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ORIGINAL ARTICLE

Design of an online-tuned model based compound controller for a fully automated artificial pancreas

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Abstract
This paper deals with the development of a control algorithm that can predict optimal insulin doses without patients' intervention in fully automated artificial pancreas system. An online-tuned model based compound controller comprising an online-tuned internal model control (IMC) algorithm and an enhanced IMC (eIMC) algorithm along with a meal detection module is proposed. Volterra models, used to develop IMC and eIMC algorithms, are developed online using recursive least squares (RLS) filter. The time domain kernels, computed online using RLS filter, are converted into frequency domain to obtain Volterra transfer function (VTF). VTFs are used to develop both IMC and eIMC algorithms. The compound controller is designed in such a way that eIMC predicts insulin doses when the glucose rate increase detector of meal detection module is positive, otherwise conventional IMC takes the control action. Experimental results show that the compound controller performs robustly in the presence of higher and irregular amounts of meal disturbances at random times, very high actuator and sensor noises and also with the variation in insulin sensitivity. The combination of compound control strategy and meal detection module compensates the shortcomings of both slow subcutaneous insulin action that causes postprandial hyperglycemia, and delayed peak of action that causes hypoglycaemia.

Keywords Type 1 diabetes mellitus · Artificial pancreas · Internal model control · Enhanced internal model control · Volterra model

1 Introduction

Type 1 diabetes mellitus is one of the most serious medical conditions with complete destruction of pancreatic β cells that causes wide and unstable fluctuations of blood glucose (BG) concentrations. Blood glucose level above 180 mg/dl, i.e., hyperglycemia, damages small blood vessels in the kidneys, heart, eyes, and nervous system. Blood glucose level below 70 mg/dl, i.e., hypoglycemia, impairs brain functions and leads to diabetic coma or death. Thus, the objective of diabetes management is to keep the blood glucose level as close as possible to the normal range of 70–140 mg/dl, i.e., *normoglycemia* or *euglycemia*, by continuous and controlled release of insulin in the presence of normal meal and activity conditions of patients [1].

Researchers have shown great interest in subcutaneous continuous glucose monitoring and subcutaneous insulin delivery (SC-SC route) systems [2–7] because unlike intravenous glucose monitoring and intravenous insulin delivery (IV–IV route) systems, SC-SC route–based systems are less invasive and do not need clinical supervision. Hence, they can give better lifestyle to a patient with type 1 diabetes. But the challenges of closed-loop control in subcutaneous insulin delivery and glucose monitoring are intra- and inter-patient parameter variability at different patient conditions, presence of significant disturbances, e.g., meals and physical activities, slow subcutaneous insulin action that causes hyperglycemia, and delayed peak of insulin that causes hypoglycemia [5, 7].

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Among both the fully automated and semi-automated algorithms developed so far for the artificial pancreas (AP) system, researchers have mainly focused on developing semi-automated algorithms due to their superior performance. But semi-automated control algorithms require patients' intervention for providing the exact time and size of the meal, and further inaccurate meal size and intra-patient parameter variations can result in an erroneous bolus dose. Though the design of fully automated control algorithms for the AP system is a major challenge, the ultimate goal of decreasing the burden of diabetes management can be achieved only by developing such a fully automated controller for the AP system.

Various linear and nonlinear control algorithms, e.g., PID [8], fuzzy logic control [9, 10], and adaptive controllers, e.g., linear quadratic Gaussian (LQG) [11] and $H\infty$ controller [12], have been developed so far for blood glucose regulation in the SC-SC route–based AP system. But most of these controllers have used feedback control based on a fixed patient model. MD-logic artificial pancreas (MDLAP) system of [9] needs patient-specific characteristics for tuning of control to target module (CTM) to overcome intra- and inter-patient parameter variability. However, in the recent past, model based controllers [13–26] are recognized as the most suitable controllers for the AP system. The dynamic model used in such controllers can capture patient dynamics in the presence of uncertainties and disturbances. There are two main types of data driven models used in model based control algorithms: parametric model and nonparametric model. Control algorithms based on nonparametric models are more suitable for the SC-SC route–based AP system because these models are mostly used for nonlinear processes [19, 27, 28]. Nonparametric models can identify nonlinear processes in off-equilibrium region where the data available is much less, whereas parametric models fail to capture all the information about the data of nonlinear processes within their parameters.

Based on the mode of tuning of model parameters, model based controllers are further classified into offline-tuned and online-tuned controllers. In offline-tuned controllers, models are identified from recorded input-output data of patients, whereas in online-tuned controllers, models are adapted online in real-time depending on the measured input-output data of patients. Consequently, online-tuned controllers can capture patient dynamics at every patient condition and hence give better performance when compared to offline-tuned controllers.

The motivation behind the current work[1] is to minimize postprandial hyperglycemia and hypoglycemia that occurs due to the slow subcutaneous insulin action and delayed peak of insulin action. Weinzimer et al. and Steil et al. studied the feasibility of minimizing postprandial hyperglycemia using full closed-loop (FCL) system [30, 31]. Both the systems were unable to achieve the improved performance of postprandial glucose excursion due to slow subcutaneous insulin action. In the recent past, an online-tuned model based control algorithm was developed using nonparametric Volterra model of patients [32, 33]. The selection of Volterra kernels are done online using recursive least squares (RLS) algorithm. The frequency domain kernels of the Volterra model are computed to obtain nonlinear transfer function of patients. The nonlinear transfer function called the Volterra transfer functions (VTFs) are then used to develop the internal model control (IMC) algorithm. The online-tuned IMC reduced the risk of hypoglycemic events for different patient conditions without using prior clinical observation and pharmacokinetic/pharmacodynamic data. But the online-tuned IMC was unable to reduce postprandial hyperglycemia without the risk of hypoglycemia. To address this critical issue, in the present work, we develop an AP system using fully automated online-tuned compound model based control algorithm with automatic meal detection module. The compound controller is based on IMC, and uses an additional controller gain to increase insulin infusion only when the detection module detects a meal. Our experiments show that this compound controller is able to effectively reduce postprandial hyperglycemia without increasing hypoglycemic events.

1.1 Contributions

A compound model based controller is designed using conventional online-tuned IMC (cIMC) [32, 33] and enhanced IMC (eIMC). The cIMC and eIMC are developed using nonlinear transfer functions, i.e., VTFs of patients. An automatic meal detection module is integrated with the compound IMC algorithm. Glucose Rate Increase Detector (GRID) of the meal detection module is used to detect meal disturbances by estimating the Rate of Change of glucose (RCG) level. The compound IMC is designed in such a way that eIMC will operate only when the GRID is positive. Otherwise, the cIMC controller will operate. Postprandial hyperglycemia and hypoglycemia can be reduced using the present control strategy with larger insulin infusion from eIMC during the initial period of meal consumption and lower insulin infusion from cIMC afterwards. We evaluate the compound IMC algorithm on 10 *in silico* adult patients from the US Food and Drug Administration (FDA)-accepted University of Virginia/Padova metabolic simulator [34] using different scenarios, particularly for validation, robustness analysis to intra- and inter-patient variabilities and comparison with

[1] This paper is a full version of the abstract that appeared in ATTD 2017 [29].

other model based controllers. The online-tuned compound IMC has yielded good compensation of unannounced meal disturbances with reduced hyperglycemia than cIMC [33] and zone-MPC [25] without any prior knowledge of patient parameters. The proposed compound IMC gives robust performance in reducing postprandial hyperglycemia without any considerable increase in hypoglycemic events with the variation in insulin sensitivity, irregular eating habits of patients, and in the presence of high sensor and actuator noises. The risk of overnight hypoglycemia is also eliminated using the compound IMC in these experiments.

2 Development of online-tuned compound IMC controller

In order to overcome the shortcomings of slow subcutaneous insulin action and delayed peak of action that causes both hyper- and hypoglycemia, online-tuned conventional IMC (cIMC) [32, 33] and enhanced IMC (eIMC) are combined to form a compound IMC algorithm. We have integrated the compound IMC with an automatic meal detection module that can detect a meal within 2 h from the start of the meal [35]. The compound IMC is designed in such a way that eIMC regulates BG level of patients during initial period of the meal consumption, i.e., when the glucose rate increase detector (GRID) of the meal detection module is positive, otherwise the cIMC takes control of patients' BG level. Both cIMC and eIMC are developed using an online patient model estimator that estimates patient states from the insulin input and glucose output data of patients in the presence of disturbances and parameter variations.

The compound IMC structure developed for type 1 diabetic patients is shown in Fig. 1. The nonlinear type 1 diabetes mellitus (T1DM) patient P is modeled by Volterra model G. The Volterra kernels of the model G are identified online using the recursive least squares (RLS) algorithm. The compound controller is composed of eIMC and cIMC shown in Fig. 1. The eIMC controller consists of a feedforward controller C_1, feedback controller C_2, a gain K, and a feedback model G [36, 37]. The cIMC controller contains the feedforward controller C_1 and the feedback model G. Two equivalent controllers C_1 and C_2 are developed using nonlinear transfer functions of the Volterra model G. Nonlinear transfer functions of the Volterra model or Volterra transfer functions (VTFs) are obtained by converting the time domain Volterra kernels into frequency domain. The controller C_2 generates an optimal insulin dose u_2 through patients' glucose output y and glucose output y_M predicted by the model G. The optimal insulin dose u_2 is added to the output u_1 generated by the cIMC controller C_1. A glucose rate increase detector (GRID) algorithm, obtained from the meal detection module in [35], is designed that runs parallel to the controllers. GRID detects meal disturbance by estimating the rate of change of glucose (RCG) level. The meal is detected in the

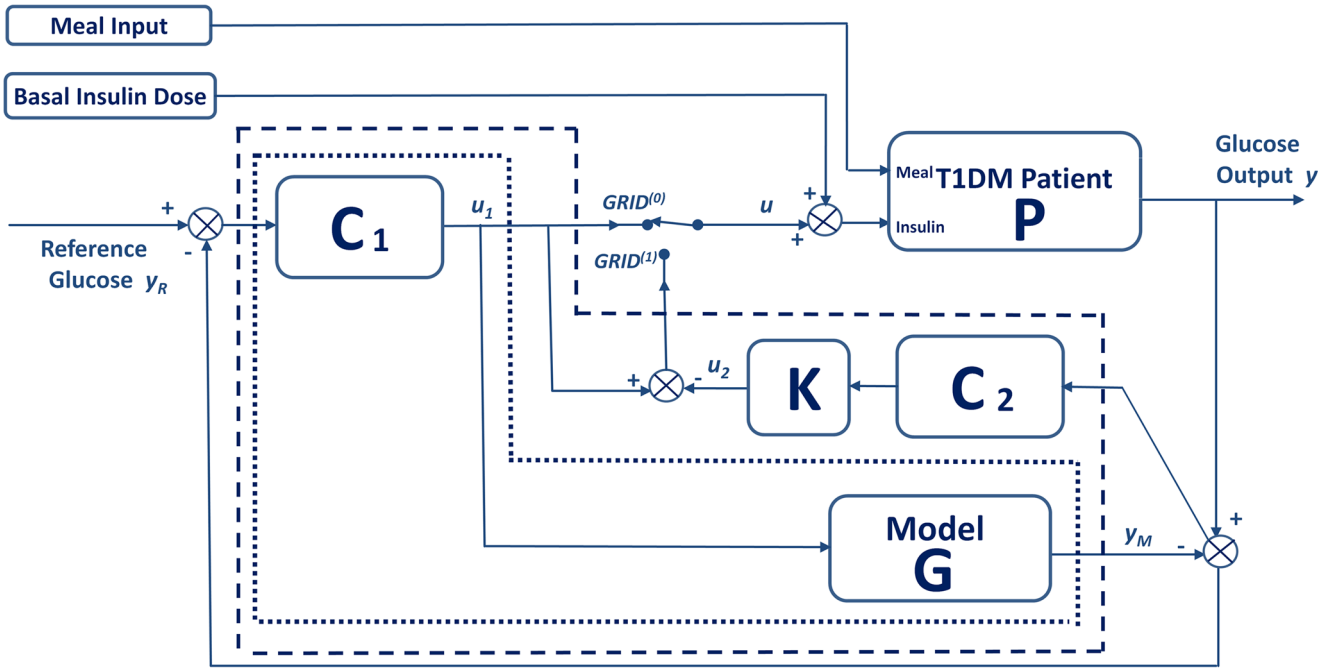

Fig. 1 Structure of a compound IMC comprising enhanced IMC (blue dashed region), conventional IMC (blue dotted region) and a meal detection module containing glucose rate increase detector (GRID). Controller structure of enhanced IMC and conventional IMC are formed when T1DM patient block is connected to $GRID^{(1)}$ and $GRID^{(0)}$ respectively

detection logic when GRID is equal to 1. $GRID^{(1)}$ of Fig. 1 is connected to T1DM patient P when the meal is detected and remains in that state until GRID value is changed to 0. In the compound IMC of Fig. 1, the structure of the eIMC controller is formed when T1DM patient P is connected to $GRID^{(1)}$ and the cIMC controller structure is formed when T1DM patient P is connected to $GRID^{(0)}$.

The closed-loop transfer function (TF_1) of cIMC is derived as:

$$TF_1 = \frac{PC_1}{1 + C_1(P - G)} = [I + ({C_1}^{-1} - G)P^{-1}]^{-1} \quad (1)$$

The closed-loop transfer function (TF_2) of eIMC is derived as:

$$TF_2 = [I + (C_1^{-1} - G)[P(I + C_2KP)^{-1}(C_2KG)]^{-1}]^{-1} \quad (2)$$

In the following sections, we provide a brief overview of the controllers C_1 and C_2 (obtained from [32]) and the meal detection module (obtained from [35]).

2.1 Conventional internal model controller synthesis

Conventional internal model controller C_1 and C_2 are built using a dynamic model of patients [32, 33]. This model can determine patient states from insulin input and glucose output data of patients in the presence of disturbances and parameter variations. The block diagram of the online-tuned cIMC algorithm, shown in Fig. 2, consists of the overall Volterra model G and the inverse of its first order linear model G_1 and second order nonlinear model G_2. The Volterra model is identified using basal insulin dose as input data and patients' blood glucose level as output

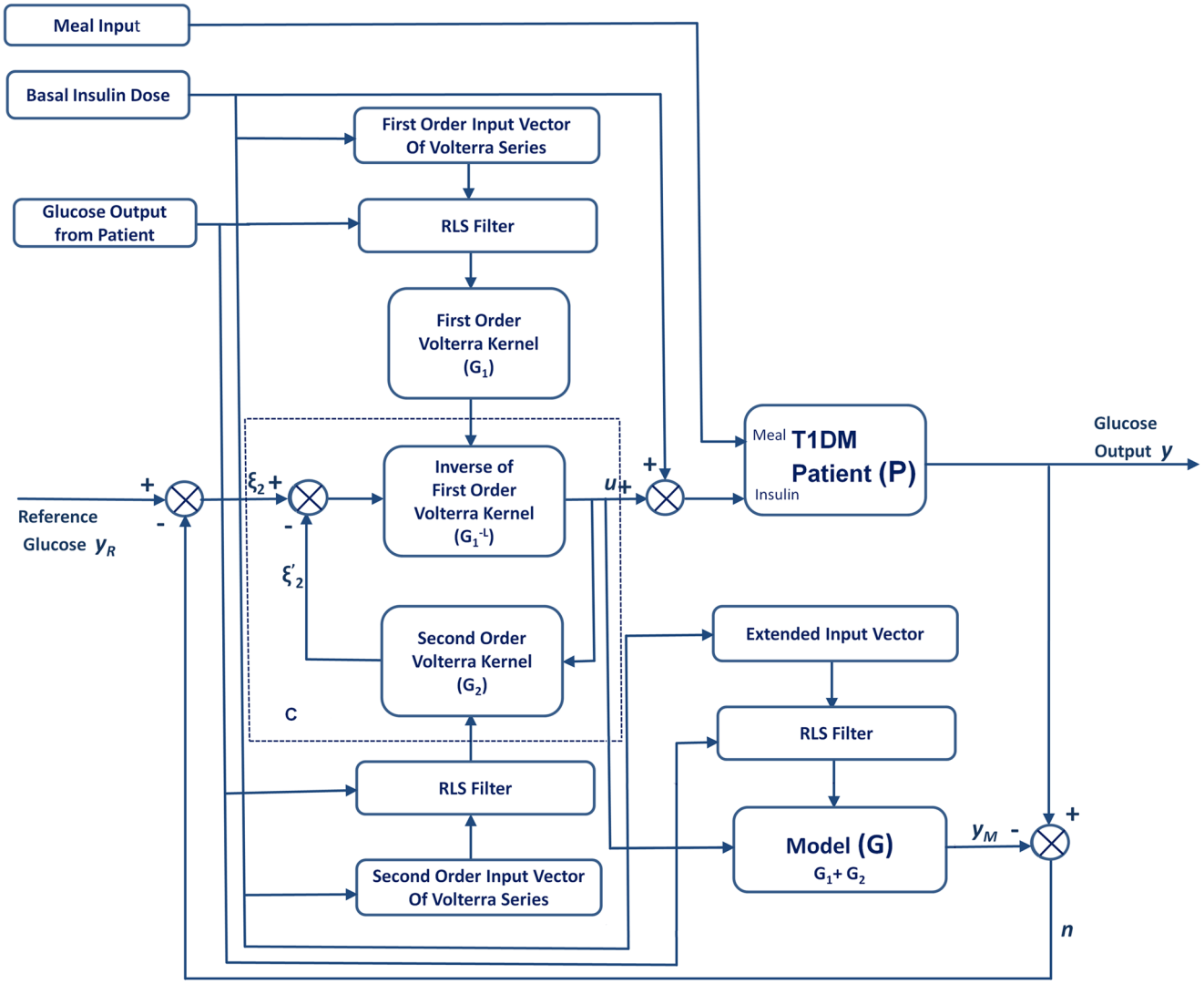

Fig. 2 Block diagram of conventional Internal Model Control scheme that comprises overall Volterra model G and a second order Volterra model G_2 in loop with the inverse of the first order Volterra model G_1 of patient identified online using RLS algorithm

data. The required Volterra kernels are computed online in an adaptive manner using the RLS algorithm [38, 39]. The nonlinear Volterra model must be represented in nonlinear transfer function form to develop the cIMC algorithm. Thus, the frequency domain kernels, called the Volterra transfer function, are computed by taking fast Fourier transforms (FFTs) on the respective time domain kernels [40]. The overall Volterra model G and its first order linear model G_1 and the second order nonlinear model G_2, shown in Fig. 2, are all frequency domain kernels.

The design objective, $J : \Re \rightarrow \Re^{+}$, is to find a C such that:

$$J = \min_{u} \|e\| \tag{3}$$

$$\text{where } u = C * \xi \tag{4}$$

$$e = y_R - y \tag{5}$$

where u is the controller output, i.e., the infused insulin dosage, y is the patients' glucose level, y_R is the target glucose level, and ξ is the input to the controller. The objective of Eq. 3 is strictly met if

$$G * C = I \; or, \; C = G^{-1} \tag{6}$$

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

Obtaining an exact inverse that satisfies (6) is not feasible in practice as such a realization can lead to steady-state offset if sensor noise or estimation error exists. Hence, it is impossible to obtain a strict zero J of the objective function (3). Thus, the frequency domain Volterra kernels of the model G are correspondingly decomposed into a linear first order and nonlinear second order Volterra kernels:

$$G = G_1 + G_2 \tag{7}$$

The controller is then synthesized by solving (6) 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 [32]. Thus, the optimization problem for first-order Volterra kernels have the solution:

$$u^{(1)} = G_1^{-L}[\xi] \tag{8}$$

Similarly, the second-order solutions are derived as

$$u^{(2)} = -G_1^{-L}[\xi^{(2)}], \tag{9}$$

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

The control signal is fed to the model G. The output of the model G, i.e., the estimated glucose output y_M, is then compared with the patients glucose output. The two outputs may differ due to the presence of both process and sensor noise. If those 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 patients glucose output.

Both the controllers C_1 and C_2 of Fig. 1 consists of the second order Volterra model G_2 of patients in loop with the inverse of the first order Volterra model G_1. C_1 and C_2 are equivalent to the controller C of Fig. 2. The operations of these controllers C_1 and C_2 are dependent on the GRID value of the meal detection module which is discussed in the following section.

2.2 Design of meal detection module

Meal detection module is used to detect meal occurrences so that the controller can deliver an optimal bolus dose of insulin as soon as the meal is detected. In the meal detection module, the rate of change of glucose (RCG) values is estimated from continuous glucose monitoring (CGM) data using GRID algorithm [35]. In the present work, we have used meal detection module not only to detect a meal, but also to use the eIMC controller for the period of time when the GRID algorithm confirms the presence of a meal. Since the eIMC controller delivers better disturbance rejection by increasing the delivery rate of bolus insulin, it improves blood glucose regulation at mealtime in the fully automated AP system. This design approach eliminates the shortcomings of slow subcutaneous insulin action and delayed peak of insulin action. Hence, the compound IMC controller with meal detection module can reduce the occurrence of postprandial hyperglycemia and hypoglycemic events.

In the meal detection module, CGM data is preprocessed to filter CGM noise using noise spike filter and to damp high frequency fluctuations using low pass filter. The rate of change of glucose (RCG) value is estimated from the filtered CGM data $y_F(k)$. The detection of meal disturbance is done using a detection logic that uses the estimated RCG values. The detection logic is as follows:

$$GRID = \begin{cases} 1 \text{ if } y_F(k) > y_{\min} \wedge \\ \quad (y'_F(k-2:k) > y'_{\min,3}) \vee (y'_F(k-1:k) > y'_{\min,2}) \\ 0 \text{ otherwise} \end{cases} \tag{10}$$

In the above detection logic, meal is detected ($GRID^{(1)}$) at the current point only if the filtered CGM data $y_F(k)$ is above a value $y_{\min}$ and either the last three RCG values are above $y'_{\min,3}$ or the last two RCG values are above $y'_{\min,2}$. The tuning parameters for the GRID algorithm are set as follows: maximum allowable RCG value in the noise spike filer Δy_a=2.7mg/dl, time constant of the low pass filter τ_F=6min, $y_{\min}$=130 mg/dl, $y'_{\min,3}$=1.2$mg/dl/$ min, $y'_{\min,2}$=1.3$mg/dl/$ min. τ_F is tuned to optimize the detection speed of the algorithm by smoothening the data. A large value of $y_{\min}$ is chosen to separate the postmeal

glucose values. $y\prime_{\min,3}$ and $y\prime_{\min,2}$ are tuned for faster meal detection with higher RCG values. We have chosen lesser values of the parameters Δy_a, $y\prime_{\min,3}$ and $y\prime_{\min,2}$ to detect the meal earlier than the parameter settings as in [35].

In this design approach, eIMC controller delivers higher insulin rate when meal is detected ($GRID^{(1)}$) to eliminate the shortcomings of slow subcutaneous insulin action at meal-time. cIMC controller delivers lesser amount of insulin when $GRID$ is zero ($GRID^{(0)}$) to eliminate the shortcomings of delayed peak of action. Hence, the compound IMC controller with meal detection module can reduce the occurrence of postprandial hyperglycemia and hypoglycemic events.

3 Simulation study

A control algorithm that regulates glucose level in the AP system is expected to operate in a large population of patients in the presence of inter- and intra-patient parameter variations. The proposed online-tuned compound IMC is evaluated in this section for 10 *in silico* adult patients with large inter-patient parameter variabilities using the FDA accepted UVA/Padova metabolic simulator for type 1 diabetic patients [34].

As type 1 diabetic patients are absolutely lacking in endogenous insulin production, patients need both basal and bolus insulin dose. Basal insulin that helps to keep blood glucose levels at a consistent value during periods of fasting and between meals is used from the simulator. Bolus insulin, delivered at the time of meal consumption to keep blood glucose levels under control after a meal, is controlled by the compound IMC. Unannounced meal disturbances are considered in the experiments. A glucose value of 110 mg/dl is used as a reference glucose level.

The performance of the compound IMC controller is evaluated for robustness to variations in insulin sensitivity, high sensor and actuator noises, as well as variations in meal disturbances. Further, the controller's performance is also compared with two existing fully automated controllers; an online-tuned conventional IMC (cIMC) controller [33], and a zone-MPC model predictive controller [25]. Both these controllers do not use any meal detection module. We have compared the online-tuned compound IMC algorithm with zone-MPC due to the following two reasons: (1) zone-MPC showed significant advantages over both open-loop

Table 1 Scenarios for the evaluation of compound IMC controller

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

treatment and MPC algorithm in [25] and (2) the published results of [25] are based on the same 10 adult patients. The evaluation is performed based on the following metrics:

1. Mean BG concentration.
2. Percentage of total time when the BG concentration remains within the clinically safe target zone (i.e., 70–180 mg/dl).
3. Percentage of total time when the BG concentration remains within the tight target zone (i.e., 80–140 mg/dl).
4. Percentage of total time when the BG concentration remains within the clinically safe target zone (i.e., 70–180 mg/dl) during 5-h postprandial period (period after a meal).
5. Percentage of total time when the BG concentration remains below 70 mg/dl.
6. Percentage of total time when the BG concentration remains below 70 mg/dl during overnight periods.
7. Percentage of total time when the BG concentration remains above 180 mg/dl.
8. 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 [41].

Furthermore, the performance of the compound IMC controller has also been demonstrated using the response of mean glucose output with standard deviation and the corresponding mean insulin infusion rate with standard deviation. Finally, we also present a visual estimation of the effectiveness of the control strategy with control-variability grid analysis (CVGA) [42]. In CVGA, each data point represents the extreme glucose excursion for each subject.

3.1 List of scenarios

The performance of the compound IMC controller is evaluated using four scenarios given in Table 1. Scenario 1, representing a typical day, is used for evaluation of the controller performance and comparison with zone-MPC of glycemic bounds 80–140 mg/dl and 100–120 mg/dl from [25]. Scenario 2 is used for robustness analysis of the controller with irregular meal amount, i.e., very high and low amount of meal in day 2. In this scenario, the experiment is done with high actuator noise which is a random variable of variance 5. Scenario 3 is used to analyze robustness of the controller in patients with irregular eating habits. In this scenario, patients are subjected to the same meal sizes as in scenario 2, but at random times, e.g., lunch is delayed by 2 h in day 1 and lunch is skipped in day 2. The simulation is also started 2 h late. Scenario 4 is used for robustness analysis of the controller to insulin sensitivity. This scenario is identical to scenario 2, except that the insulin sensitivity of patients in the metabolic simulator is varied by $\pm$ 20% and there is no actuator noise. The compound IMC controller's performance is compared with the cIMC controller [33] across all the 4 scenarios described above.

3.2 Validation using scenario 1

The average performance metrics of cIMC from [33] and the proposed compound IMC controller for scenario 1 are given in Table 2. As shown in the table, the BG concentration of the compound IMC remains within the target zone during $5h$ postprandial period for a longer period of time than cIMC. Among both the model based controllers, the average percentage of time when the BG concentration remains within the target and tight target zones are also better in compound IMC. Patients using both the controllers do not experience any hypoglycemic event for this scenario.

Thus, the results reveal that compound IMC controller avoids hypoglycemia as well as postprandial hyperglycemia in typical day regime of patients. Figure 3 shows the performance of the compound IMC for scenario 1 in terms

Table 2 Results for validation experiments (scenario 1)

Performance metrics	cIMC	Compound IMC
Mean	172.47 $\pm$ 14.21	165.8 $\pm$ 11.69
% time in normoglycemia (70–180 mg/dl)	59.35	62.95
% time in tight target (80–140 mg/dl)	38.51	40.16
% time in normoglycemia (70–180 mg/dl) during 5h postpradial period	30.89	39.33
% of time below 70 mg/dl	0	0
% of time above 180 mg/dl	40.64	37.04
LBGI	0.026	0.032
HBGI	8.75	7.4

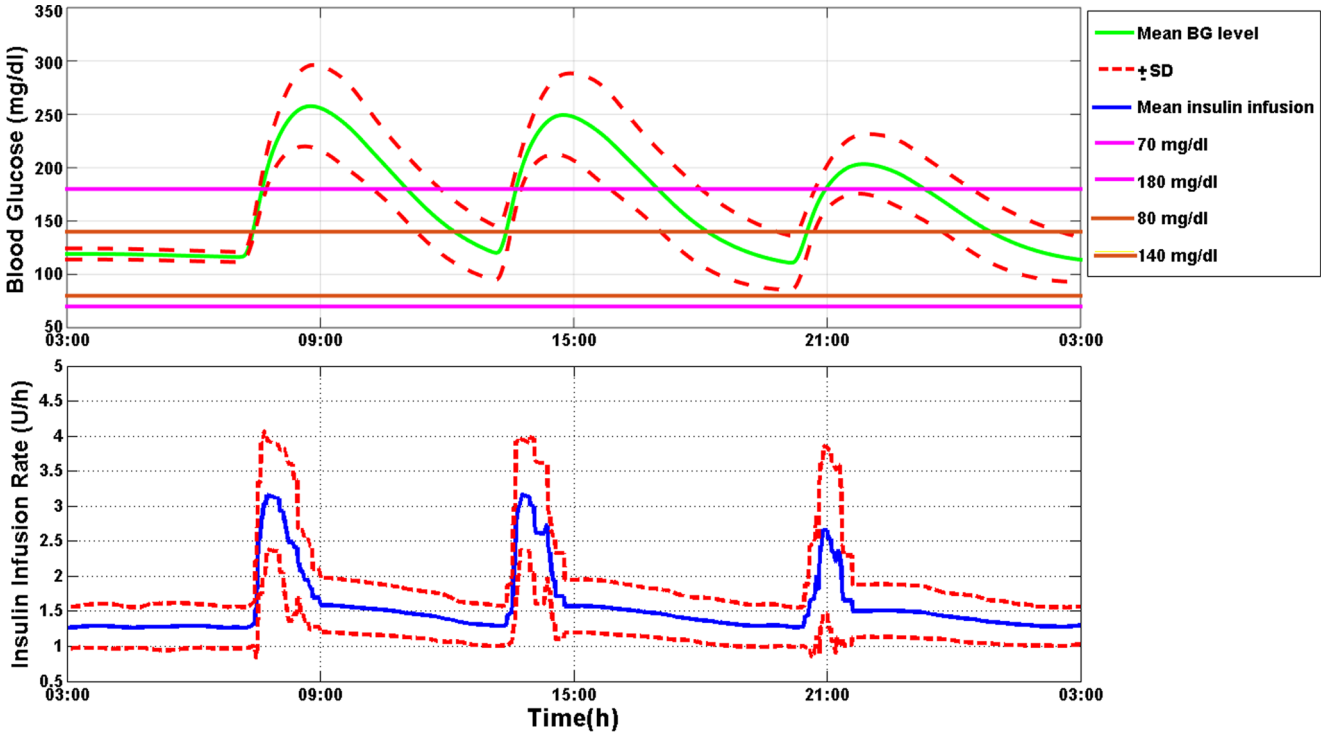

Fig. 3 Response of the mean blood glucose regulation (green solid line) and standard deviation (red dotted line) with the corresponding mean insulin infusion rate (blue solid line) and standard deviation (red dotted line) for scenario 1. Yellow solid line represents 80 mg/dl and 140 mg/dl. Magenta solid line represents 70 mg/dl and 180 mg/dl

of controlled mean and standard deviation of the BG concentration and the corresponding mean and standard deviation of secreted insulin. The larger infusion of insulin due to the action of eIMC with the automatic meal detection module during the initial period of meal consumption, shown in Fig. 3, helps in reducing the problem of slow subcutaneous insulin action. Also, the low infusion of insulin from the cIMC component of the compound controller during periods of no meal overcomes the problem of delayed peak of action. Thus, the proposed compound IMC controller is able to effectively combine the benefits of both cIMC as well as the meal detection module.

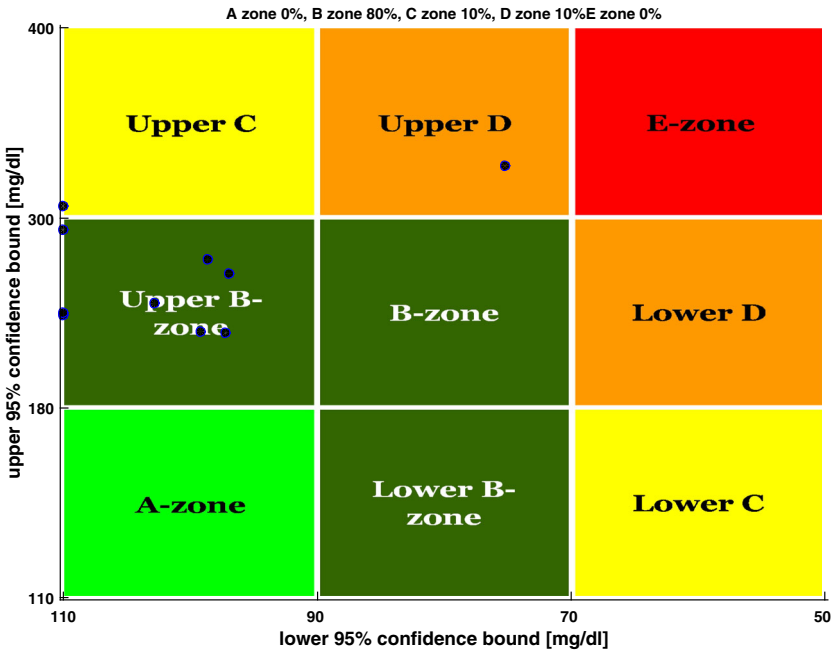

Fig. 4 CVGA of 10 *in silico* adult patients for two 75gm of meal disturbances and one 50gm of meal disturbance (Scenario 1). Each circle point represents the glucose level of 1 *in silico* adult patient regulated by the compound IMC controller

The control-variability grid analysis (CVGA) representation for compound IMC for scenario 1 is shown in Fig. 4. CVGA representation shows that among 10 *in silico* adult patients, 8 patients are in the upper B-zone, 1 patient is in the lower part of the upper C-zone and 1 patient is in the upper D-zone. The extreme glucose excursion of 8 patients is in the permissible hyperglycemic zone and most importantly, extreme glucose excursion for no patient is in lower C, lower D and E zones, i.e., below 70 mg/dl. This indicates that the compound IMC prevents dangerous hypoglycemic events effectively.

3.3 Comparison with fully-automated model based controllers using scenario 1

The compound IMC controller was compared with cIMC [33] and zone-MPC of glycemic bounds 80–140 mg/dl and 100–120 mg/dl [25] using scenario 1. Table 3 shows the comparison with respect to time over 180 mg/dl (TO_{180}) and number of occurrences of hypoglycemic events < 60 mg/dl ($Hypo_{\#}$). The average of time over 180 mg/dl using the compound IMC is only 533.4 min, whereas the same using cIMC, zone-MPC (bound 80–140 mg/dl) and zone-MPC (bound 100–120 mg/dl) are 585.2 min, 639.9 min, and 512.4 min respectively. Zone-MPC (bound 80–140 mg/dl) reduces control move variability with minimum loss of performance [25]. Thus, it is revealed that zone-MPC (bound 80–140 mg/dl) is more steady controller compared to zone-MPC (bound 100–120 mg/dl). In this paper, the performance of the online-tuned compound IMC is better than both online-tuned IMC and zone-MPC (bound 80–140 mg/dl) in avoiding hyperglycemic events. It is evident from the result that the proposed compound IMC controller is able to effectively reduce hyperglycemia without introducing any hypoglycemic events as indicated by $Hypo_{\#}$ in Table 3. This evaluation shows that the proposed controller is able to achieve this superior performance without any prior clinical observation or data and without any retuning of the controller for every patient.

3.4 Robustness analysis using scenarios 2, 3, and 4

Tables 4 and 5 show the average performance metrics of robustness analysis to variation in meal amount (scenario 2) and meal time (scenario 3) respectively. As shown in the tables, compound IMC has a better performance than cIMC across all hyperglycemia-related metrics. In particular, it has a significantly better performance in reducing hyperglycemia during the 5-h postpradial period, and is also able to reduce the periods of hypoglycemia in scenario 3. This evaluation shows that compound IMC is robust to size and time fluctuations of meal disturbances.

Table 3 Comparison of the compound IMC algorithm with cIMC and zone MPC algorithms with respect to [TO_{180}(min)] and [$Hypo_{\#}$] (scenario 1)

Patient #	cIMC with set point 110 mg/dl		Compound 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	473.61	0	398.73	0	1074	0	970	0
2	359.71	0	296.78	0	587	0	412	0
3	489.6	0	510.62	0	486	0	471	0
4	474.62	0	550.65	0	587	0	480	0
5	936.28	0	895.39	0	635	0	538	0
6	550.65	0	466.7	0	766	0	596	0
7	728.49	0	563.61	0	428	0	309	0
8	890.35	0	873.36	0	855	0	585	0
9	559.58	0	440.64	0	385	0	319	0
10	389.66	0	337.82	0	596	0	444	0

Table 4 Results for robustness analysis using irregular meal amount and high noise (scenario 2)

Performance metrics	cIMC	Compound IMC
Mean	153.24 ± 14.9	165.71 ± 12.49
% time in normoglycemia (70–180 mg/dl)	61.51	63.71
% time in tight target (80–140 mg/dl)	42.14	42.91
% time in normoglycemia (70–180 mg/dl) during 5h postpradial period	37.83	44.55
% of time below 70 mg/dl	0	0
% of time below 70 mg/dl during overnight period	0	0
% of time above 180 mg/dl	38.48	36.28
LBGI	0.08	0.06
HBGI	8.45	7.5

Table 5 Results for robustness analysis using irregular meal amount at irregular time (scenario 3)

Performance metrics	cIMC	Compound IMC
Mean	155.6 ± 13.66	153.18 ± 12.27
% time in normoglycemia (70–180 mg/dl)	68.48	72.53
% time in tight target (80–140 mg/dl)	50.06	51.7
% time in normoglycemia (70–180 mg/dl) during 5h postpradial period	40.73	48.13
% of time below 70 mg/dl	0.88	0.2
% of time below 70 mg/dl during overnight period	0	0
% of time above 180 mg/dl	30.39	27.26
LBGI	0.37	0.13
HBGI	6.6	5.67

Table 6 Results for robustness analysis using ± 20% variation in insulin sensitivity (scenario 4)

Performance metrics	+ 20% variation in insulin sensitivity		− 20% variation in insulin sensitivity	
	cIMC	Compound IMC	cIMC	Compound IMC
Mean	159.47 ± 14.69	154.3 ± 12.89	182.38 ± 15.6	178.83 ± 13.33
% time in normoglycemia (70–180 mg/dl)	66.19	69.75	55.04	57.01
% time in tight target (80–140 mg/dl)	47.58	47.98	35.82	34.96
% time in normoglycemia (70–180 mg/dl) during 5h postpradial period	45.05	52.17	30.39	35.33
% of time below 70 mg/dl	0.46	1.01	0	0
% of time below 70 mg/dl during overnight period	0	0	0	0
% of time above 180 mg/dl	33.33	29.24	44.95	42.98
LBGI	0.28	0.35	0.01	0.003
HBGI	7.12	6.02	10.42	9.41

The performance metrics for scenario 4 when the patient parameter insulin sensitivity is varied by ± 20% are given in Table 6. High dose of insulin from eIMC during the initial period of meal consumption slightly increases the risk of hypoglycemic events when the insulin sensitivity is increased by + 20%. In this evaluation as well, compound IMC has a better performance than cIMC across all hyperglycemia related metrics. Of particular relevance is the significant reduction in the BG concentration during the 5h postprandial period.

The robustness analysis reflecting real-life situation in scenarios 2, 3, and 4 are performed using more complex meal scenarios. Any false-positive detection of meal may give rise to serious hypoglycemic events due to the infusion of undesired insulin bolus. But during evaluation of the present algorithm using real-life scenarios, it is observed that the false-positive detection of meal occurs in the postprandial period after accurate detection of meal. These false-positive meals are the small amount of meal that are caused by the effect of previous accurately detected large meal for which insulin is already administered. Thus, low effective insulin can reduce the undesirable consequence of the false positive detection of meal.

It is evident from the above results that compound IMC is able to effectively utilize the meal detection module and eIMC to reduce postprandial hyperglycemia without any significant increase in hypoglycemia. Further, it is able to achieve this superior performance even in the presence of extreme variations such as ±20% change in insulin sensitivity, high and low meal amounts, skipped and delayed meals, and high sensor and actuator noises.

4 Conclusion

An online-tuned compound IMC algorithm is developed and evaluated in 10 *in silico* adult subjects of UVA/Padova metabolic simulator for the purpose of improving the insulin dose delivery system. The compound IMC controller is built using conventional IMC (cIMC) and enhanced IMC (eIMC), along with a meal detection module. Both cIMC and eIMC are developed using online predicted Volterra models to obtain patient dynamics online at different patient conditions. The nonlinear transfer function required to develop both cIMC and eIMC algorithm is obtained from the frequency domain kernels of Volterra model. The frequency domain kernels or the VTFs are computed from the time domain Volterra kernels. The proper selection of the time domain Volterra kernels is done online using the recursive least squares (RLS) algorithm. The automatic meal detection module is incorporated in the control strategy in such a way that eIMC will compute the amount of insulin to be infused only when the GRID of the meal detection module is positive, otherwise cIMC will operate.

The proposed control algorithm has yielded robust performances with the variation in insulin sensitivity, high and low meal amounts, skipped and delayed meals, and high sensor and actuator noises. The online-tuned compound control strategy shows improved performances in avoiding postprandial hyperglycemia due to minimization of the effect of slow subcutaneous insulin action with eIMC and meal detection module and also in avoiding hypoglycemia due to the compensation of delayed peak of insulin action.

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Compliance with ethical standards

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