Stochastic Differential Equations in Artificial Pancreas Modelling

Type 1 diabetes accounts for approximately 5% of the total diabetes population. It is caused by the destruction of insulin producing β-cells in the pancreas. Various treatment strategies are available today, some of which include advanced technological devices such as an insulin pump and a continuous glucose monitor (CGM). Despite these technological advances in the treatment of type 1 diabetes, the disease still poses an enormous and constant challenge for the patients. To obtain tight glucose control the patients are required to assess how much they will eat prior to the meal. They have to assess the timing, intensity and duration of physical exercise in advance, to adjust the insulin dose accordingly. Additionally, several uncontrollable and unpredictable factors such as stress, hormonal cycles and sickness changing the metabolic state make this task even more difficult.

The development of the insulin pump and the CGM has paved the way for a fully automatic treatment regime, the artificial pancreas. The idea is to connect the CGM with the insulin pump via a control algorithm running on e.g. the patients smart phone. The CGM observations are sent to the smart phone and based on this information, the control algorithm computes the optimal dose adjustment and sends instructions to the insulin pump.

To develop control algorithms, mathematical models of the physiological dynamics are needed. They attempt to describe the significant dynamics of the system and hence they approximate the system behavior. However, uncertainty in the model occurs due to the nature of physiological systems and due to the presence of unknown disturbances. An attractive approach to deal with this uncertainty is to use stochastic differential equations (SDEs). In a model based on SDEs, the noise is separated into two terms: 1) a diffusion term occurring from model misspecifications, effects of unknown disturbances, or just true stochastic behavior of the system and 2) a measurement noise term representing the serially uncorrelated error occurring due to the imperfect analysing equipment. The diffusion term affects the evolution of the system directly.

The purpose of this PhD-project was to investigate the potential of SDEs in the artificial pancreas development. Especially, the emerging continuous monitoring of glucose levels makes SDEs highly applicable to this field. The current thesis aims at demonstrating and discussing the benefits and challenges by using SDEs compared to traditional methods on the basis of the results of the project.

First of all, we designed a clinical study to obtain high quality data from type 1 diabetes patients to identify the models from. The study included the main factors influencing the glucose level: insulin boluses, meals, and exercise. A modelling study showed that using SDEs in model development can be advantageous in several ways. We were able to pinpoint model deficiencies in a well-known model and to track parameter variation probably caused by a differences in meal type. This information could be added to the model to improve the fit. The study was limited by the lack of a software capable of handling SDE models of population effects instead of single-subject effects. A prototype of this type of software was developed parallel to the end of the project. Thus, we could finally identify a population model of the effect of exercise on the insulin absorption rate. The small amount of observations made it impossible to use SDEs to track parameter variation. Instead, we formulated a model structure with showed to be significantly better than the base model with a constant rate.

Two studies specifically related to the CGM observations were performed during the project. In the first study, we showed that SDEs could be used to tune a control algorithm for overnight glucose control on the basis of CGM observations. The tuned algorithm improved the controller performance in a subsequent clinical study. Further attempts to deal with the problems related to the CGM included a Bayesian estimation scheme. By incorporating prior knowledge about the uncertainty in the CGM observations into the estimation method, we succeeded in predicting the plasma glucose level with acceptable confidence from the CGM observations only.

Overall, the project confirms that SDEs have a large potential within this field. However, future modeling requires a robust software capable of handling the nonlinear population SDE models. When this is available, larger modeling studies can be initiated and the impact of SDEs would be expected to increase.

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