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Evaluation of an artificial pancreas in *in silico* patients with online-tuned internal model control

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ABSTRACT

A fully-automated controller in the artificial pancreas (AP) system designed to regulate blood glucose concentration can give better lifestyle to a type 1 diabetic patient. This paper deals with evaluating the benefit of fully-automated online-tuned controller for the AP system over offline-tuned and semi-automated controller based on internal model control (IMC) strategy. The online-tuned controller is fully-automatic in the sense that it can automatically deal with intra- and inter-patient variabilities and compensate for unannounced meal disturbances without any prior knowledge of patient parameters, patient specific characteristics or patient specific input–output data. A data driven Volterra model of patients is used to design IMC algorithms. For online-tuned controller, the Volterra kernels of the model are computed online by recursive least squares algorithm. The IMC algorithms are evaluated using different scenarios in the UVA/Padova metabolic simulator for validation, comparison with a fully-automatic zone model predictive controller and robustness analysis. Unlike offline-tuned IMC and semi-automated IMC, the online-tuned IMC in the AP system performs satisfactorily for every patient condition without patients' intervention. Experimental results show that the online-tuned IMC compensates unannounced meal disturbances with low frequency of hypoglycemic events and most importantly, with low insulin infusion even with variations in insulin sensitivity, in the presence of irregular amounts of meal disturbances at random times, and in the presence of very high noise levels in the sensors and actuators. Patients experience hypoglycemia 0.46%, 1.01% and 20% of the time using online-tuned, offline-tuned and semi-automated IMC respectively when the insulin sensitivity is increased by +20%.

1. Introduction

Type 1 diabetes mellitus is an autoimmune condition with complete destruction of pancreatic β-cells, leading to wide and unstable fluctuations of blood glucose (BG) concentrations. Optimal glycemic control of type 1 diabetes is needed to avoid chronic complications such as nephropathy and retinopathy, resulting from sustained high glucose level, i.e., *hyperglycemia* (above 180 mg/dl or 10 mmol/l), and also to avoid *hypoglycemia* (below 70 mg/dl or 4 mmol/l) that can lead to diabetic coma and possibly death. Thus, continuous and controlled infusion of insulin is required to maintain BG level within a specified normal range of 72–144 mg/dl i.e., *normoglycemia* or *euglycemia*, in the presence of normal meal and activity conditions of patients [1].

There were several efforts in the past on the development of a controller that automates the infusion of insulin either via the intravenous path or the subcutaneous path. Intravenous delivery devices require venous access and have limited lifetime, whereas subcutaneous delivery devices are less invasive and they can give better lifestyle to type 1 diabetic patients. Thus, it has become possible to develop an AP system suitable for outpatient use with the availability of subcutaneous continuous glucose monitoring devices and subcutaneous insulin infusion pumps (SC-SC route).

The challenges in the design of a satisfactory closed-loop control algorithm for nonlinear SC-SC route based glucose-insulin system are inter-individual variability, dynamic nonlinearities, presence of significant disturbances (i.e. meals and physical activities), and delays due to the absorption of insulin from the subcutaneous tissue to the blood and glucose from the blood to the subcutaneous tissue [2,3].

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Controllers that are designed for the SC-SC route based AP system can be classified into two main types; fully-automated and semi-automated. Fully-automated control algorithms do not use information of meal time and size to generate insulin doses. Hence, these controllers do not require patients' intervention. On the other hand, semi-automated control algorithms consider a signal of meal time and size to provide satisfactory controller performance. This means that patients should always be aware of time and size of the meal consumed so that the controller gets the correct information. The calculated optimal bolus dose for feedforward path in semi-automated control algorithm will be erroneous if patient parameters e.g., insulin to carbohydrate ratio, insulin sensitivity varies. Though semi-automated control algorithms give improved performance in avoiding hyperglycemia, these are not designed for fully-automated AP systems that can regulate the BG level without patients' effort and therefore can give better lifestyle to a patient. Due to extremely diverse patient dynamics and their time-varying characteristics, it is difficult for any control algorithm to maintain the BG level without prior information about meals. Thus, the design of a fully-automated controller is a major challenge.

Modern control methodologies have demonstrated adequate performance in the SC-SC route based AP system. But the variability in the glucose-insulin regulatory system of patients is difficult to be explicitly addressed. To avoid re-tuning of the controller for every patient condition, many controllers use patient model that is capable of capturing such variations in dynamics. Thus, the effective control of SC-SC glucose-insulin system requires a *model* that can adequately acquire the dynamic behavior of a patient.

Various model-based control algorithms have been developed so far for BG regulation in closed loop via the SC-SC route [4–15,17]. These model-based controllers are designed based on data driven models of which there are two types; parametric model, and nonparametric model. Parametric model-based controllers capture all the information about the data within their model parameters. But they fail to provide full information of nonlinearities in the coupled glucose-insulin process. Hence, it is difficult to build a detailed and dynamic model of patients and generate optimal insulin dose using a parametric model-based controller. The determination of the order and structure of the model is also difficult in such controllers.

Controllers based on nonparametric models are better suited for SC-SC route based AP system. Such controllers can identify the coupled nonlinear process in the off-equilibrium region[1] where the data available is much less. The nonparametric model can also grow in size to accommodate the complexity of patient data due to flexibility in the number and nature of parameters.

Model-based controllers can be further classified depending on how the parameters of the model are tuned; offline-tuned versus online-tuned. In offline-tuned controllers, models are identified and fixed from previously collected input–output data. On the other hand, in online-tuned controllers, models are adapted online depending on the measured input–output data of patients. Since patient conditions, and consequently model parameters, can vary depending on various factors, online-tuned controllers can give better performance when compared to offline-tuned controllers. This is particularly true when the data used for offline-tuning does not sufficiently capture all the different patient conditions that may occur. Thus, online-tuned controllers can predict insulin doses for different patient conditions without prior patient-specific information, and hence are more adaptive.

In the present work, we use a nonparametric model to represent the SC-SC route based glucose-insulin system, and develop AP system using fully-automated offline-tuned, online-tuned and semi-automated internal model control (IMC) algorithm. IMC algorithm is a particular design approach of model-based control algorithm. The objective of IMC is to minimize the error between the input to the controller and the model output. In our case, input to the controller is the difference between the reference glucose measurement and obtained measurement from patient and model mismatch, and model output is the glucose estimate from the nonparametric model. The online-tuned IMC algorithm does not require prior knowledge of patient parameters, patient specific characteristics or patient specific input–output data. The controller uses online basal insulin dose as input and BG from the continuous glucose monitoring (CGM) sensor as output to predict an optimal insulin dose.

In this paper, we evaluate the both offline- and online-tuned fully-automated IMC algorithms and also semi-automated online-tuned IMC algorithm on *in silico* patients, particularly its robustness to intra- and inter-patient variabilities. We perform the evaluation for different scenarios in 10 *in silico* patients from the U.S. Food and Drug Administration (FDA)-approved University of Virginia/Padova metabolic simulator [18]. The main contributions of this work can be summarized as follows.

1. A nonparametric time domain Volterra model is developed both offline and online using recursive least squares (RLS) algorithm for *in silico* patients. The online generated Volterra model captures large intra- and inter-patient parameter variations without any prior information about patients, and helps the controller to rapidly predict an optimal insulin dose.
2. The frequency domain Volterra kernels of the model are computed by taking fast Fourier transforms (FFTs) on respective time domain kernels. The frequency domain kernels called the Volterra transfer functions (VTF) are then used to develop an IMC algorithm for *in silico* patients.
3. The VTF is derived both offline and online from the input–output data of *in silico* patients and consequently, the offline- and online-tuned IMC algorithm is developed using the VTF.
4. Semi-automated controller is also developed by introducing a feedforward loop in the online-tuned IMC.
5. IMC algorithms are evaluated for different scenarios in 10 adult patients for validation, robustness analysis and comparison with other model-based controllers.
   - Validation experiments show that both online- and offline-tuned IMC gives satisfactory performance in compensating unannounced meal disturbances with less hypoglycemic events without patients' intervention. The performance of the offline-tuned IMC is adequate just because the validation experiment is done at the same patient condition as is used to tune the model of the controller. On the other hand, semi-automated control algorithm reduces more hyperglycemic events than the fully-automated IMC at the expense of higher hypoglycemic events.
   - Performance of online- and offline-tuned IMC are compared with fully-automated zone model predictive controller (zone-MPC) [17]. This controller uses offline-tuned parametric models. Since we have access to only 10 adult patients from the UVA/Padova metabolic simulator, we have chosen this zone-MPC controller for comparison because their published results are also based on the same 10 adult patients and this enables a direct comparison.[2] The IMC algorithms compen-

[1] This is the region where models struggle to identify the glucose-insulin process due to lack of data.

[2] Although the fully-automated nonparametric model based controller in [14] is most closely related to our work, experimental comparison with [14] is not feasible because they have used 100 in silico patients in their published experiments. Nevertheless, the comparison with [17] would highlight the benefits of using non-