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# Adaptive control in an artificial pancreas for people with type 1 diabetes ☆

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ABSTRACT

In this paper, we discuss overnight blood glucose stabilization in patients with type 1 diabetes using a Model Predictive Controller (MPC). We compute the model parameters in the MPC using a simple and systematic method based on a priori available patient information. We describe and compare 3 different model structures. The first model structure is an autoregressive integrated moving average with exogenous input (ARIMAX) structure. The second model structure is an autoregressive moving average with exogenous input (ARMAX) model, i.e. a model without an integrator. The third model structure is an adaptive ARMAX model in which we use a recursive extended least squares (RELS) method to estimate parameters of the stochastic part. In addition, we describe some safety layers in the control algorithm that improve the controller robustness and reduce the risk of hypoglycemia. We test and compare our control strategies using a virtual clinic of 100 randomly generated patients with a representative inter-subject variability. This virtual clinic is based on the Hovorka model. We consider the case where only half of the meal bolus is administered at mealtime, and the case where the insulin sensitivity increases during the night. The numerical results suggest that the use of an integrator leads to higher occurrence of hypoglycemia than for the controllers without the integrator. Compared to other control strategies, the adaptive MPC reduces both the time spent in hypoglycemia and the time spent in hyperglycemia.


## 1. Introduction

Type 1 diabetes is a metabolic disease characterized by destruction of the insulin-producing $\beta$-cells in the pancreas. Therefore, patients with type 1 diabetes need exogenous insulin administration. However, the dosage of insulin must be done carefully. An insulin overdose may lead to low blood glucose (hypoglycemia). Hypoglycemia has immediate effects, such as seizures, coma or even death. In contrast, prolonged periods of too high blood glucose (hyperglycemia) are associated with complications such as retinopathy, neuropathy and nephropathy (American Diabetes Association, 2015).

An increasing number of patients with type 1 diabetes apply a therapy approach based on continuous subcutaneous (sc) insulin infusion (CSII) using insulin pumps combined with continuous glucose monitoring devices (CGMs). CGMs provide frequent subcutaneous (sc) glucose measurements. The CSII pump provides a preprogrammed continuous infusion of rapid acting insulin to mitigate the endogenous glucose production (EGP) from the liver. Larger amounts of insulin are administered in relation to meals to compensate the effects of carbohydrates (CHO) intake. However, the decisions on the timing and amount of meal insulin injection as well as the profile of the EGP insulin injection are left to the patient. By automating the decisions on insulin injections, closed-loop control of the blood glucose concentration by an Artificial Pancreas (AP) has the potential to ease the life and reduce the burden and risk of complications for patients with type 1 diabetes. The first version of the AP (Biostator) was developed 40 years ago (Albisser et al., 1974; Pfeiffer, Thum, & Clemens, 1974). It used intravenous insulin, dextrose injections, and intravenous glucose measurements. However, this setup is only usable for in-clinical studies and does not mimic everyday life of a type 1 diabetes patient. Current prototypes of the AP use the sc–sc route for glucose sensing and injection of insulin. They include a CGM, a control algorithm, and an insulin pump. Fig. 1 illustrates the principle of an AP. Even more recently, glucagon has been tested as a safety

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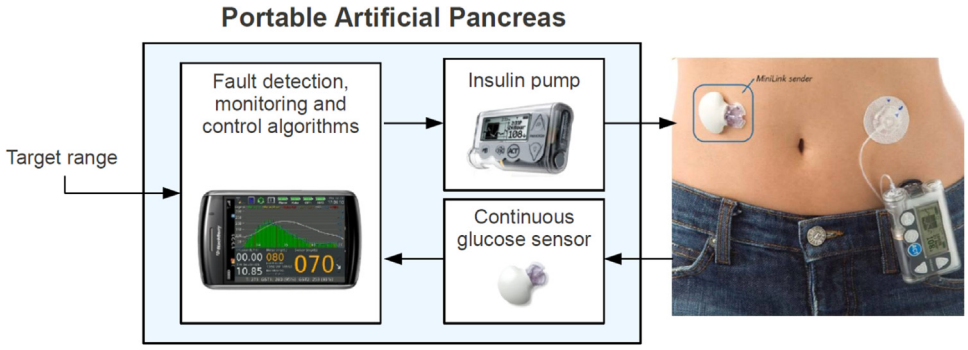


**Fig. 1.** Closed-loop glucose control. Glucose is measured subcutaneously using a continuous glucose monitor (CGM). Insulin is dosed by an insulin pump.

hormone (Bátora et al., 2014; Herrero et al., 2013; Russell et al., 2014), but the use of glucagon is not considered in this paper. Several research groups worked on the implementation of APs and tested their implementation with virtual patients (Eren-Oruklu, Cinar, Quinn, & Smith, 2009; Magni et al., 2009; Soru et al., 2012) as well as in vivo clinical studies (Breton et al., 2012; Hovorka et al., 2010; Kovatchev et al., 2014; Phillip et al., 2013; Schmidt et al., 2013). Regardless of the control algorithm used, the performance of current APs is limited by several factors: (1) the intra- and inter-patient variability; (2) the lags and delays associated to the choice of the sc–sc route for glucose monitoring and insulin administration (Boiroux, Finan, Poulsen, Madsen, & Jørgensen, 2010); and (3) the accuracy and reliability of the CGM.

Model Predictive Control (MPC) is one of the most commonly used methods for the AP. The main advantage of MPC is the ability to handle hard constraints on input variables and soft constraints on output variables in a systematic way. Insulin on board (IOB) constraints in the linear MPC can reduce the risk of overdosing insulin due to nonlinearities in glucose–insulin dynamics (Ellingsen et al., 2009). MPC can easily incorporate a feedforward–feedback mechanism that reduces the postprandial glucose peak by administering meal boluses in anticipation of meals (Abu-Rmileh & Garcia-Gabin, 2010; Marchetti, Barolo, Jovanovič, Zisser, & Seborg, 2008). Disturbances such as meal intake, physical exercise, stress, and illness affect the insulin needs throughout the day. Patients with type 1 diabetes usually reject the disturbance coming from meals by taking a large amount of insulin. In this procedure, it is implicitly assumed that people with type 1 diabetes can accurately estimate their meal sizes and have an accurate knowledge of their postprandial dynamics. In practice, patients typically do not have such information available (Brazeau et al., 2013). Moreover, other sources of disturbances cannot easily be measured and are usually included in a stochastic term. An adaptive control algorithm has the potential to cope with these unknown disturbances (Eren-Oruklu et al., 2009; Fischer et al., 1987).

This paper presents an adaptive control strategy for overnight BG stabilization. We describe an AP using a CGM for glucose feedback, an insulin pump, and a control algorithm based on MPC. The considered control strategy requires a priori available patient information for computing a subject-specific set of parameters. The required information is the basal insulin infusion rate, the insulin sensitivity factor (also called the correction factor), and the insulin action time. We discuss MPCs based on three different structures for the stochastic part of a deterministic–stochastic input–output model. The first MPC is based on an autoregressive integrated moving average with exogenous input (ARIMAX) model. The integrator in the ARIMAX based MPC provides steady-state offset free control at the expense of a deliberate model-plant mismatch that increases the variance of the control error (Huusom, Poulsen, Jørgensen, & Jørgensen, 2012; Jørgensen, Huusom, & Rawlings, 2011). The ARIMAX based MPC is described in Boiroux, Duun-Henriksen, Schmidt, Nørgaard, et al. (2012) and tested in an overnight clinical study (Schmidt et al., 2013). The key novelties in this paper are that we investigate by simulation if the integrator is needed in the MPC for an AP and introduce adaptive estimation. Therefore, the second MPC is based on an autoregressive moving average with exogenous input (ARMAX) model, i.e. a model without an integrator. This model cannot guarantee offset-free steady state control to step disturbances but provides lower control error variance (Huusom et al., 2012; Jørgensen et al., 2011).The third MPC is based on an adaptive ARMAX model in which we use a Recursive Extended Least Square (RELS) method to estimate parameters of the moving average part. The controllers are tested and compared using a cohort of 100 virtual patients. The use of simulations prior to in vivo clinical studies serves two purposes. First, simulations are able to reproduce exactly the same scenario, while the intra-individual variability limits the reproducibility in real patients. Therefore, simulations allow a more rigorous comparison between different controllers. Second, simulations can be conducted on a larger population and allow to test several control strategies at a much lower cost than tests using real patients. It would not even be ethically permissible to conduct some in silico tests in vivo.

The paper is structured as follows. In Section 2, we describe the model and the methods used to simulate a cohort of patients with type 1 diabetes and noise-corrupted CGM measurements. Section 3 presents a procedure for computation of the deterministic part of the model used by the MPC. The parameters in this part of the model are derived from prior patient information and are common for the three model classes. In Section 4, we introduce the stochastic models for the three different MPCs. Furthermore, we describe the realization of the deterministic–stochastic input–output models as state space models in innovation form and present the corresponding Kalman filtering and prediction equations. Section 5 presents the MPC algorithm used in the AP. The MPC is based on a state space model in innovation form and uses soft output constraints to define a zone of desirable glucose concentrations. In Section 6, we evaluate and discuss the performance of the three different controllers using a cohort of 100 virtual patients. We consider the case where half of the ideal meal bolus is administered at mealtime, and the case where the insulin sensitivity increases during the night. Conclusions are provided in Section 7.

## 2. Physiological models for patients with type 1 diabetes

Several physiological models have been developed to simulate virtual patients with type 1 diabetes (Bergman, Phillips, & Cobelli, 1981; Dalla Man, Rizza, & Cobelli, 2007; Hovorka et al., 2004). They describe subcutaneous insulin transport, intake of carbohydrates through meals, and include a model of glucose–insulin dynamics.

In this paper, we use the Hovorka model to simulate patients

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