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Identification of intra-patient variability in the postprandial response of patients with type 1 diabetes☆

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ABSTRACT

Background: Identification of individualized models for patients with type 1 diabetes is of vital importance for the development of a successful artificial pancreas and other model-based strategies of insulin treatment. However, the huge intra-patient glycemic variability frequently prevents the identification of reliable models, especially in the postprandial period. In this work, the identification of postprandial models characterizing intra-patient variability is addressed.
Methods: Regarding the postprandial response, uncertainties due to physiological variability, input errors in insulin infusion rate and in meal content estimation are characterized by means of interval models, which predict a glucose envelope containing all possible patient responses according to the model. Multi-objective optimization is performed over a cohort of virtual patients, minimizing both the fitting error and the output glucose envelope width. A Pareto Front is then built ranging from classic identification representing average behaviors to interval identification guaranteeing full enclosure of the measurements. A method for the selection of the best individual in the Pareto Front for identification from home monitoring data with a continuous glucose monitor is presented, reducing the overestimation of patient's variability due to monitor inaccuracies and noise.
Results: Identification using glucose reference data provide model bands that accurately fit all data points in the used virtual data set. Identification from continuous glucose monitor data, using two different width estimation procedures yield very similar prediction capabilities of around 60% of the data points predicted, and less than a 5% average error.
Conclusions: In this work, a new approach to evaluate intra-patient variability in the identification of postprandial models is presented. The proposed method is feasible and shows good prediction capabilities in a 5-h time horizon as compared to reference measurements.

1. Introduction

Type 1 diabetes mellitus (T1DM) is a chronic disease characterized by absolute insulin deficiency due to the lack of insulin secretion by the pancreas, requiring its replacement with exogenous insulin administration. Multiple daily injections (MDI) or continuous subcutaneous insulin infusion (CSII) are the preferred insulin regimens in these patients. However, successful insulin replacement is a complex empirical process that requires trained and motivated healthcare professionals and high patient compliance. This explains in part why a minority of subjects with T1DM achieve glycemic targets, while many are at risk to suffering acute and chronic complications from either hyper- and hypoglycemia. Recently, continuous glucose monitoring devices (CGM) have been a springboard for the development of new technologies helping T1DM patients to have an easier life, such as sensor-augmented pumps and the so-called artificial pancreas (AP) for the automation of insulin delivery.

Prototypes of the AP have already been tested in some in-patient studies being successful in achieving a good nocturnal control [1]. Furthermore, the first out-patient study has recently been completed [2]. However, postprandial glucose control is still challenging with frequent late hypoglycemia due to controller over-correction when it is tuned aggressive for a tight control. Using model-based control, such as model predictive

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control (MPC) [3] is challenging because it requires a good patient's model representative for prediction. Indeed, patient-model mismatch has shown often to be a strong limitation in the performance of closed-loop control [4]. This limitation extends also for other model-based strategies such as methods for hypoglycemia prediction [5] or model-based insulin pump therapy [6,7]. In addition, population-based models have shown a limited accuracy due to the large inter-subject variability. Data-based models for selected individuals have shown also poor predictive capabilities [8,9]. Physiology-based models (*e.g.*, [10]), which are theoretically superior, require complex clinical procedures that limit its availability. Searching for alternatives, conservative control-oriented linear models individualized from *a priori* patient characteristics have been proposed for reducing the likelihood of hypoglycemia episodes [4].

It is well known that the postprandial glycemic response in patients with T1DM shows a high variability, both inter- and intra-patient. Its causes are not fully understood although variability of subcutaneous insulin absorption and changes of insulin sensitivity (either in physiological or pathological conditions) seem to play a major role [11]. In addition, the effect of meal ingestion on glucose homeostasis is variable depending among other factors on the meal composition (carbohydrates, protein, fat) [12].

Therefore, it remains a major issue to characterize the individual postprandial glycemic responses by an appropriate model. Previous poor results in the identification of patient individual models may be attributable in part to the high intra-patient glycemic variability and, as importantly, to the lack of accurate enough continuous glucose measurements. It is well accepted that CGM accuracy needs improvement, especially in the hypoglycemic range. This may be a limitation for model identification from outpatient registries and the performance of model-based approaches. Indeed, identification should be ideally based on frequent and accurate blood glucose measurements by means of a reference method. However, in clinical practice this is unfeasible and less accurate CGM must be used in an outpatient setting. The error of the CGM measurements may overestimate the intra-patient glycemic variability reducing the likelihood of successful identification.

Using intervals is the logical approach to express this variability in terms of uncertainty in model parameters, inputs and initial conditions (interval model). Interval methods [13] have been successfully applied in a great variety of engineering applications to yield robust control strategies for uncertain systems. In the context of T1DM, interval models have been used previously for robust model-based insulin pump therapy [6,7] and in developing decision support tools in MDI insulin therapy [14]. Kirchsteiger et al. [15] developed a method to estimate interval models in patients with T1DM for robust glycemic control. However, derived models do not mathematically guarantee the enclosure of all glucose profiles despite reliable blood glucose (BG) measurements. Furthermore, a classical model with constant parameter values was used for validation purposes.

In this manuscript, we address identification of interval models for characterizing intra-patient variability, either in the context of accurate reference (gold standard) glucose measurements or CGM home-monitored data. To this end, an *in silico* trial is carried out. Multi-objective optimization is used to analyze different identification strategies ranging from classic identification which leads to average models, to interval identification yielding a glucose envelope than includes all measurements. Finally, a methodology is presented to choose an adequate solution in the Pareto Front counteracting inaccuracies of outpatient CGM registries.

2. Methods

2.1. Virtual patients cohort

A cohort of 14 virtual patients was generated by means of the model proposed by Hovorka et al. in [3]. Three postprandial periods were simulated for each patient, according to the optimal experiment design described in [16]: on day 1 and day 3 a meal with 100 g of carbohydrates (CHO) was ingested and the insulin bolus was advanced 30 min; on day 2 the patient ate a 40-g CHO meal and delayed the bolus for 120 min. For all simulated days the patient was considered at euglycemia before the meal intake (model initial conditions). This experimental set-up was shown [16] to be beneficial for model identification due to the separation of insulin and meal dynamics.

The virtual patients were considered to have intra-patient variability (time-varying model parameters). Input errors were also considered for the insulin infusion rate and the estimation of carbohydrate intake.

The parameters considered time-varying are listed next:

- S_{iT}: insulin sensitivity on glucose transport from blood to interstitium;
- S_{iD}: insulin sensitivity on glucose utilization;
- S_{iE}: insulin sensitivity on endogenous glucose production;
- k_e: insulin elimination rate;
- k_{12}: rate of glucose transport from interstitium to blood.

The following parameters were treated as patient-dependent and time-invariant, due to constraints of the interval simulator:

- t_{maxG}: time constant for glucose absorption in the gut;
- t_{maxI}: time constant for insulin absorption.

Additionally, the following input errors were introduced:

- *pump*: a random time-varying error for the insulin infusion rate from the insulin pump;
- *meal estimation*: a repeated bias plus a random time-varying error for the carbohydrates estimation given by the patient.

Variability in the meal absorption is characterized by uncertainty in the meal estimation and variability in insulin pharmacokinetics is characterized by the parameter k_e and uncertainty in the insulin pump infusion. For the sake of simplicity, the time-varying parameters and errors considered were assumed constant throughout a postprandial period. However, they were changed from one day to another following a random process with mean equal to the nominal value of the parameter (0 for the errors) and a standard deviation of 10%. As demonstrated by Calm et al. [17] using optimal interval simulation methods, the consideration of 10% uncertainty in the model parameters may produce glucose trajectories differing in 100 mg/dL, so it is considered a sensible value for the reproduction of variability. Nominal values of all parameters were extracted from [3].

Finally, measurement errors induced by a CGM device during home-monitoring were simulated. Few models of CGM simulation can be found in literature, possibly the most relevant being the one published by Breton and Kovatchev in [18] and later reviewed in [19] by Facchinetti et al. However, that model is based on data recalibrated retrospectively. In this work the model presented in [20] was used for simulation of the real-time CGM Dexcom® SEVEN® PLUS (Dexcom®, San Diego, CA).