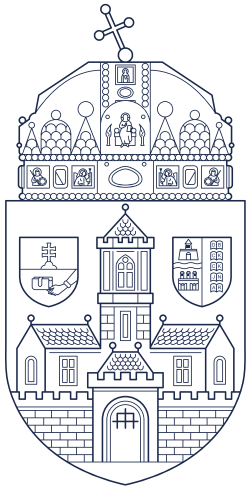
Óbuda University

PhD Thesis summary



Model-based investigation of physiological systems and signals

by
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Applied Informatics and Applied Mathematics Doctoral School
Budapest, 2023

Contents

List of abbreviations

Abbreviation	Meaning
MHE	Moving Horizon Estimation
IVP	Identifiable Virtual Patient
MPC	Model Predictive Control
BG	Blood glucose
KF	Kalman filter
NSMO	Nonlinear sliding mode observer
LPV	Linear Parameter Varying
LHS	Latin Hypercube Sampling
NRMSE	Normalized root-mean-square error
CGMS	Continuous Glucose Monitoring System
CHO	Carbohydrate
LSCI	Laser Speckle Contrast Imaging
TVI	Time varied illumination
CW	Continuous wave
ROI	Region of interest

1

Background of the research

Diabetes is a chronic disease that is estimated to affect 537 millions of people worldwide [R1]. Type 1 diabetes is a specifically dangerous form of the disease, since the ceasing of insulin hormone production requires a constant exogenous insulin intake. The constant insulin is needed to keep the patient's blood glucose level in a healthy range; without it, the insulin dependent cells cannot withdraw glucose from the plasma, and the high blood glucose level (hyperglycemia) leads to various physiological complications such as retinopathy, nephropathy, neuropathy, macrovascular complications [R2]. Also, insulin cannot be injected or infused arbitrarily as increased levels of plasma insulin can lead to low glucose values (hypoglycemia), which creates life-threatening condition by not providing fuel to the brain, whose main nutrition is glucose.

Type 1 diabetes management have come a long way since the invention of insulin [R3]. Insulin delivery moves from multiple daily injections to continuous infusion, from insulin pens to insulin pumps. Glucose measurement moves from intermittent sampling to continuous measurement, from finger prick to minimal invasive sensors. Lastly, but not least automated delivery systems gain popularity by utilizing the continuous manner both in the input and the measurement. An automated delivery system (or artificial pancreas) aims to alleviate the burden of constant monitoring and controlling of blood glucose by assigning the task to an algorithm. In the last decade or so four such systems got the approval of the Food and Drug Administration of the United States [R4, R5, R6, R7].

The control algorithms of automated insulin delivery systems take into account the past values of the blood glucose concentration, and try to calculate an insulin amount which will – based on the information the system has – keep the blood glucose in a healthy range. The calculation is a difficult task for several reasons, few important ones are as follows: 1) The algorithm has to face interpatient variability. (Physiology of the patients can differ greatly, making it difficult for a single algorithm to handle a heterogeneous group of people.) 2) Variability also occurs during the day, due to the circadian rhythm of the patient – usually referred to as intrapatient variability. 3) Carbohydrate intakes, physical activity, stress and such introduce disturbances which need a constant compensation. So that the algorithm could make informed decisions, one approach is to provide additional information about the dynamics of the patient and disturbances. My journey joins this path, where I started off with different Kalman filters for state and disturbance estimation; I continued my way through moving horizon estimation based methods. Laser speckle contrast imaging (LSCI) is situated on the other side of the medical workflow of diabetes; so far I described the tools I investigated and related to diabetes treatment. On the other hand, LSCI is tied to the diagnosis part by the possibility to monitor microcirculation in diabetic feet [R8]. A significant factor in causing diabetic foot ulcers is the microvascular dysfunction which leads to impaired perfusion. Noninvasive tools which can quantify the

state of the microvascular system in diabeted feet are sparse. LSCI could be a potential tool in providing 2-dimensional maps of blood flow with high resolution.

2

Aims of the research

The aim of the research was to move forward methods in personalized therapy and diagnosis for type 1 diabetic patients. The disseration has two major parts. In the first part I aimed to provide methods to efficiently estimate the parameters of mathematical models, then those models were used to track the dynamics of the patient and to generate insulin therapies. The second part aims to improve laser speckle contrast imaging as a method to remotely measure skin perfusion which is of great importance in monitoring diabetic feet.

Cheap, smart measuring devices (smartphones, continuous glucose monitors (CGM) and fitness trackers) in recent years generate a vast amount of data. This motivates my research to utilize the data to better understand the patient's temporary glucose metabolism. The personalized models make it possible to reason about the patient's glycemia and to predict future blood glucose values or generate insulin therapies. Personalization was achieved by fitting physiological models of various complexity to glucose, insulin, carbohydrate intake and if it was possible to heart rate data. Emphasis was placed to acquire consistent results in terms of parameter estimation by imposing constraints and limiting the complexity of the studied models. Aim was to provide solutions that can be used in real-world applications, so the method was implemented as a microservice and can be utilized in various web or smartphone applications.

Laser speckle contrast imaging as a tool for monitoring blood flow maps has disadvantages. It has a relatively low dynamic range in terms of flow speeds and under- or overexposed images can alter the results. My research aimed to address these issues. Dynamic range was improved by making the profile of the laser illumination optimized during the exposure. First, the method was tested in an offline manner where data were gathered and a developed model was fitted to the data and the measurements were repeated with the optimized illumination profiles, later the aim was to implement it in real-time as a possible tool for real-world applications. Furthermore, I modeled the sensitivity of the method to overexposure, which can be used to compensate for it.

In both respects, I utilized mathematical models and their fitting to data from simulations and real-world measurements. Throughout the research real-time implementation was a key focus, thus the simulation and optimization methods were developed accordingly.

3

Materials and methods

Thesis 1:

- Dual and Joint Extended Kalman filters
- Linear Parameter Varying discretization methods
- Simulation of diabetes metabolic models
- Sensitivity and identifiability analysis of diabetes metabolic models

Thesis 2:

- Moving horizon estimation
- Population-based optimization algorithms
  - Physiological constraints to improve consistency and convergence
  - Numba Just-In-Time compilation to improve runtimes
  - Parallelization on the central processing unit and on graphical processing units
- Simulation of diabetes metabolic models
  - Numba Just-In-Time compilation to improve runtimes

Thesis 3:

- Fitting mathematical model to data
  - Gradient-based optimization algorithms
- Real-time implementation
  - Laser pulse sequence optimization algorithm (gradient-based)
  - Cost function definitions based on different regions of interests
  - Physical realization using USB camera, Raspberry Pi and a near-infrared laser

Thesis 4:

- Fitting mathematical model of static and dynamic scatterers to simulated and real-world data
- Derivation of overexposure compensation in laser speckle contrast imaging

4

New scientific results

Thesis group 1: State and disturbance estimation in Artificial Pancreas using Kalman filters

Thesis 1
I developed and investigated Kalman filters for state/parameter and disturbance estimation in Artificial Pancreas applications. My focus was on developing extended Kalman filters based on linear parameter varying methodology.

Thesis 1.1
I have developed Joint and Dual Kalman filters for state and disturbance estimation using linear parameter varying methodology. I analyzed different linear parameter varying discretization methods and scheduling parameter selections.

Thesis 1.2
I developed a Kalman filter tuning method to acquire consistent results and outcomes in the evaluated scenarios. I contributed to the comparison of the developed filters. The filters were compared across different models, estimated variables and to a sliding mode observer.

Publications relevant to the theses: [C1, C2, J1, J2].

Tackling nonlinearity is an essential part in designing control algorithms for artificial pancreas. Physiological systems are highly nonlinear and time varying, thus designing efficient algorithms that can handle them are important aspects of the field. My goal was to design discretized Kalman filters based on linear parameter varying methodologies as they proved to be an efficient method to tackle state estimation problem in nonlinear systems. Also, my aim was to evaluate how the method compares to different estimation methods, and how the underlying mathematical models affect the performance. In [C1] I designed Dual Kalman filters based on linear parameter varying methodology, in [J1] a Kalman filter has been applied in simulations for closed-loop blood glucose control. Then in [C2, J2], the Kalman filters were analyzed based on different models, disturbance estimation and state estimation capabilities. Also, the tuning process of the filters were standardized.

Thesis group 2: Moving horizon estimation-based digital twin in artificial pancreas

Thesis 2
I developed and investigated moving horizon estimation-based digital twin methodologies to represent the patient's glucose metabolism and trace intrapatient variability.

Thesis 2.1
I have developed moving horizon estimation based methodology to trace parameter variability of the patient with a strong focus on constraining the parameters to represent the physiologically relevant values.

Thesis 2.2
I developed and investigated the meal estimation accuracy in a moving horizon estimation-model predictive control scenario.

Thesis 2.3
I implemented the moving horizon estimation as just-in-compiled functions and on the graphical processing unit to make the method scalable for large patient populations.

Publications relevant to the theses: [C3, C4, C5, C6, C7].

Findings in my first thesis led to the conclusion that the structure of the mathematical model and the accuracy of the patient parameters can have greater impact on the estimation accuracy than the state observer algorithm itself. Thus, I focused on parameter estimation methods, with a particular focus on constraining the free parameter space to improve the speed, convergence and consistency. Also, the estimated parameters can be of great use in various applications such as blood glucose prediction, replaying different insulin and meal scenarios, also observing daily or long-term trends in insulin sensitivity. The method and its use-cases fall under the umbrella of digital twins. In [C3], I developed moving horizon estimation based methodology to track intrapatient variability. In [C4], the focus was on the estimation of the endgenous glucose production and extending the model with heart rate as a potential, easy-to-access parameter to describe physical activity. In [C5], the estimation algorithm was extended with a model predictive controller and its performance was evaluated in a simulation environment. In [C6], I optimized the parameter estimation algorithm for tackling large populations as a cloud-based service.

Thesis group 3: Time varied illumination in laser speckle contrast imaging

Thesis 3
I contributed to the theory of laser speckle contrast imaging by modeling the effect of varying laser illumination. I contributed to the validation through simulations and in vivo experiments. I contributed to the real-time implementation of the time varied illumination methodology.

Thesis 3.1
I developed a mathematical model which describes the speckle contrast with regards to the laser illumination. I generalized a well-known model which assumed constant illumination.

Thesis 3.2
I validated the model of varied illumination by fitting it to invitro and invivo measurements.

Thesis 3.3
I contributed to the implementation of the time varied laser speckle contrast imaging on a Raspberry Pi coupled with a Basler camera. The system was able to optimize the laser illumination in real-time.

Publications relevant to the theses: [J3, J4].

Laser speckle contrast imaging is a method with great potential, as it can be a cheap, noninvasive imaging modality in medical applications. It is capable of generating blood flow maps and recently was used in assessing the microcirculation in diabetic feet. On the other hand, the method has some drawbacks and lacks models which can be used to interpret measurements and make optimizations. In [J3], we introduced time varied illumination laser speckle contrast imaging, which is a method to improve the dynamic range of the technique by varying the laser light during the camera exposure. I developed the model which describes the effect of varying illumination and defined optimization scenarios to improve the dynamic range. In [J4], I developed the laser illumination optimization method on a Raspberry Pi, which realizes a real-time implementation of the technique.

Thesis group 4: Models of exposure and scattering medium in laser speckle contrast imaging

Thesis 4
I contributed to the theory of laser speckle contrast imaging by developing a mathematical model of static and dynamic scatterers. Also, I contributed to the theory by developing a model of overexposure compensation. I validated the models through simulations and invivo experiments.

Thesis 4.1
I developed a mathematical which describes the effect of static and dynamic scatterers on the measured contrast; the model also describes how ensemble averaging affects the contrast.

Thesis 4.2
I developed a mathematical model which describes how overexposure affects the measured contrast, and how can the model be used to compensate for the overexposure.

Thesis 4.3
I validated the mathematical models through simulations and invivo experiments by fitting the model parameters to the measured variables. The fitted models showed good accuracy and consistency with the data.

Publications relevant to the theses: [J5, J6].

The signal-to-noise ratio of laser speckle contrast imaging can be improved with taking multiple independent images – also called as ensemble averaging. In [J5], I proposed a model based on statistical distributions which describes how the method depends on the number of captured images and also describes the dependency of static and dynamic scatterers. Differentiating between static and dynamic scatterers is important because taking multiple images improves the signal-to-noise ratio only in terms of the dynamic scatterers. The model was validated in simulations and also on real-world measurements. Exposing properly the image in laser speckle contrast imaging is important to acquire consistent results, overexposing the image distorts the statistical distributions, rendering the observed contrast lower than the contrast of the real distribution. In [J6], we proposed a model which describes the effect of overexposure and I described how it can be used to compensate for overexposed images.

5

Applications

5.1 Application of real-time patient parameter estimation

The patient parameter estimation and blood glucose prediction method has been implemented in a context of a diabetes decision support system, with the goal of handling large populations simultaneously in a real-time manner. Fitting complex mathematical models to large quantities of data can be a computationally expensive task. To achieve a real-time implementation of the patient parameter estimation algorithm the method was heavily optimized and parallelized. In the event of a new glucose measurement (which is being pushed to the database), the patient parameter estimation algorithm is called automatically. The results of the patient parameter estimation are also saved into the database. In Fig. 5.1 a schematic of the estimation pipeline can be seen. The results of the estimation can be used to either predict future blood glucose values or define "what if" scenarios as a digital twin of the patient. The "what if" scenario refers to a series of carbohydrate and insulin intakes that did not actually happened but could have happened. For instance, the patient consumed 30 g of carbohydrate at 7 PM, and we are interested in an alternative scenario, what would have happened in terms of glycemia if the patient would have consumed 40 g.

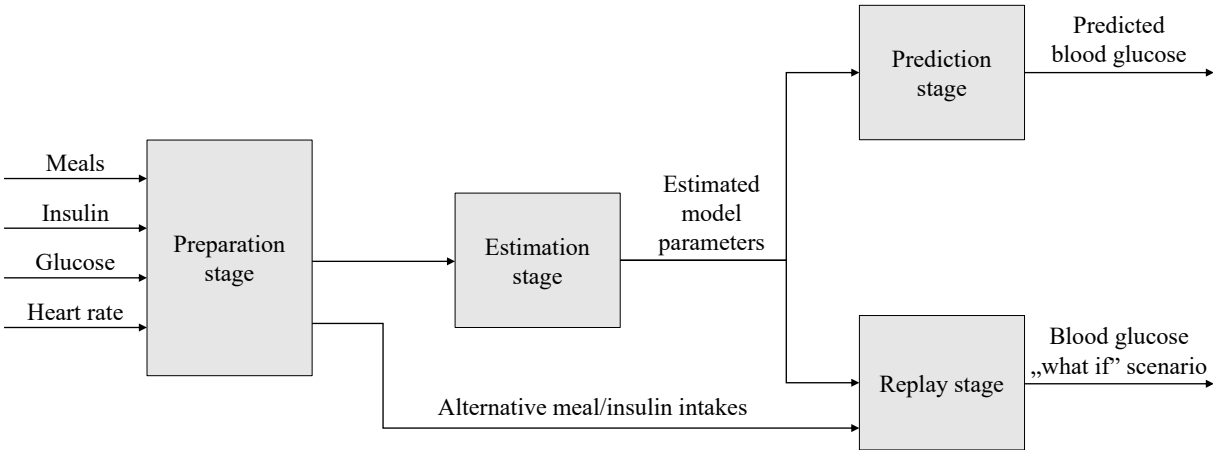

Figure 5.1: Block diagram of the digital twin method for replay and prediction purposes.

5.2 Application of time varied illumination laser speckle contrast imaging

The validity of the time varied laser speckle contrast imaging was first tested in simulations. Later invitro and invivo measurements were collected and the developed mathematical model was fitted to the data. In the last step, I developed the real-time implementation where a USB camera captured a sequence of images and a Raspberry Pi processed and evaluted them in each iteration. Based on the current conditions the Raspberry Pi modified the laser pulse sequence and converged to a setting which provided superior characteristics compared to a constant illumination. The developed samle-in-the-loop approach can be a useful tool in microscopic µ-channel slide experiements. The outline of the project is illustrated in Fig. 5.2.

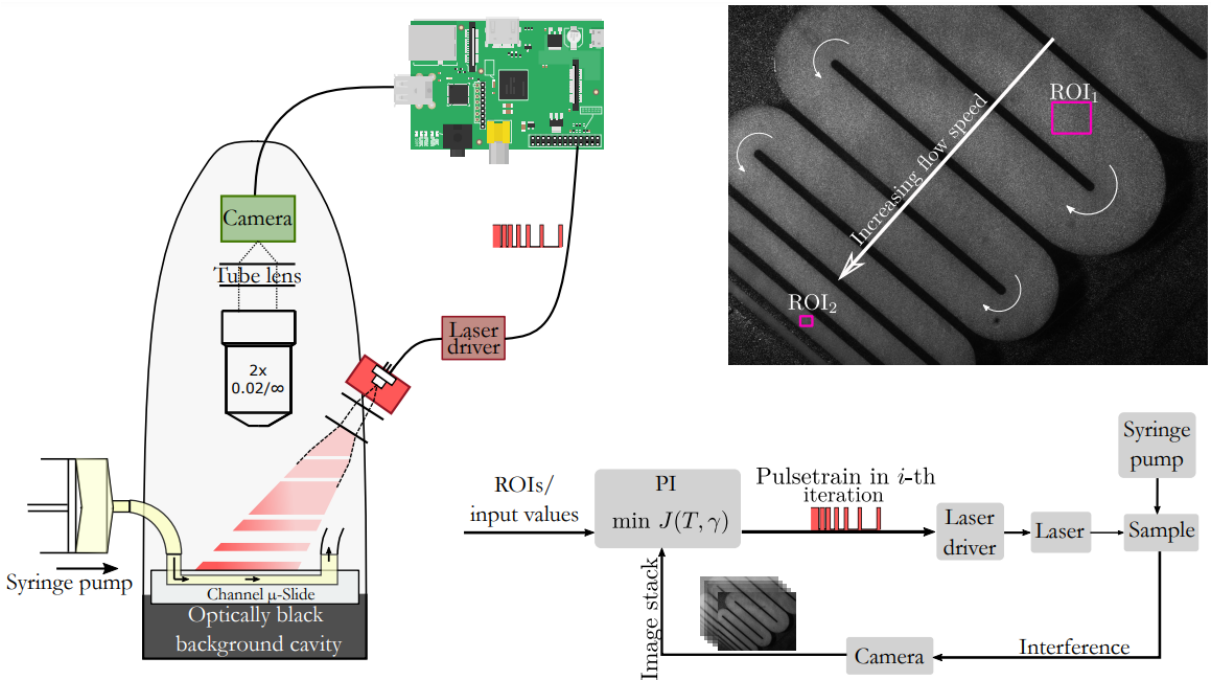

Figure 5.2: The real-time implementation of the varied illumination laser speckle imaging. A medical syringe pump provides a constant flow speed, while the laser and the digital camera are controlled by the Raspberry Pi. A raw speckle image with a typical ROI selection is illustrated in the upper right corner. The schematic diagram in the lower right corner summarizes the sample-in-the-loop LSCI method.

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