKew].

Thesis Group 3 (Chapter 5)

I performed the in silico validation of the observer and controller algorithms proposed in Thesis groups 1 and 2.

The simulation environment is based on the Cambridge model and simulator.

Publications related to the theses are: [KSAB13, KSF$^+$13, KSS$^+$13, KKSE13, SEK14, SMM$^+$14, KKS$^+$14, KSE$^+$14, KFS$^+$15, SDKew].

Thesis 3.1

I examined the effect of the number of sigma points on state estimation accuracy for a commonly used T1DM model. The results indicate that using more than 2L+1 sigma points provide no significant benefit.

Based on the evaluation, the sigma points shall have a symmetric configuration containing at least $2L$ points, where L represents the dimension of the model. Increasing the number of sigma points beyond that value does not lead to significant benefits. Both Cubature and Unscented Kalman filters with $2L$ and $2L+1$ sigma points provide sufficient estimation capabilities.

The effectiveness of lognormal transformation is verified via simulations as well, but only for sigma point selection strategies, where the sigma points have moderate spread.

Publication related to this thesis: [SMM$^+$14].

Thesis 3.2

I performed the in silico validation of a robust qLPV $\mathcal{H}_2/\mathcal{H}_\infty$ state feedback controller. An Artificial Pancreas undergoing clinical trial can incorporate the proposed control algorithm, provided that Cambridge model based representation of the participants is available.

Based on control variability grid analysis, the controller could provide satisfactory blood glucose control for two 24-hour meal intake scenarios.

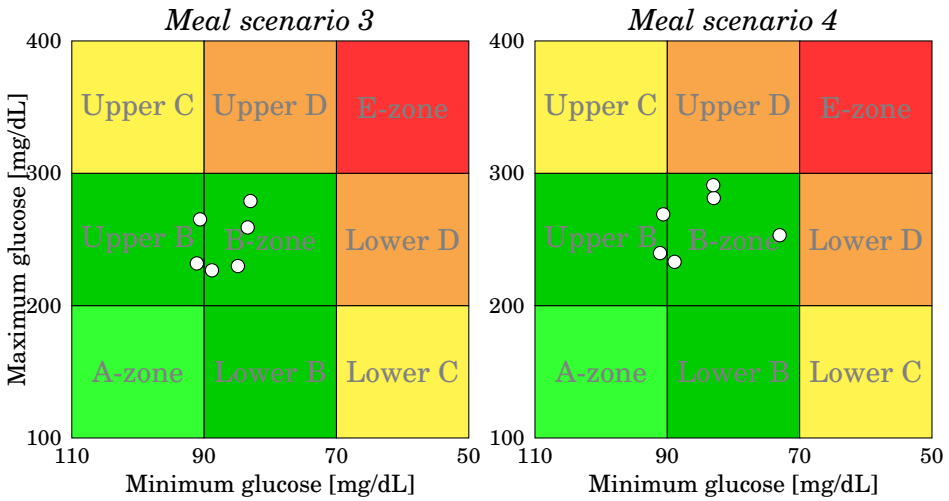

Figure 2: Control variability grid analysis of a robust qLPV state feedback controllers using hybrid $\mathcal{H}_2/\mathcal{H}_\infty$ norm. Left and right subplot shows results for two different meal intake scenarios. Each white circle denotes a simulation of a single virtual patient.

Publications related to this thesis: [KSAB13, KSF+13, KSS+13, KKSE13, SEK14, KKS+14, KSE+14, KFS+15, SDKew].

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