Towards Personalized Verification and Synthesis for the Artificial Pancreas.

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Abstract

People with type-1 diabetes exhibit a large range of variations in the physiological characteristics that affect their response to blood glucose levels, including gender, weight, insulin sensitivity, dietary habits, exercise and hormonal fluctuations. At the same time, control algorithms for the artificial pancreas can be tuned using numerous parameters that affect the correctness and performance of the closed-loop system. We present a new approach using non-deterministic relational models of human insulin-glucose regulation inferred from patient data using multiple time scales. Treating the equations of this model as constraints, we model the behavior of the entire closed loop system over a time horizon using an optimization problem. Next, we demonstrate this approach using patient data gathered from a previously conducted outpatient clinical study and perform reachability analysis for a PID control scheme taken from the literature.

Keywords: Artificial Pancreas, Data-Driven Models, Static Analysis, Personalized Medical Devices.

1 Introduction

The artificial pancreas refers to a device that automates insulin delivery to patients with type-1 diabetes in a closed loop. Such a device is responsible for reacting to rapid changes in the blood glucose level caused by meals and exercise [13,6,18]. However, the artificial pancreas is a safety-critical system. Excess insulin can lead to extremely low blood glucose levels (termed *hypoglycemia*) causing seizures, loss of consciousness, coma or even death in extreme cases. On the other hand, a lack of insulin can lead to elevated blood glucose levels (termed *hyperglycemia*), damaging critical organs such as the eyes, kidneys, heart and the nervous system in the long term. Thus, the central goal of the artificial pancreas controller is to maintain the patient's blood glucose level inside a narrow *euglycemic* range $[70, 180]$ mg/dl [4].

A large number of control algorithms have been proposed over the past decades, ranging from a simple low glucose suspend [20], pump suspension using glucose prediction [3], PID-based approaches [24,26,25], rule-based approaches [1,21], Model-Predictive Control (MPC) [11,16,15,14,2,5,10], and multihoromone control that

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combines the use of insulin with the counter-regulatory hormone glucagon and the hormone amylin [9,8]. A classification of these approaches is proposed by Kowalski [18]. Further, the control systems are currently all under various stages of clinical evaluation. In particular, the Medtronic 670G is a hybrid closed loop device that received regulatory approval from the US FDA in 2016 [12].

2 Personalized Devices

The control algorithms used in AP devices rely on parameters such as gains and thresholds that affect their performance. At the same time, patients exhibit a large range of variations based on factors that include age, gender, weight, exercise, dietary habits and hormonal fluctuations, to name a few. Furthermore, the same patient may exhibit variations in their insulin glucose regulation over time.

Personalization of the device is the process of choosing the parameters of the device to ensure that key correctness properties are maintained for the specifics of the patient's physiology.

The problem of personalized design of control algorithms has received increasing attention for medical devices in general, and the artificial pancreas domain, in particular. Model Predictive Control (MPC) algorithms provide for personalization by learning model parameters from patient data. Hovorka et al propose a nonlinear MPC scheme that updates the parameters of the model periodically using the patient data [15,14]. Dassau et al use a data driven approach to derive plant models that are used to construct an explicit MPC system [7]. Capel et al. evaluate a rule-based approach that is based on training a neural network model that predicts the future course of the patient glucose values. This network is trained from historical data collected from the patient [17]. To address patient safety concerns, these approaches place limits on the insulin-on-board for the patient. However, they fail to account for the uncertainty in the system identification process. The recent work of Paoletti et al uses a robust MPC scheme that accounts for meal uncertainties but uses a deterministic patient model with numerous parameters that are hard to estimate without highly intrusive lab measurements on the patient [23]. Figure 1 proposes a more systematic approach based on verification of a nondeterministic model inferred using patient data. The overall procedure may then be placed in an outer loop that adjusts the controller parameters to satisfy the correctness properties.

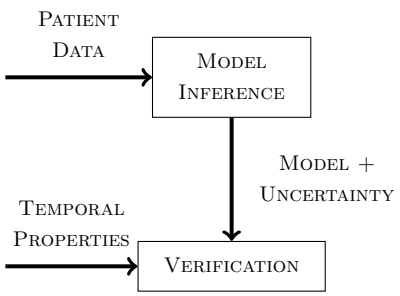

Fig. 1: A verification approach to personalized artificial pancreas.

3 Data Driven Nondeterministic Modeling

We demonstrate our approach through a relational model inference scheme devised by the authors to perform reachability analysis of a PID controller with saturation

and anti-windup compensation.

3.1 Data Source

The demonstration is based on outpatient clinical study data collected from 50 patients with roughly 40 nightly monitoring session for each patient, leading to a total of 2254 nightly sessions in total across all patients. The study was intented to test a closed loop predictive pump shutoff algorithm for controlling night time insulin delivery [3]. Each session provides values of blood glucose levels $G(t)$ measured using a continuous glucose monitor and the insulin inputs $i_d(t)$ logged automatically by an insulin pump [19]. The CGM readings are recorded for every minute.

As part of the pre-processing step, we omitted nights wherein the patient suffered hypoglycemia, requiring rescue Carbohydrates. Since no meal data was provided, we omitted data prior to 11 PM and after 6 AM to minimize the influence of post-prandial glucose increase and the pre-meal boluses. We calculated the insulin on board from the given data using a standard formula taken from the Open Artificial Pancreas project source code [22]. We note that the insulin on board calculation used is not patient-specific. In particular, we assumed a peak action time of 75 minutes and a total duration of insulin action of 180 minutes.

3.2 Relational Models

The relational model infers simple relations from the data of the form:

$$G(t+\Delta_g) \in a_1 G(t) + a_2 G(t-\Delta_g) + a_3 u(t-\Delta_I) + [l,u] \tag{1}$$

The model predicts a future value of the patient's blood glucose $G(t+\Delta_g)$ in terms of a linear combination of the current value $G(t)$, a past value $G(t-\Delta_g)$ and the insulin-on-board calculated at time $t-\Delta_I$. We note that rather than assigning a value, the model provides a constraint over the value at time $t+\Delta_g$. The uncertainty interval $[l,u]$ captures the deviation between the model and reality. To discover such models, we adopt a simple statistical procedure as follows:

(a) First, we discover a_1, a_2 and a_3 through linear regression, with the constraint $a_3 \leq 0$ to reflect the inhabiting effect of insulin action on glucose values. The regression was carried out using MATLAB.

(b) Next, we find limits $[l,u]$ by analyzing the residual error. In particular, we use the 99% confidence intervals around the mean value of the residual error.

Figure 2 shows the relations obtained for various time delays that were set using our background knowledge of insulin kinetics, including the peak insulin action and insulin action delay times. The relations are viewed as constraints that jointly constrain the possible values of blood glucose over time.

Figure 3 shows the predicted ranges for the blood glucose levels by our models against the actual blood glucose levels measured in the patient for two sessions. Note that the blood glucose level can sometimes lie outside the predicted range due to two sources of errors: the approximation error in the model itself and the use of 99% confidence intervals over the residuals.

$$
\begin{aligned}
G(t) &\in [0, 500]\ t \in [0, T] \\
G(t) &\in [120, 300]\ t < 0 \\
G(t+5) &\in G(t) + [-10, 10] \\
G(t+30) &\in 0.36G(t) + 0.59G(t-30) - 2.25u(t-30) + [-5.9, 7.1] \\
G(t+45) &\in 0.38G(t) + 0.67G(t-45) - 13.35u(t-45) + [-4.6, 7.4] \\
G(t+60) &\in 0.51G(t) + 0.52G(t-60) - 13.31u(t-60) + [-2, 3] \\
G(t+120) &\in 0.46G(t) + 0.46G(t-120) - 17.01u(t-120) + [-3.1, 4.9]
\end{aligned}
$$

$$
\begin{aligned}
u(t) &= 1.89u(t-5) - 0.9u(t-10) \\
&\quad + \tfrac{1}{60}\left(\textstyle\sum_{j=1}^{5} i_d(t-j) - 0.9\sum_{j=6}^{10} i_d(t-j)\right)
\end{aligned}
$$

$$
\begin{aligned}
I_e(t) &= I_e(t-5) + (G(t) - G_0) \\
D(t) &= \tfrac{G(t)-G(t)}{5} \\
I_p(t) &= K_0 i_d(t-5) + K_1 I_p(t-5) + K_2 I_p(t-10) \\
r(t) &= \begin{pmatrix} K_p(G(t) - G_0) + K_i I_e(t) + \\ K_d D(t) - \gamma I_p(t) \end{pmatrix} \\
i_d(t) &= \begin{cases} 0 & r(t) \le 0 \\ r(t) & 0 \le r(t) \le i_{max} \\ i_{max} & r(t) \ge i_{max} \end{cases}
\end{aligned}
$$

Fig. 2. (Top) Model relations showing the dependence of the glucose $G(t)$ on the insulin-on-board $u(t)$ and the insulin delivery rate $i(t)$ for Patient ID PSO3-001-0001. (Bottom) The PID control law that is run in a 5 minute time-triggered loop. Control parameters are shown in blue.

3.3 Control Feedback Law

The value of insulin $i_d(t)$ is controlled by a discrete PID controller described by Steil at al. [24,26,25]. The controller executes synchronously once every 5 minutes and the insulin delivery is held constant over the subsequent 5 minute interval. This controller has been evaluated in numerous inpatient and outpatient clinical trials. The PID gains and parameters are currently chosen using a rule of thumb approach based on the patient weight and daily insulin requirement, as described by Weinzimer at al. [26]. Figure 2 shows the equations of the controller.

3.4 Reachability Analysis

Our goal is to predict the maximum/minimum value of blood glucose levels achieved by the closed loop composition of the model and controller shown in Figure 2. We encode the action of the entire closed loop over some time interval $[0, T]$ as an mixed integer program, that is solved to find the maximum and minimum values of glucose achievable at time T. In particular, the integer variables arise from the saturation

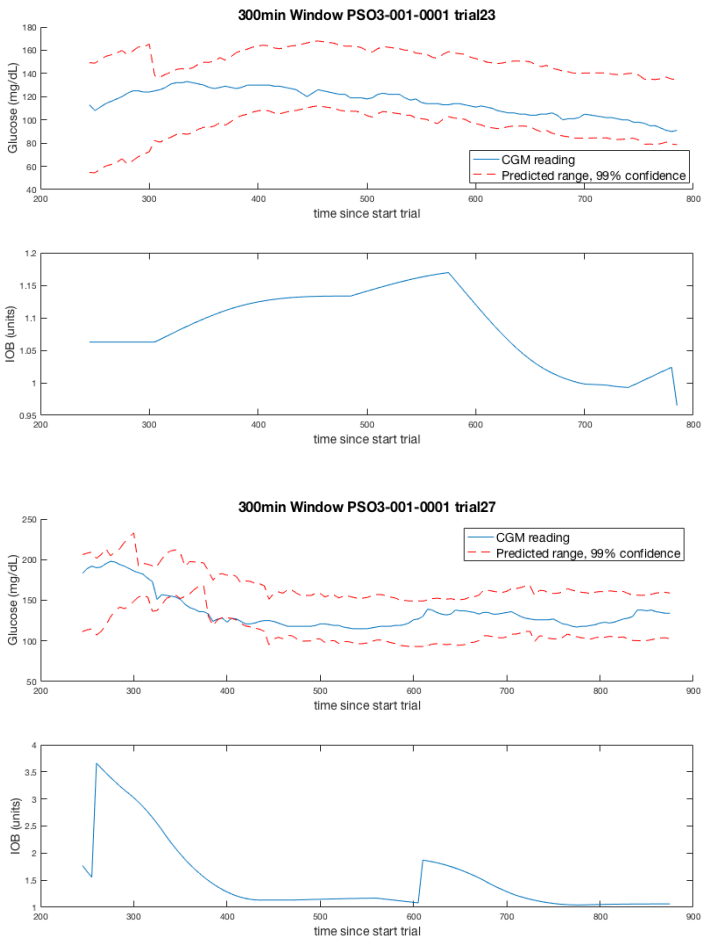

Fig. 3. Comparison of the predicted ranges by our relational models against the actual blood glucose levels for patient PSO3-001-0001.

terms in the PID controller. By varying the time horizon over a range from $T = 10$ minutes to $T = 5$ hours (in steps of 10 minutes), we obtain range estimates for the blood glucose levels. The reachability analysis was performed in Python, using the state-of-the-art Gurobi solver for mixed integer programs.

Figure 4 shows the overall bounds obtained over the entire time horizon. The solution to the MILPs required 71 minutes of wall clock time measured in a Macbook Air laptop with 8GB RAM, 1.8 GHz Intel Core i5 processor, running OSX 10.12. We compare two different settings of the parameter K_p, while setting the remaining parameters in relation to K_p, as recommended by the control design [26]. The first setting is the one calculated using the rule of thumb that uses the patient's daily insulin requirement. The second setting was chosen by repeated trial and error.

Reachability analysis is unable to establish safety in the nominal case. However, it establishes that the controller is able to maintain the blood glucose within a normal range using the modified values. Furthermore, as the controller is allowed to run longer, it is able to narrow the gap between the worst and the best case, indicating the possible stabilization of glucose values under the action of the controller. We also note the initial violations are expected due to the delay in the action of

insulin that is captured in our model. We also notice a jump in the range at time $t = 30$ likely caused by the introduction of a new relation from Figure 2.

3.5 Threats to Validity

We briefly note that our model is fit using linear relations, wherein the times Δ_G, Δ_I are chosen by us with some insight into the nature of insulin action. However, considering the uncertainty in the model mitigates against this choice. The calculation of the insulin on board $u(t)$ is not patient specific. It is a standard calculation performed for a given type of insulin assuming average time to peak action (75 minutes) and average duration of insulin action (180 minutes). Finally, our model does not incorporate meal or exercise disturbances that can cause hypoglycemia due to the persistence of insulin in the patient well after the meal. Likewise, patient boluses are not factored into our model. Handling these limitations will form an important part of our future work.

4 Conclusion

In conclusion, we have outlined a preliminary approach that can infer simple relations from data through a combination of regression and statistical analysis of the residuals. By combining multiple relations, we obtain nondeterministic models that are suitable for verification of properties of control systems. In the future, we wish to investigate the problem of finding optimal parameters for this controller and translate our findings into the clinical practice for setting parameter values for devices such as the Medtronic 670G.

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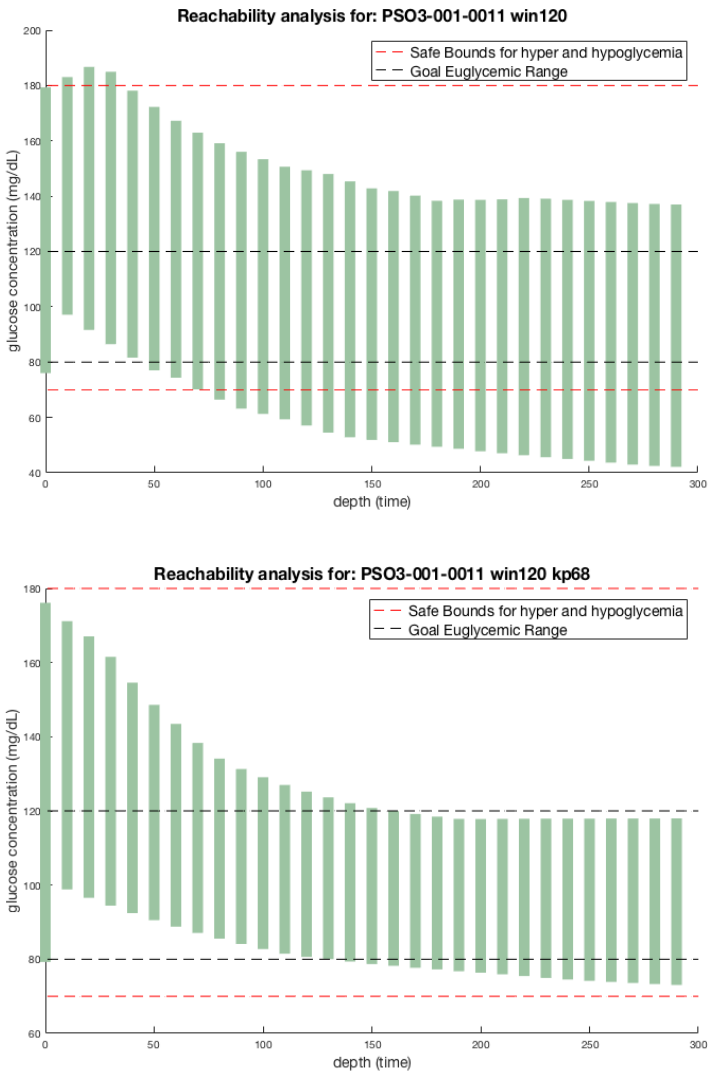

Fig. 4. Predicted worst case reachable ranges for glucose values over time using two different parameter settings for the proportionality gain K_p for patient ID PSO3-001-0011. The red dashed lines show hypoglycemia limit (70 mg/dl) and hyperglycemia limit (180 mg/dl).

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