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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-

sate unannounced meal disturbances with no hypoglycemic event like zone-MPC. But the performance of the IMC algorithms are better in avoiding hyperglycemia than zone-MPC (bound 80–140 mg/dl).
- Robustness experiments show that at various patient conditions the online-tuned controller performs better than both the offline-tuned and semi-automated IMC in avoiding hypoglycemia. It is observed that the percentage of time when patients are in the hypoglycemic zone is only 0.46% in online-tuned IMC even when insulin sensitivity was increased by +20% whereas this percentage is 1.01% and 20% in offline-tuned and semi-automated IMC respectively.

The paper is organized as follows. The next section gives a brief review of related work. In Section 3, the overview of the internal model control based AP system and the mathematical and algorithmic details of the IMC algorithm are presented. Finally in Section 4, we present the experimental results and validation of our approach, followed by a concluding discussion in Section 5.

1.1. Related work

The goal of diabetes management is to tightly regulate the insulin infusion rate of type-1 diabetics so that the BG level is maintained within a reasonable range. Researchers have been working on the development of a controller that automates the infusion of insulin. Linear and nonlinear algorithms were employed for insulin delivery based on glucose measurement using proportional-derivative control [19], fuzzy logic control [20], artificial neural network [21], adaptive control methods [22–24] and model predictive control [4–15,17,25–27].

Early development of control algorithm for the AP system was mainly based on the infusion of insulin via intravenous or intraperitoneal routes. Parker et al. [23] developed a fully-automated $H\infty$ controller and parametric model-based control algorithms [25] to maintain normoglycemia through the intravenous path. They compared the performances of parametric model-based control algorithms with $H\infty$ and showed that the performances of both the controllers are excellent, but $H\infty$ controller is superior in reference tracking. Dua et al. [27] also developed a parametric model-based control algorithm for BG regulation through the intravenous path. Both Parker et al. [23] and Dua et al. [27] showed the robustness of the controller in the presence of intra- and inter-patient parameter uncertainties. These fully-automated controllers do not need meal announcements. However, offline parameter identification of patient model employed by these controllers needs a record of the input–output data of patients.

Control of the intravenous insulin delivery system gives an improved controller performance due to rapid insulin delivery with negligible dead-time, whereas delays in the effect of subcutaneous insulin action and subcutaneous glucose monitoring are the major challenges for the design of a controller for the SC-SC system. In spite of the challenges, there have been recent efforts for the SC-SC system as it is less invasive and does not require clinical supervision. Though the PID controller [19] and adaptive controllers, e.g., linear quadratic Gaussian (LQG) [22] and $H\infty$ controller [24], have been employed to control the BG level in the SC-SC system, model-based control algorithms have been recognized as the most suitable approach for this case [4–15,17]. Model-based controllers use dynamic patient model that can predict the diversity of patient dynamics and also their time-varying characteristics. In order to compensate for the delays in the effect of insulin action, there are recent efforts in designing model-based control algorithms using both feedback and feedforward control actions [5,6]. Feedforward control action considers a signal of announced meal time and size to provide a satisfactory controller performance. Technosphere insulin at meal time was also employed as feedforward control action [7]. Though these semi-automated control algorithms give improved performances, these are not designed for fully-automated AP system that can regulate the BG level without patients' intervention.

In the recent past, researchers have employed prior knowledge of patient characteristics or patient specific input–output data to build a fully-automated but offline-tuned model-based control algorithm with enhanced controller performance for the SC-SC system [14–16]. These patient specific characteristics are required to tune the control action so that the chance of patient and model mismatch can be fully eliminated. Messori et al. [14] has built a fully-automated individualized model-based controller using prior knowledge of patient specific input–output data. Turksoy et al. developed a fully-automated controller using autoregressive moving average (ARMAX) model [15]. The model has been identified offline using input–output data. Wang et al. [16] built individualized learning-type model predictive controller (L-MPC) where 2-day open loop clinical trial was conducted to get offline patient data. The offline patient data are used to identify the individualized model of patients. L-MPC algorithm is used to compute both basal and bolus insulin infusion rate and also to update the set-point of the BG concentration. To prevent hypoglycemia, 10g of oral carbohydrate is given to patients if CGM sensor reading fell below 3.3 mmol/l for 15 min and venous BG concentration fell below 3.3 mmol/l for 10 min.

Compared to the existing methods, we have developed a fully-automated online-tuned model-based control algorithm without any prior knowledge of patient parameters, patient specific characteristics or patient specific input–output data. The nonparametric Volterra model identification and internal model control algorithm are developed using online input–output data. Thus, the variation of patient characteristics, e.g., insulin sensitivity in the presence of stress and physical activities in real life, is captured by the model online, and hence, reduces the risk of hypoglycemia due to insulin dose mismatch. The list of acronyms and variables are given in Tables 1 and 2 respectively.

Table 1
List of acronyms.

AP	Artificial pancreas
IMC	Internal model control
BG	Blood glucose
SC-SC	Subcutaneous glucose monitoring-subcutaneous insulin infusion
GI	Glucose-insulin
CGM	Continuous glucose monitoring
FDA	Food and Drug Administration
RLS	Recursive least squares
FFTs	Fast Fourier transforms
VTF	Volterra transfer function
ARMAX	Autoregressive moving average
CVGA	Control variability grid analysis
TO_{180}	Time over 180 mg/dl
LBGI	Low blood glucose index
HBGI	High Blood glucose index

2. System overview

2.1. Model-based closed-loop artificial pancreas (AP) system

An internal model control structure based artificial pancreas system is shown in Fig. 1. In the present work, 10 *in silico* adults from UVA/Padova metabolic simulator have been entered into the

parametric (as opposed to parametric models in [17]) and online-tuned (as opposed to offline-tuned in both [14,17]) models.

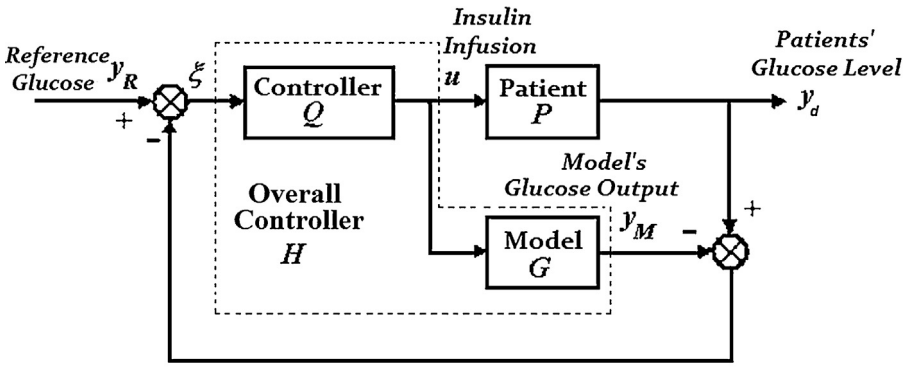

Fig. 1. Structure of an IMC based artificial pancreas system.

Table 2
List of variables.

$y_M(t)$	Estimated glucose output
$g^{(0)}, g^{(1)}, g^{(2)}$	Zero, first and second order Volterra kernel
$u(t)$	Insulin input
M	Memory length
τ	Time lag
G	Volterra kernels in vector form
G_1,G_2	Volterra kernels for linear and nonlinear models
$U(t)$	Extended input vector
$U_1(t)$, $U_2(t)$	First order and second order input vector
$e(t)$	Error signal
$y_d(t)$	Patients' glucose output
λ	Forgetting factor
y_R	Target glucose level
ζ	Input to the controller

research protocol as 'Patient' to develop the AP system. Insulin is delivered through the Subcutaneous insulin pump and glucose is measured from continuous glucose monitoring (CGM) sensor. Noisy BG measurements from the CGM sensor and noise in insulin delivery device of UVA/Padova metabolic simulator are used by the controller. The developed offline- and online-tuned fully-automated IMC delivers insulin without prior information about the size or time of the test meals.

2.2. Control challenges

The key component of an AP system is the control algorithm. Specifically, the control algorithm should address the following objectives [11]:

1. It should prevent or reduce the duration of *hypoglycemic* events.
2. A common clinical problem of great concern for type 1 diabetic patients is the overnight glucose control. So the controller must reduce the risk of an overnight *hypoglycemic* event.
3. It should maximize the time during which the patients' BG concentration remains in a target zone (i.e. 70–180 mg/dl).
4. It should avoid insulin over-delivery. Insulin over-delivery may cause severe *hypoglycemia* in the short term, as well as lead to long term complications such as risk of cardiovascular diseases, atherosclerosis, weight gain and even higher cancer risk [28,29].

To develop an effective and safe AP system, the controller must meet all the above mentioned criteria.

3. Development of internal model control algorithm

Internal model control (IMC) has recently found wide acceptance in process industries as its design procedure provides for both perfect control and a mechanism to impart robust properties. IMC algorithm developed for AP system requires a patient model estimator that estimates patient states from the insulin input and glucose output of patients. The nonlinear patient P, shown in Fig. 1, is modeled by Volterra model G. The Volterra kernels are identified by RLS algorithm. The time domain Volterra kernels are converted into frequency domain to obtain the VTF. VTF represents the nonlinear transfer function of the patient model and is used to develop the IMC algorithm. Thus, an overall controller H is composed of a feed-forward path controller Q and the feedback model G. The feed-forward controller Q generates an optimal insulin dose u using observed patients' glucose output y and glucose output predicted by the model G [30,31]. In the following sections we provide a brief overview of the controller H, but more details can be found in [32].

3.1. Volterra model

The finite Volterra series up to second order kernel for the present single-input single output (SISO) glucose-insulin process is expressed as:

$$y_M(t) = g^{(0)} + \sum_{\tau=0}^{M-1} g^{(1)}(\tau)u(t-\tau) + \sum_{\tau_1=0}^{M-1}\sum_{\tau_2=0}^{M-1} g^{(2)}(\tau_1,\tau_2)u(t-\tau_1)u(t-\tau_2) \quad (1)$$

where $y_M(t)$ is the estimated glucose output at time instant t for a kernel memory length M and lag τ. $g^{(0)}$, $g^{(1)}$ and $g^{(2)}$ are the zero, first and second order Volterra kernels respectively, associated with the insulin input $u(t)$ in time domain [33,34]. The estimated glucose output $y_M(t)$ can also be expressed in terms of the nonlinear kernel operator G as:

$$y_M(t) = G[u(t)] \quad (2)$$

$$\text{where,} \quad G_t = [g^{(0)} g_1^{(1)}(0)\cdots g_1^{(1)}(M-1) g_{11}^{(2)}(0,0) \cdots g_{11}^{(2)}(0,M-1) \; g_{11}^{(2)}(1,0) \; \cdots g_{11}^{(2)}(1,M-1) \cdots g_{11}^{(2)}(M-1,0)\cdots g_{11}^{(2)}(M-1,M-1)]$$

The Volterra model has been developed by taking the constant zeroth order Volterra kernel $g^{(0)} = 0$, since for input $u(t) = 0$ we can define $y_M(t) = 0$ without loss of generality [35]. G represents the kernels of the Volterra model expressed in vector form, which is the sum of the kernels for linear model and nonlinear models of different degrees of nonlinearity:

$$G = G_1 + G_2 + \cdots \quad (3)$$

The required Volterra kernels are computed recursively from extended input vector using RLS algorithm. The extended input vector is given by:

$$U(t) = [U_1(t) \;\; U_2(t)] \tag{4}$$

where, the first order input vector $U_1(t)$ and second order input vector $U_2(t)$ respectively are:

$$U_1(t) = [u(t) \;\; u(t-1)\cdots u(t-M+1)] \tag{5}$$

$$\begin{aligned} U_2(t) \;\; &= [u^2(t) \;\; u(t)u(t-1)\cdots u(t)u(t-M+1) \;\; u^2(t-1) \\ &\quad u(t-1)u(t-2)\cdots u(t-1)u(t-M+1)\cdots u^2(t-M+1)] \end{aligned} \tag{6}$$

RLS filter is used to find the filter coefficients i.e., Volterra kernels [33,34], and these coefficients are updated the same with new data set by minimizing the following cost function:

$$J(t) = \sum_{\tau=0}^{t} \lambda^{t-\tau} e(\tau) = \sum_{\tau=0}^{t} \lambda^{t-\tau} (y_d(\tau) - y_M(\tau))^2 \tag{7}$$

where, $e(\tau)$ is the error signal, $y_d(\tau)$ is the patients' glucose output and $y_M(\tau)$ is the estimated glucose output. $\lambda \in [0,1]$ is a 'forgetting factor' used to control the memory span of the adaptive filter.

The Volterra model G must be represented in nonlinear transfer function form to develop the IMC algorithm. Thus, frequency domain kernels have been computed by taking fast Fourier transforms (FFTs) on the time domain kernels for a specific length of extended input vector. The set of kernels $G^{(1)}(f), G^{(2)}(f_1, f_2)$ obtained from the frequency domain Volterra model describes the nonlinear transfer function or the VTF [36].

3.2. Internal model controller synthesis based on Volterra model

An internal model controller shown in Fig. 1 for the AP system has been designed using VTF of patients. The design objective, $J: \Re \rightarrow \Re^+$, is to find a Q such that:

$$J = \min_u \|e\| \tag{8}$$

$$\text{where,} \quad u = Q * \xi \tag{9}$$

$$e = y_R - y \tag{10}$$

where u is the controller output i.e., the infused insulin dosage, y is patients' glucose level, y_R is the target glucose level i.e., 110 mg/dl and ξ is the input to the controller. The objective of (8) is strictly met if

$$G * Q = I \quad \text{or,} \; Q = G^{-1} \tag{11}$$

Hence, an optimal solution of Q is found as G^{-1} i.e. inverse of the frequency domain kernels or VTF [30,31].

Obtaining an exact inverse that satisfies (11) is not feasible in practice as it can lead to steady state offset if disturbance exists. Hence, it is impossible to obtain a strict zero J of the objective function (8). Thus, the frequency domain Volterra kernels of the model G are decomposed into a linear first order Volterra kernel and nonlinear second order Volterra kernel [30,31]:

$$G = G_1 + G_2 \tag{12}$$

The controller is then synthesized by solving (11) with the above equation. Now, only the inverse of the linear part of the Volterra model i.e., G_1 is required for controller synthesis. However, G_1 is unrealizable as G_1 is not a square matrix. Hence, a 'generalized inverse' synthesis method is used. More details are provided in [32]. Thus, the optimization problem for first order Volterra kernel has the solution:

$$u^{(1)} = G_1^{-L}[\xi] \tag{13}$$

Similarly, the second order solution is derived as:

$$u^{(2)} = -G_1^{-L}[\xi^{(2)}] \tag{14}$$

where $\xi^{(2)}$ consists only of quantities dependent upon $u^{(1)}$.

The nonlinear Volterra model with short memory length $M = 2$ is identified offline from basal insulin input secreted from the subcutaneous insulin infusion pump and measured glucose output of patients' from CGM sensor of the UVA/Padova metabolic simulator. A data set of insulin input and glucose output obtained in open loop condition throughout a day is collected from patients subjected to meal disturbances of 75 g at breakfast (7:00 a.m.) and lunch (1:00 p.m.) and 50 g at dinner (8:00 p.m.) to generate the Volterra model. The overall Volterra kernels G shown in Fig. 1 and its first order Volterra kernels G_1 and second order Volterra kernel G_2 are computed offline using the proposed identification algorithm. G, G_1 and G_2 are converted into frequency domain to obtain VTF that is used to develop the offline-tuned IMC algorithm. The offline-tuned controller Q of Fig. 1 are composed of inverse of G_1 is in loop with G_2. The output of the model G i.e., the estimated glucose output, is then compared with the patients' glucose output. The two outputs may differ due to the presence of both process and sensor noise. If the two outputs differ, the difference can be fed back as an input into the entire system again so that the adjusted control signal is used to minimize the difference between the target glucose level and the patients' glucose output.

3.3. Development of online-tuned internal model controller

As the physiological condition of type 1 diabetic patient in real life scenario can vary depending on various factors, the data used to build the model in offline-tuned controller may not sufficiently capture different patient conditions at different period of time. This requires retuning of the controller for every patient condition. But, it is possible to obtain robust performance at different patient conditions with online-tuned control algorithm. The models used in online-tuned controller are adapted online depending on the measured input–output data of patients. Thus, online-tuned controller can capture the variation in patient parameters, dynamic nonlinearities and disturbances without re-tuning of the controller for each patient and every patient condition.

Online-tuned IMC controller is developed using adaptive RLS filter in an online manner. The RLS filter learns the model used in IMC algorithm recursively with each measured input–output data of patients. Thus, the model can capture the variation in patient dynamics and consequently the IMC cotroller can predict insulin doses for different patient condition. The block diagram of the overall online model identification and control process is shown in Fig. 2. As type 1 diabetic patient is completely lacking of endogenous glucose production, patient needs constant basal dose as well as bolus dose of insulin. Basal insulin dose keeps the blood glucose level at a consistant value during fasting and in between meals consumption. Bolus insulin, delivered at meal time, is required to be controlled by the IMC. Meal is the disturbance input and glucose is the controlled output. The overall Volterra model G and its first order linear model G_1 and the second order nonlinear model G_2 of patients are identified online using RLS filter with each measured input–output data. The IMC controller is developed with the frequency domain Volterra kernels i.e., VTF of G, G_1 and G_2. The estimated glucose output of the adaptive Volterra model is compared with patients glucose output. The difference is fed back to the adaptive controller Q to generate optimal insulin dose in different physiological condition of patients.

Semi-automated control algorithm with meal announcement always performs better in avoiding postprandial hyperglycemia than fully-automated control algorithm. Thus, we have developed

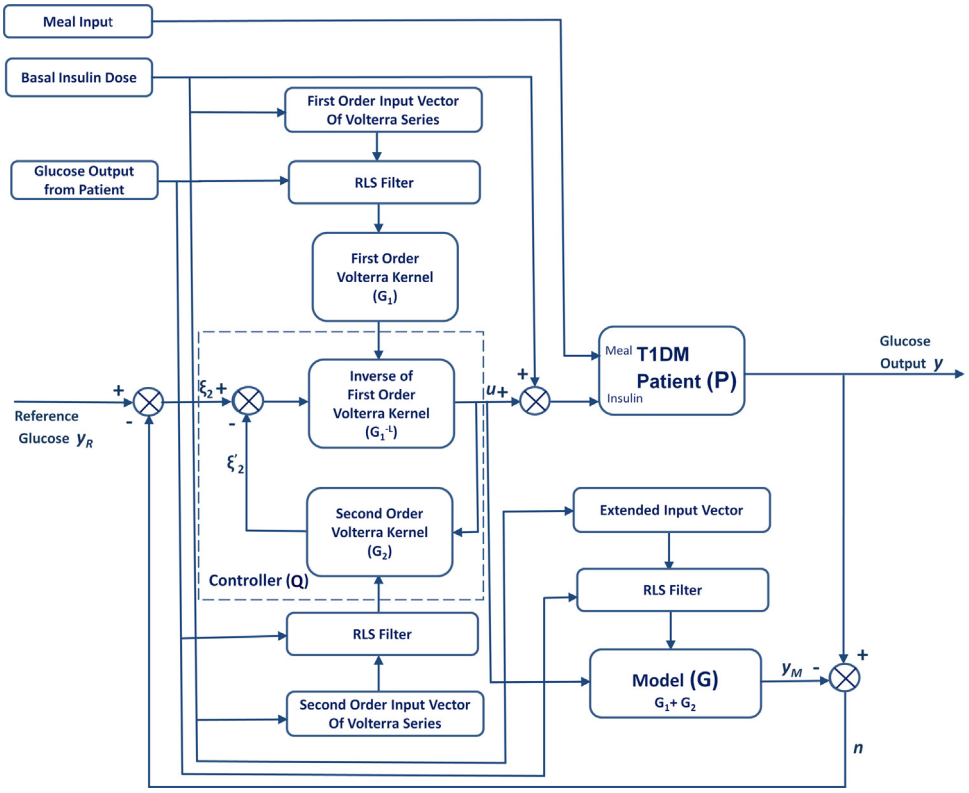

Fig. 2. Block diagram of online-tuned internal model control scheme.

a semi-automated control algorithm by introducing a feedforward loop in the online-tuned IMC control algorithm. Feedforward path is basically an optimal bolus treatment that assumes the information of meal intake i.e., the exact size and time of meal. But it is difficult to determine the exact size of meal. This may create the risk of occurrence of hypoglycemic event.

4. Simulation study

Assurance of satisfactory performance of control algorithm in large population of patients is a major challenge of the AP, due to intra- and inter-patient variability. The performance of the proposed offline- and online-tuned fully-automated IMC and online-tuned semi-automated IMC algorithms is evaluated in this section for 10 *in silico* adult patients with large inter-patient parameter variabilities [18].

As type 1 diabetic patient is absolutely deficient in endogenous insulin secretion, the insulin secretion module is substituted by a continuous subcutaneous insulin infusion module. Patients need both basal and bolus insulin regimen. Basal insulin helps to keep BG levels at a consistent value during periods of fasting and between meals, whereas bolus insulin is administered at meal times to keep BG levels under control after a meal. CGM output is used as the feedback signal to adjust the online-tuned controller and estimate the desired bolus delivery rate. *Basal insulin delivery rate from the UVA/Padova metabolic simulator and unannounced meal is considered to evaluate fully-automated offline- and online-tuned IMC algorithm. Optimal bolus insulin delivery rate for the feedforward path from the UVA/Padova metabolic simulator is considered in the semi-automated online-tuned IMC algorithm. A reference glucose level* (y_R) *of 110 mg/dl is used.*

The controller performance is evaluated using four scenarios. The first scenario is used for validation and comparison with zone-MPC [17], scenarios 2 is used for robustness analysis by subjecting patients to irregular meal amount i.e., very high and low amount of meal in the presence of both actuator and sensor noise, scenario 3 is used for robustness analysis by subjecting patients to irregular meal amount at random times and scenario 4 is also used for robustness analysis by variation of insulin sensitivity in scenario 2 without actuator noise. Actual measurement noise from the CGM sensor of the UVA/Padova metabolic simulator is used in all the scenarios and actuator noise is used only in scenario 2.

The control algorithm is also evaluated using the following performance metrics:

1. Mean blood glucose concentration.
2. Percentage of total time when the patient BG concentration remains within the clinically safe target zone (i.e. 70–180 mg/dl).
3. Percentage of total time when the patient BG concentration remains within the tight target zone (i.e. 80–140 mg/dl).
4. Percentage of total time when the patient BG concentration remains below 70 mg/dl.
5. Percentage of total time when the patient BG concentration remains below 70 mg/dl during overnight.
6. Percentage of total time when the patient BG concentration remains above 180 mg/dl.
7. Low BG index (LBGI) i.e., probability of patients' risk for hypoglycaemia and High BG index (HBGI) i.e., probability of patients' risk for hyperglycaemia [37].

Additionally, we plot the mean glucose output with standard deviation and the corresponding mean basal-bolus insulin infusion rate with standard deviation to evaluate the controller performance. Control-variability grid analysis (CVGA) is also done for illustrating the quality of glycemic control. In CVGA, each data point is a representation of the extreme glucose excursion for each patient. The boundaries of the zones are: 70–180 mg/dl is accepted range; lower value of 90 mg/dl for zone A is minimal safe zone;

Table 3
Scenarios for the evaluation of IMC algorithms.

Scenarios	Simulation time (hours)	Start time of simulation	Number of meal disturbances	Administration of meal time and size
Scenario 1 [17]	24	3:00 a.m.	3	Two 75 g at 7:00 a.m. and 1:00 p.m. One 50 g at 8:00 p.m.
Scenario 2	48	3:00 a.m.	6	Two 75 g at 7:00 a.m. and 1:00 p.m. One 50 g at 8:00 p.m. (day 1) One 75 g at 7:00 a.m. and one 90 g at 1:00 p.m. One 25 g at 8:00 p.m. (day 2)
Scenario 3	48	5:00 a.m.	6	Two 75 g at 7:00 a.m. and 3:00 p.m. One 50 g at 8:00 p.m. (day 1) One 75 g at 7:00 a.m. and lunch skipped One 25 g at 8:00 p.m. (day 2)
Scenario 4	48	3:00 a.m.	6	Two 75 g at 7:00 a.m. and 1:00 p.m. One 50 g at 8:00 p.m. (day 1) One 75 g at 7:00 a.m. and one 90 g at 1:00 p.m. One 25 g at 8:00 p.m. (day 2)

Table 4
Results for validation experiment (scenario 1).

Performance metrics	Offline-tuned IMC	Online-tuned IMC	Semi-automated online-tuned IMC
Mean	177.41	172.47	115.12
% time in normoglycemia (70–180 mg/dl)	56.83	59.35	94.1
% time in tight target (80–140 mg/dl)	37.17	38.51	72.39
% of time below 70 mg/dl	0	0	3.54
% of time above 180 mg/dl	43.16	40.64	2.34
LBGI	0.025	0.026	1.15
HBGI	9.31	8.75	0.83

300 mg/dl is the upper value of permissible hyperglycemic excursions. CVGA provides a visual estimation of the effectiveness of a control strategy [38].

4.1. List of scenarios

The list of scenarios is given in Table 3. Scenario 1 represents a typical day with three meal disturbances. It is used to evaluate the controller response and compare with zone-MPC of glycemic bounds 80–140 mg/dl and 100–120 mg/dl mg/dl in [17]. Scenario 2 is used to analyze the robustness of the controller performance in 48 h protocol with irregular meal amount in day 2. In this scenario, patients are subjected to very high and low amount of meal in day 2 in the presence of high actuator noise which is a random variable of variance 5.[3] Scenario 3 illustrates the robustness of the controller performance if a patient has irregular eating habits. In this scenario, the experiment is done with the same meal sizes as in scenario 2, but at random times e.g., lunch is delayed by 2 h in day 1 and in day 2, lunch is skipped. the start time of simulation is also delayed by 2 h. Robustness of the controller performance is again evaluated using scenario 4 with ±20% variation in insulin sensitivity [8]. The experiment is done with the same meal time and size as in scenario 2, but without actuator noise.

4.2. Validation using scenario 1

The average performance metrics for scenario 1 using fully-automated offline- and online-tuned IMC and semi-automated online-tuned IMC are given in Table 4. The model of the offline-tuned IMC are developed using the input–output data collected in open loop condition from patients subjected to the same meal disturbances as in scenario 1. Thus, the offline-tuned IMC gives satisfactory performance in terms of avoiding both hyper- and hypoglycemic events. As shown in Table 4, among both the fully-automated IMC, the average percentage of time when the BG concentration remains within the target and tight target zones are slightly better in online-tuned IMC. The required infusion of insulin that maintains the BG level in the target zone in online-tuned IMC is only 1.82 U/h. Although semi-automated online-tuned IMC has reduced hyperglycemic events, the average of 3.54% of time BG level is in the hypoglycemic zone in semi-automated controller whereas there is no hypoglycemia in both the fully-automated IMC.

The results signify that fully-automated online-tuned IMC maintain BG level in the normoglycemic zone without the need for retuning of the controller for each patient and every patient condition. The low infusion of insulin reduces the risk of hypoglycemia at the expense of higher BG level on average than semi-automated online-tuned IMC. Unlike fully-automated online-tuned IMC, the semi-automated online-tuned IMC uses high insulin doses to reduce hyperglycemic events that increases the risk of hypoglycemia and other long term complications such as cardiovascular diseases, atherosclerosis, weight gain and even higher cancer risk that are caused due to overdelivery of insulin [28,29]. Fig. 3 shows the performance of the online-tuned IMC for scenario 1 in terms of controlled mean and standard deviation of the BG concentration and the corresponding mean and standard deviation of secreted insulin.

The control-variability grid analysis (CVGA) representation of fully-automated online-tuned IMC for scenario 1 is shown in Fig. 4. CVGA representation shows that 7 patients are in the upper B-zone, 1 patient is in the upper C-zone and 1 patient is in the upper D-zone. This indicates that online-tuned IMC algorithm avoids hypoglycemia in patients with a slight increase in BG level on average. Thus, the present fully-automated online-tuned IMC control algorithm prevents dangerous hypoglycemic events more effectively with low insulin excursion.

[3] Random variable noise of variance 5 is a very high noise level as compared to [13].

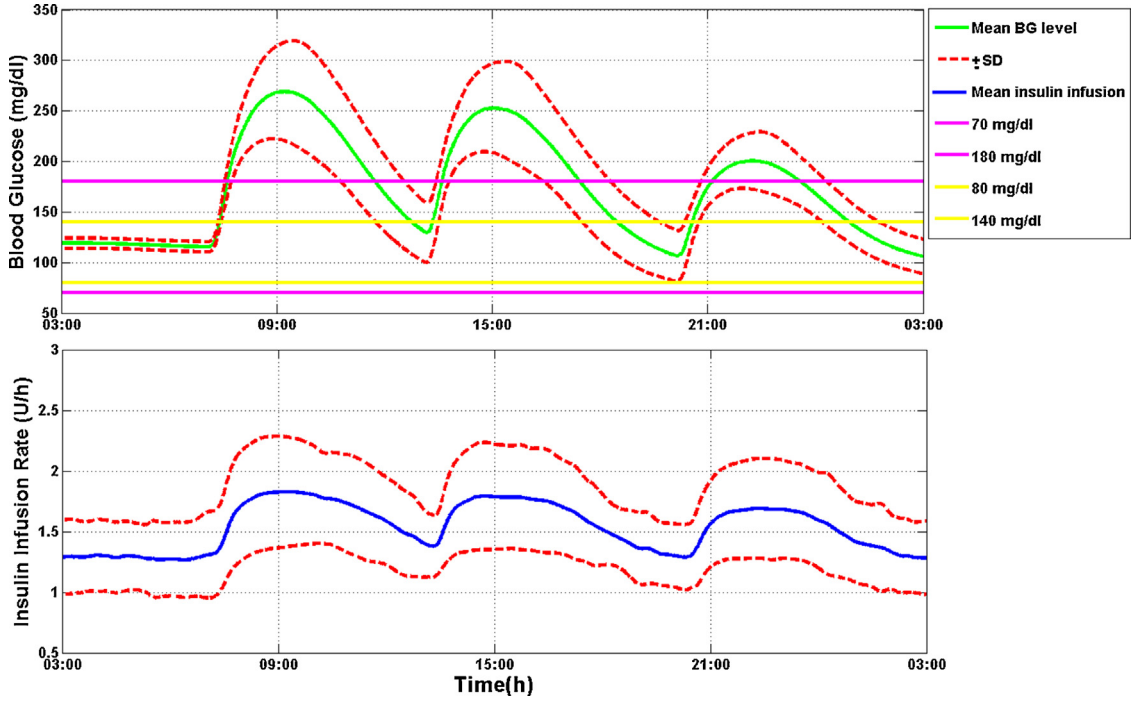

Fig. 3. Response of the mean blood glucose regulation (green solid line) and standard deviation (red dotted line) with the corresponding mean insulin infusion rate (blue solid line) and standard deviation (red dotted line) for scenario 1. Yellow solid line represents 80 mg/dl and 140 mg/dl. Magenta solid line represents 70 mg/dl and 180 mg/dl. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

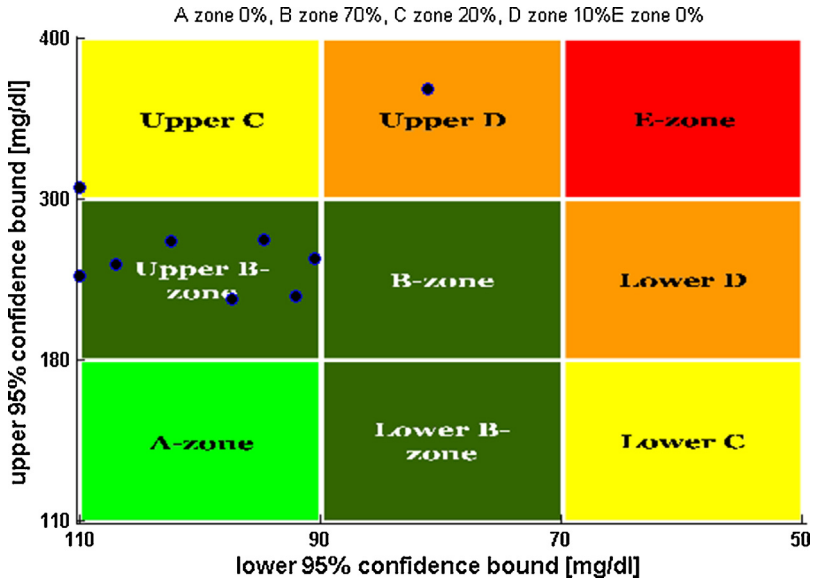

Fig. 4. CVGA for two 75 g of meal disturbances and one 50 g of meal disturbance (scenario 1).

Table 5
Comparison of the fully-automated IMC algorithm with zone MPC with respect to [TO_{180}(min)] and [$Hypo_{\#}$] (scenario 1).

Patient #	Offline-tuned IMC with set point 110 mg/dl		Online-tuned IMC with set point 110 mg/dl		Zone-MPC set between 80 and 140 mg/dl		Zone-MPC set between 100 and 120 mg/dl	
	TO_{180}	$Hypo_{\#}$	TO_{180}	$Hypo_{\#}$	TO_{180}	$Hypo_{\#}$	TO_{180}	$Hypo_{\#}$
1	512.64	0	473.61	0	1074	0	970	0
2	294.79	0	359.71	0	587	0	412	0
3	625.53	0	489.6	0	486	0	471	0
4	581.81	0	474.62	0	587	0	480	0
5	963.31	0	936.28	0	635	0	538	0
6	530.62	0	550.65	0	766	0	596	0
7	860.35	0	728.49	0	428	0	309	0
8	910.39	0	890.35	0	855	0	585	0
9	565.56	0	559.58	0	385	0	319	0
10	361.8	0	389.66	0	596	0	444	0

Table 6
Results for robustness analysis using irregular meal amount and high noise (scenario 2).

Performance metrics	Offline-tuned IMC	Online-tuned IMC	Semi-automated online-tuned IMC
Mean	170.88	153.24	113.59
% time in normoglycemia (70–180 mg/dl)	59.8	61.51	92.85
% time in tight target (80–140 mg/dl mg/dl)	40.37	42.14	72.91
% of time below 70 mg/dl	0.25	0	4.26
% of time below 70 mg/dl during overnight period	0.17	0	0
% of time above 180 mg/dl	39.93	38.48	2.88
LBGI	0.09	0.08	1.35
HBGI	8.74	8.45	0.85

Table 7
Results for robustness analysis using irregular meal amount at irregular time (scenario 3).

Performance metrics	Offline-tuned IMC	Online-tuned IMC	Semi-automated online-tuned IMC
Mean	146.7	155.6	113.09
% time in normoglycemia (70–180 mg/dl)	70.34	68.48	94.64
% time in tight target (80–140 mg/dl)	51.27	50.06	77.94
% of time below 70 mg/dl	3.02	0.88	2.43
% of time below 70 mg/dl during overnight period	0	0	0
% of time above 180 mg/dl	26.62	30.39	2.92
LBGI	2.02	0.37	1.11
HBGI	5.67	6.6	7.66

Table 8
Results for robustness analysis using ±20% variation in insulin sensitivity (scenario 4).

Performance metrics	+20% variation in insulin sensitivity			−20% variation in insulin sensitivity		
	Offline-tuned IMC	Online-tuned IMC	Semi-automated online-tuned IMC	Offline-tuned IMC	Online-tuned IMC	Semi-automated online-tuned IMC
Mean	158.24	159.47	97.61	182.84	182.38	130.11
% time in normoglycemia (70–180 mg/dl)	67.08	66.19	79.23	53.97	55.04	90.47
% time in tight target (80–140 mg/dl)	45.01	47.58	60.47	34.34	35.82	68.97
% of time below 70 mg/dl	1.01	0.46	20	0	0	0
% of time below 70 mg/dl during overnight period	0.56	0	1.18	0	0	0
% of time above 180 mg/dl	31.9	33.33	0.76	46.02	44.95	9.52
LBGI	4.08	0.28	4.66	0.01	0.01	0.19
HBGI	7.03	7.12	0.39	10.6	10.42	1.85

4.3. Comparison with fully-automated model based controllers using scenario 1.

The fully-automated IMC algorithms can be compared with fully-automated personalized zone-MPC of glycemic bounds 80–140 mg/dl and 100–120 mg/dl using scenario 1 [17]. We have compared the IMC algorithm only with zone-MPC because zone-MPC showed significant advantages over both open-loop treatment and MPC algorithm in [17]. Table 5 shows the comparison with respect to time over 180 mg/dl (TO_{180}) and occurrence of hypoglycemic events (<60 mg/dl) for all patients. The average of time over 180 mg/dl obtained using the offline- and online-tuned IMC algorithm is 620.68 min and 585.25 min, and the same for zone-MPC (bound 80–140 mg/dl) and zone-MPC (bound 100–120 mg/dl) are 639.9 min and 512.4 min respectively. It is evident from the paper [17] that zone-MPC (bound 80–140 mg/dl) is more reliable controller compared to zone-MPC (bound 100–120 mg/dl) as it reduces control move variability with minimum loss of performance. In the present paper, results show that the performance of the online-tuned IMC is better than both offline-tuned IMC and zone-MPC (bound 80–140 mg/dl) in avoiding hyperglycemic events. It reveals that online-tuned IMC algorithm handles unannounced meal disturbances well with no hypoglycemic event. But unlike zone-MPC and offline-tuned IMC, online-tuned IMC has achieved these outcomes without using prior clinical observation or data and retuning of the controller for every patient.

4.4. Robustness analysis using scenario 2, scenario 3 and scenario 4

The average performance metrics for robustness analysis by subjecting irregular meal amount to patients (scenario 2) and also by subjecting irregular meal amount to patients at random times (scenario 3) are given in Tables 6 and 7 respectively. The model of the offline-tuned IMC are developed using the input–output data of scenario 1. The patient conditions in scenario 2 and scenario 3, used for robustness analysis, are different from scenario 1. Thus, among both the fully-automated control algorithms, offline-tuned IMC gives worse performance in avoiding hypoglycemia. The results show that the online-tuned controller gives better performance than offline-tuned controller at every patient condition. A major concern for people with type 1 diabetes is overnight hypoglycemia. The BG level is maintained using online-tuned IMC without the occurrence of overnight hypoglycemia in both scenario 2 and scenario 3 with an average maximum insulin infusion of 1.88 U/h and 1.83 U/h respectively. The low insulin infusion in online-tuned IMC, sufficient to maintain BG level in the euglycemic range, also reduces the risk of hypoglycemia during overnight period. The infusion of high amount of insulin that is used to minimize the hyperglycemic events in semi-automated online-tuned IMC increases the risk of hypoglycemia both in 48 h window and during overnight. Figs. 5 and 6 show the performance of the online-tuned IMC for scenario 2 and scenario 3 in terms of controlled mean and standard deviation of the BG concentration and the corresponding mean and standard deviation of secreted insulin.

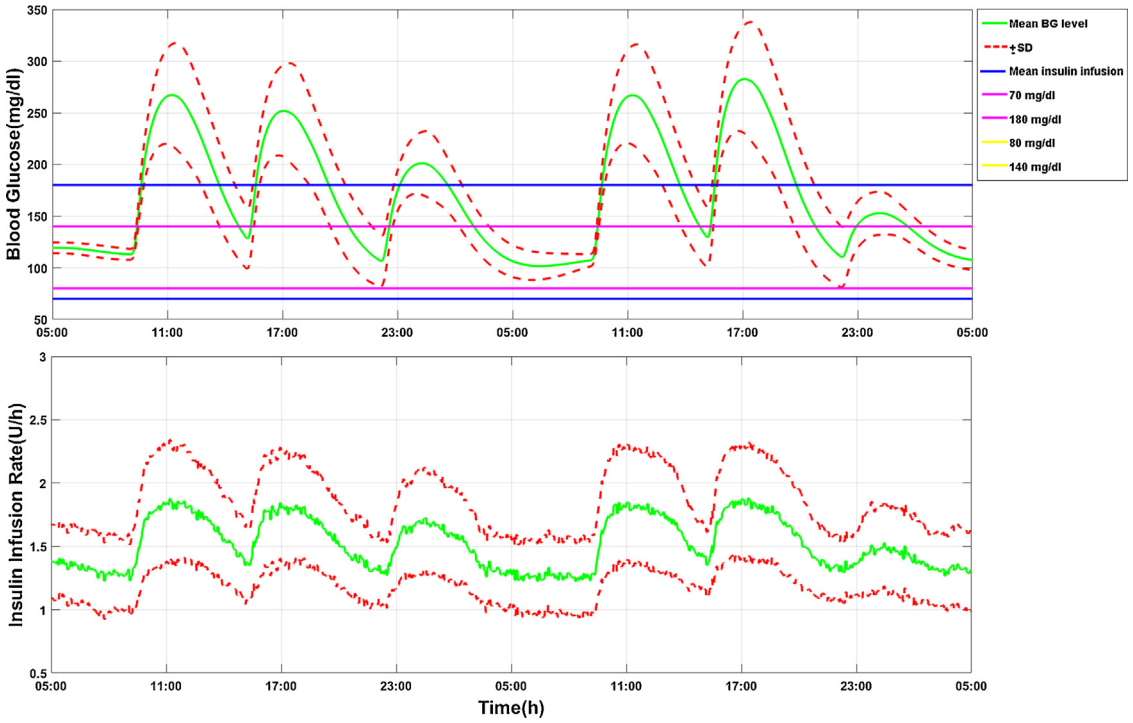

Fig. 5. Response of the mean blood glucose regulation (green solid line) and standard deviation (red dotted line) with the corresponding mean insulin infusion rate (blue solid line) and standard deviation (red dotted line) for scenario 2. Yellow solid line represents 80 mg/dl and 140 mg/dl. Magenta solid line represents 70 mg/dl and 180 mg/dl. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

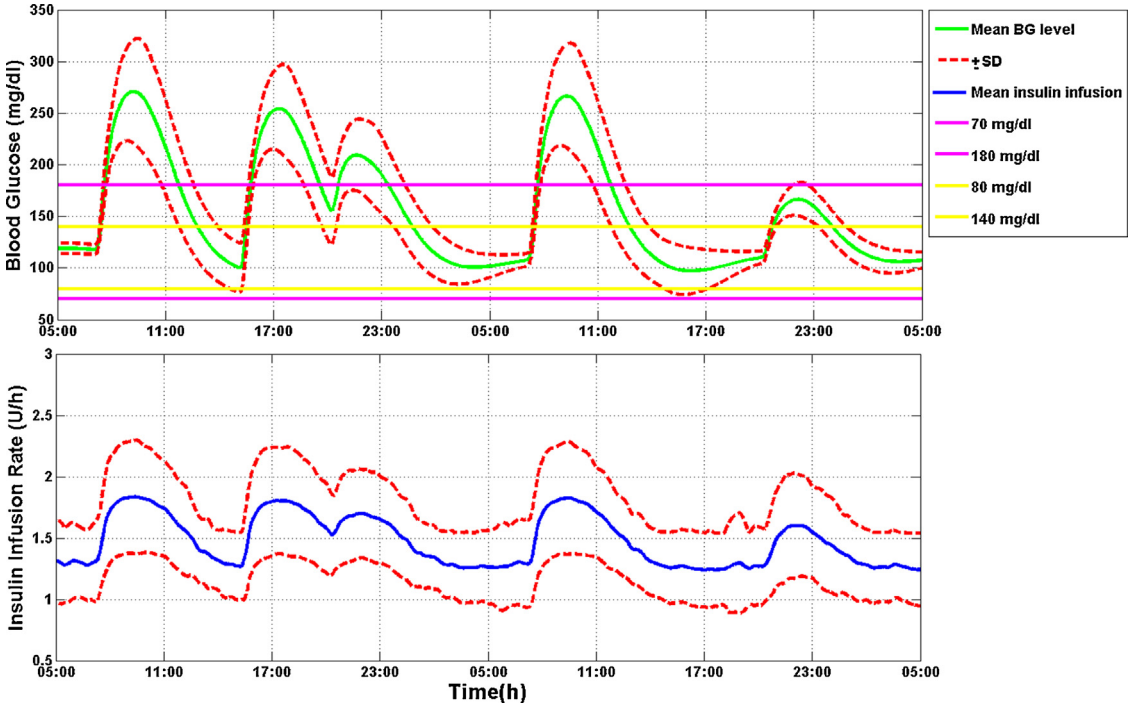

Fig. 6. Response of the mean blood glucose regulation (green solid line) and standard deviation (red dotted line) with the corresponding mean insulin infusion rate (blue solid line) and standard deviation (red dotted line) for scenario 3. Yellow solid line represents 80 mg/dl and 140 mg/dl. Magenta solid line represents 70 mg/dl and 180 mg/dl. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

The performance metrics for scenario 4 when the insulin sensitivity is varied by ±20% are given in Table 8. When the insulin sensitivity is increased by +20%, the percentage of time when patients are in the hypoglycemic zone under the online-tuned IMC is only 0.46%. This percentage for offline-tuned IMC is 1.01% and 20% for semi-automated online-tuned IMC. In this scenario, patient condition as well as patient parameter i.e., insulin sensitivity, both are different from scenario 1 with which the model of offline-tuned IMC is developed. As the feedforward open loop bolus in semi-automated online-tuned IMC is calculated using patient parameter,

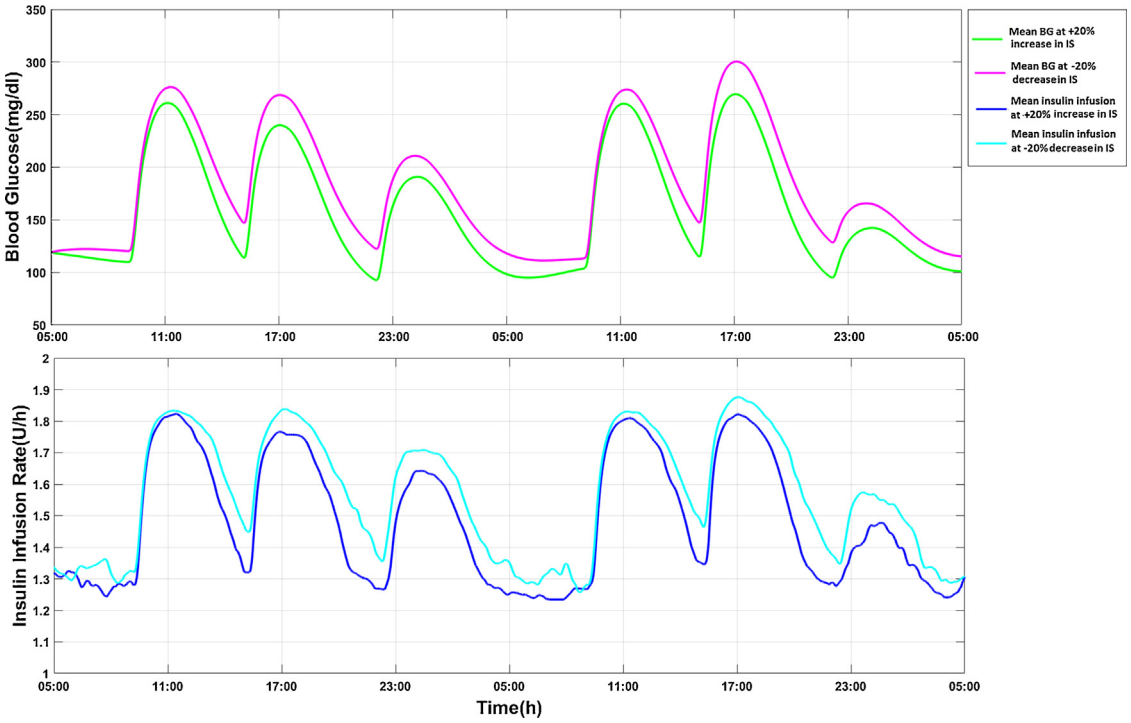

Fig. 7. Response of the mean blood glucose regulation (green solid line) at +20% variation of insulin sensitivity and mean blood glucose regulation (magenta solid line) at −20% variation of insulin sensitivity with the corresponding mean insulin infusion rate (blue solid line) at +20% variation of insulin sensitivity and mean insulin infusion rate (cyan solid line) at −20% variation of insulin sensitivity for scenario 4. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article).

the change in insulin sensitivity causes erroneous feedforward bolus dose. Thus, the performance of these two control algorithms are inferior than online-tuned IMC in avoiding hypoglycemia when the insulin sensitivity is varied by +20%. When it is decreased by −20%, the percentage of time when patients are in the hyperglycemic zone is 44.95% under the online-tuned IMC algorithm, 46.02% under offline-tuned IMC and 9.52% under semi-automated offline-tuned IMC. Due to high insulin infusion in semi-automated offline-tuned IMC, percentage of time when patients are in the hypoglycemic zone is large and percentage of time when patients are in the hyperglycemic zone is small. Fig. 7 shows the performance of the online-tuned IMC for scenario 4 in terms of controlled mean of the BG concentration when the insulin sensitivity is varied by ±20% and the corresponding mean of secreted insulin. Thus, the proposed online-tuned IMC controller shows robust performances for variations in insulin sensitivity without meal announcements and prior information of insulin to carbohydrate ratio and correction factor.

5. Conclusion

The benefit of online-tuned internal model control (IMC) algorithm based on online predicted Volterra model for an AP system is evaluated in 10 *in silico* adult patients. A data driven Volterra model is developed to obtain patient dynamics. The set of kernels obtained from the Volterra model is converted to frequency domain kernels to obtain the nonlinear transfer function or Volterra transfer function (VTF). VTFs of the *in silico* adult patients are then used to develop both online- and offline-tuned IMC algorithms. Online selection of insulin dose was done using the recursive least squares (RLS) algorithm. A semi-automated IMC is also designed by incorporating a feedforward control path to the online-tuned IMC.

The proposed online-tuned IMC algorithm is able to compensate unannounced meal disturbances with low infusion of insulin doses and reduces the risk of hypoglycemic events for different patient conditions unlike offline-tuned and semi-automated IMC. It gives robust performances with the variation in insulin sensitivity, in the presence of higher and irregular amounts of meal disturbances at random times and in the presence of very high actuator and sensor noise. Unlike zone-MPC, the online-tuned IMC algorithm shows improved performance in avoiding both hypo- and hyperglycemia without using prior clinical observation and pharmacokinetic/pharmacodynamic data.

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