An Insulin Infusion Advisory System Based on Autotuning Nonlinear Model-Predictive Control

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***Abstract*—This paper aims at the development and evaluation of a personalized insulin infusion advisory system (IIAS), able to provide real-time estimations of the appropriate insulin infusion rate for type 1 diabetes mellitus (T1DM) patients using continuous glucose monitors and insulin pumps. The system is based on a nonlinear model-predictive controller (NMPC) that uses a personalized glucose–insulin metabolism model, consisting of two compartmental models and a recurrent neural network. The model takes as input patient's information regarding meal intake, glucose measurements, and insulin infusion rates, and provides glucose predictions. The predictions are fed to the NMPC, in order for the latter to estimate the optimum insulin infusion rates. An algorithm based on fuzzy logic has been developed for the online adaptation of the NMPC control parameters. The IIAS has been *in silico* evaluated using an appropriate simulation environment (UVa T1DM simulator). The IIAS was able to handle various meal profiles, fasting conditions, interpatient variability, intraday variation in physiological parameters, and errors in meal amount estimations.**

***Index Terms*—Artificial pancreas (AP), autotuning model-predictive control, personalized model, type I diabetes mellitus (T1DM).**

I. Introduction

INSULIN-dependent diabetes mellitus is a metabolic disorder, characterized by the disability of the body to regulate blood glucose (BG) levels. Particularly, it is an autoimmune disease in which the β-cells of the pancreas are destroyed, resulting in the absence of insulin secretion. Chronic elevation of BG level leads to damage of blood vessels (angiopathy), resulting in serious long-term complications, such as blindness, neuropathy, heart disease, and kidney failure. According to the diabetes control and complications trial [1], the aforementioned complications can be reduced by intensive glycemic control, which involves regular glucose measurements and exogenous insulin administration. Latest advances in technology have led to the development of continuous glucose monitors (CGMs) that provide subcutaneous (sc) glucose measurements at a high frequency [2], and insulin pumps for continuous sc insulin infusion.

The experience with CGMs and insulin pumps, along with advances in computational algorithms for the automatic estimation and adjustment of appropriate insulin infusion rates makes the development of a wearable artificial pancreas (AP) feasible [3]. Closed-loop glucose control systems can be categorized according to the way mealtime insulin delivery is handled. In "fully closed-loop" mode, insulin is delivered without information about the time or size of the meal. In "semiclosed-loop" control, the controller is provided with information regarding the meal size and generates advice on prandial insulin. A significant benefit to controller performance can be obtained, when meal information is provided. Although a wide range of algorithms have been proposed [4], the most common approaches are based on proportional integral derivative controller [5], [6], and model-predictive controller (MPC) [7]–[16]. MPC (linear and nonlinear) seems to be the most appropriate for the development of AP, since it is able to handle problems related to 1) high nonlinearity of the glucose–insulin metabolism, caused by saturation and inhibition effects evidenced by chemical substrates and hormones involved in enzyme dynamics and hormonal control effects, 2) time delays in sc–sc route due to the delayed effect of infused sc insulin and food intake to the blood and, consequently, of glucose diffusion from the blood to the sc space, and the lag time between sc glucose value and glucose sensor (in the case of sensors based on microdialysis or microperfusion), and 3) noise to the sc glucose measurements. The models used to develop glucose controllers based on linear MPC are usually discrete linearized state-space models obtained from the average original nonlinear patient's model, which serves as the *in silico* T1DM patient for the evaluation of the glucose controllers [7], [8], [12]. However, such an approach would suffer from the lack of personalization [4] and from dependences between the predictive model integrated in the glucose controller and the *in silico* patient model, thus limiting the reliability of the *in silico* evaluation of the controller. A model-predictive iterative learning control has been proposed based on

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a data-driven linear autoregressive exogenous model (ARX) [9]. Although this model cannot describe accurately the real relationship between glucose and insulin in T1DM, the proposed control law performed well, especially in the case of repetitive diets. Meal detection and meal size estimation algorithms have been developed to improve meal glucose disturbance rejection when incoming meals are not announced [11]. Furthermore, several attempts have been made toward the development of glucose controllers based on nonlinear model-predictive control (NMPC), [10], [13] [14] and the effectiveness of the NMPC over the linear MPC has been studied [14]. The models used to develop glucose controllers based on NMPC are usually derived by compartmentalizing the various physiological components involved in the human metabolic process [10], [14]. The fact that some of the endocrine processes affecting glucose metabolism are still not fully understood may limit the effectiveness of these controllers. Moreover, experiments on real patients using NMPC have been performed [14]–[16]. Clinical trials have been conducted to investigate whether the closed-loop insulin delivery could control overnight BG [17], [18].

A very important issue toward the implementation of MPC is its tuning. Traditionally, the MPC has a set of tuning parameters, which add flexibility and influence its performance and stability. Usually, their values are adjusted either via trial and error procedures or by following general tuning guidelines [19]. Because of the overlapping effect of the MPC parameters, trial and error is a rather cumbersome task [20]. Furthermore, systematic approaches following tuning guidelines cannot be implemented online by control operators because the glucose metabolism is subject to severe disturbances and changing operating conditions. In order to overcome the aforementioned problems, an on-line adaptive strategy for MPC based on fuzzy logic has been proposed [20], which enables automatic tuning of the parameters and results in good control performance.

To account for the highly nonlinear nature of the glucoregulatory system, this study aims at the design, development, and evaluation of a novel Insulin Infusion Advisory System (IIAS) based on NMPC, which makes use of a new personalized model for the simulation of glucose–insulin metabolism in type 1 diabetes mellitus (T1DM). To address the day-to-day variability in the glucose dynamics of a T1DM individual and the interpatient variability, the proposed personalized approach incorporates a data-driven model, able to capture the glucose metabolic behavior taking into account patient specific information. Moreover, an automatic algorithm for the adaptation of the NMPC's control parameters over time is introduced. The IIAS has been evaluated using the UVa-type T1DM simulator [21], which has been approved by the Food and Drug Administration as a substitute for animals' trial in preclinical testing of closed-loop AP control algorithms.

II. Methodology

The proposed IIAS comprises two modules: 1) the personalized glucose–insulin metabolism model; and 2) the NMPC. These modules along with the automatic algorithm for on-line tuning of NMPC control parameters are described in the following.

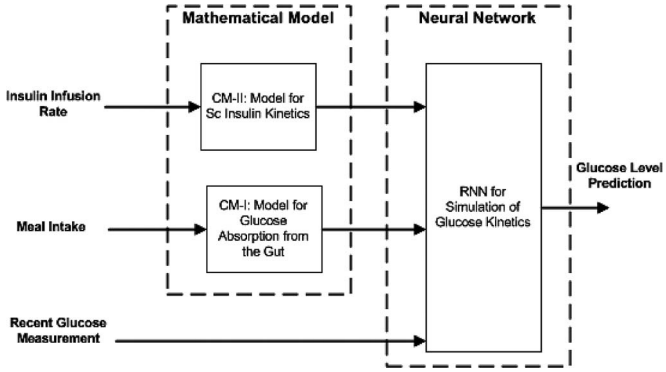

Fig. 1. Outline of the personalized glucose–insulin metabolism model used by the IIAS.

A. Personalized Glucose–Insulin Metabolism Model

In order to provide the controller with glucose predictions ahead in time, a personalized glucose–insulin metabolism model (see Fig. 1) has been developed. The model is based on the combined use of a mathematical model (MM) module and a neural network (NN) module. The MM module consists of two Compartmental Models (CMs), which simulate sc insulin kinetics and glucose absorption into the blood from the gut, respectively, while the NN module incorporates a recurrent neural network (RNN), which models the patient's glucose kinetics. Information regarding recent sc insulin infusion rate and meal intake are fed to the MM module. CMs' outputs along with the recent sc glucose measurement are applied to the RNN that provides glucose predictions.

1) CM for sc Insulin Kinetics: Following an sc insulin injection, the rate of appearance of insulin in plasma $[R_i(t)]$ is described by a linear CM [22]:

$$\dot{I}_{sc1}(t) = -(k_d + k_{a1}) \cdot I_{sc1}(t) + u(t), \quad I_{sc1}(0) = I_{sc1ss} \tag{1}$$

$$\dot{I}_{sc2}(t) = k_d \cdot I_{sc1}(t) - k_{a2} \cdot I_{sc2}(t), \quad I_{sc2}(0) = I_{sc2ss} \tag{2}$$

$$R_i(t) = k_{a1} \cdot I_{sc1}(t) + k_{a2} \cdot I_{sc2}(t) \tag{3}$$

where I_{sc1} and I_{sc2} represent the amount of nonmonomeric and monomeric insulin in the sc space, respectively, $u(t)$(pmol/kg/min) is the exogenous insulin infusion rate, $k_d(0.0164\,\text{min}^{-1})$ is the rate constant of insulin dissociation, and $k_{a1}(0.0018\,\text{min}^{-1})$ and $k_{a2}(0.0182\,\text{min}^{-1})$ are the rate constants of nonmonomeric and monomeric insulin absorption, respectively.

2) CM for Glucose Absorption From the Gut: The physiological model of glucose intestinal absorption is a three-compartment nonlinear model with two compartments representing the stomach (solid and liquid phases) and the third compartment representing the intestine [22], [24]. The model assumes a constant rate of the intestinal absorption

but describes gastric emptying rate to be dependent on the total amount of nutrient in the stomach. Following a meal, the appearance rate of glucose in plasma, Ra (in mg/kg/min), is estimated by the following differential equations:

$$Q_{\text{sto}}(t) = Q_{\text{sto1}}(t) + Q_{\text{sto2}}(t), \quad Q_{\text{sto}}(0) = 0 \tag{4}$$

$$\dot{Q}_{\text{sto1}}(t) = -k_{\text{gri}} \cdot Q_{\text{sto1}}(t) + D \cdot d(t), \quad Q_{\text{sto1}}(0) = 0 \tag{5}$$

$$\dot{Q}_{\text{sto2}}(t) = -k_{\text{empt}}(Q_{\text{sto}}) \cdot Q_{\text{sto2}}(t) + k_{\text{sto}} \cdot Q_{\text{sto1}}(t), \quad Q_{\text{sto2}}(0) = 0 \tag{6}$$

$$\dot{Q}_{\text{gut}} = -k_{\text{abs}} \cdot Q_{\text{gut}}(t) + k_{\text{empt}}(Q_{\text{sto}}) \cdot Q_{\text{sto2}}(t), \quad Q_{\text{gut}}(0) = 0 \tag{7}$$

$$Ra(t) = \frac{f \cdot k_{\text{abs}} \cdot Q_{\text{gut}}(t)}{BW}, \quad Ra(0) = 0 \tag{8}$$

where Q_{sto}(in mg) is the amount of glucose in the stomach (Q_{sto1}, solid and Q_{sto2}, liquid phase), Q_{gut}(in mg) is the glucose mass in the intestine, k_{gri}(0.0558 min^{-1}) is the rate of griding, $k_{\text{empt}}(Q_{\text{sto}})$ (min^{-1}) is the rate constant of gastric emptying, which is a nonlinear function of Q_{sto} [22], and k_{abs}(0.057 min^{-1}) is the rate constant of intestinal absorption. Moreover, f(0.90), D(in mg) and BW (in kg) represent the fraction of intestinal absorption which appears in plasma, the amount of ingested glucose, and the body weight, respectively.

3) RNN: The use of the RNN toward the development of glucose–insulin metabolism model has been studied and its ability to accurately simulate glucose kinetics taking into account previous insulin and meal intakes, along with recent glucose levels, has been proven [25].

The RNN used in the proposed personalized glucose–insulin metabolism model is a fully connected multilayered perceptron NN with two recurrent loops, whose initial weights are set to unity [27], [28]. Subcutaneous glucose levels are considered as the state variable, while the rate of appearance of insulin in plasma and the glucose absorption into the blood from the gut as external inputs. Future glucose predictions are calculated as

$$y_{NN}(k+1) = y_{NN}(k) + RNN(y_{NN}(k), R_{\alpha}(k+1), R_i(k)) \tag{9}$$

where $y_{NN}(k+1)$ and $y_{NN}(k)$ are the sc glucose level predictions at instant k+1 and k, respectively. The RNN is trained using the Real-Time Recurrent Learning (RTRL) algorithm [29]. RTRL is a sequential, error-correction learning-based algorithm, which allows the RNN to update the weights while operating. The teacher-force version of the RTRL [29] has been applied, according to which the RNN replaces the previous glucose level prediction with the corresponding glucose level value, when available, in order to produce future predictions. During the operation of the IIAS, the RNN's weights are updated based on the RTRL algorithm, whenever a new glucose measurement is applied. This effectively enables the adaptation of the glucose–insulin metabolism model to the special characteristics of the patient and to the diurnal variation of the glucose metabolism. Thus, the on-line training of the RNN ensures its stable performance for the entire input space.

B. NMPC

As already mentioned, the NMPC uses a model that provides estimates of the future outputs of the system to be controlled. The NMPC is based on an optimizer, which computes at each sample time future control movements based on the minimization of an appropriate cost function. Particularly, at each instant: 1) future outputs $y_{NN}(k+i), i = N_1, ..., N_p$ are generated by the prediction model; 2) a cost function of the future control movements is minimized providing a set of future control signals; and 3) only the first element of the suggested control sequence is applied to the system. The procedure is repeated at the next instant.

The definition of the cost function is critical to controller's performance. The cost function used in this paper [see (10)], consists of the standard MPC formulated cost function [30] and one penalty term [31]. Particularly, in (10), first and second terms represent the deviations of the glucose predictions from the reference glucose level r, and the changes in future insulin infusion rates, respectively, while the third term consists of two penalty terms, which add soft constraints ($LG \leq y_{NN}(k+i) \leq HG$) to the optimization problem. The penalty terms increase the cost function whenever the glucose predictions are outside the acceptable range determined by the lowest (LG) and the highest (HG) desired glucose level. In (10), N_p is the prediction horizon, N_1 is the minimum prediction horizon, N_c is the control horizon, and Γ_e and Γ_u are the prediction and control weighting coefficients, respectively, while Γ_L, Γ_H are penalty coefficients:

$$J = \Gamma_e \sum_{i=N_1}^{N_p} (y_{NN}(k+i) - r)^2 + \Gamma_u \sum_{j=0}^{N_c} \Delta u^2(k+j) + \sum_{i=N_1}^{N_p} \left[\Gamma_L [\min(0, y_{NN}(k+i) - LG)]^2 \; \Gamma_u \sum_{j=1}^{N_c} \Delta u^2(k+j-1) + \Gamma_H [\min(0, HG - y_{NN}(k+i))]^2\right] \tag{10}$$

where

$$\Delta u(k) = u(k) \quad u(k\,1). \tag{11}$$

The cost function is minimized, subject to the constraints

$$u_{\min} \leq u(k) \leq u_{\max}. \tag{(12)}$$

Regarding the values of the aforementioned parameters, N_p is usually chosen to encompass all the response, which is significantly affected by the current control signal (sc insulin infusion). If there is no evidence about the dead time, $N_1 = 1$. The choice of N_c is usually based on a compromise between good glucose control performance and minimization of on-line computation. Furthermore, the selection of $r, LG, HG, \Gamma_L,$ and Γ_H is based on a compromise between ability to handle high glucose levels (caused by meal disturbances) and simultaneously prevent high values of insulin infusion rates, which would cause severe hypoglycaemic episodes.

In this paper, an automatic tuning algorithm, similar to the one proposed in [20], is adopted for the on-line update of the parameters N_p and Γ_u. These parameters play an important role

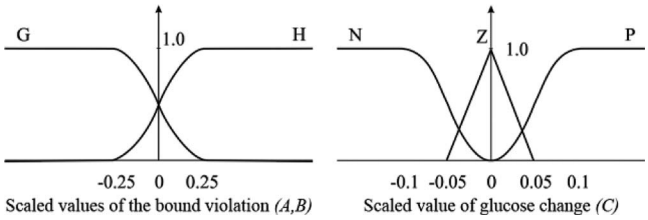

Fig. 2. Fuzzy sets for (a) bound violation and (b) bound violation rate.

to the controller's performance and stability. Although the time to the peak action of sc insulin is considered to be 50 min, the prediction horizon of 50 min is not always optimal, especially in the presence of meal disturbances where glucose levels change rapidly. This is of particular importance, since the sc glucose measurements are subject to inaccuracies and there are lags between the sc and the BG levels. The prediction weighting coefficient Γ_e is chosen to be constant in order to avoid simultaneous increase of N_p and Γ_e, which would increase on-line computation for the minimization of the cost function (10).

C. On-Line Tuning Algorithm of the NMPC Control Parameters

In order for the IIAS to rapidly reject meal disturbances and maintain postprandial glucose levels within the acceptable range, an automatic tuning algorithm has been developed. The tuning technique adapts on-line the NMPC control parameters in order to steer the closed-loop glucose response to satisfy preset time-domain specifications, which are provided by the user in the form of vectors of upper and lower bounds y^u and y^l, respectively. The new values of the NMPC control parameters are determined by fuzzy logic rules.

1) Overview of the Adaptation Algorithm: The proposed tuning method consists of two phases: the observation phase and the triggered phase. In the former, the future glucose profile is predicted, through the minimization of (10), by applying fixed values to the prediction horizon P_w and the control weighting coefficient Γ_{uw}. The obtained glucose profile is checked against the performance envelope. In case a bound violation occurs, the algorithm enters the triggered phase, otherwise the calculated insulin infusion rate is applied to the system and the whole procedure is repeated at the next instant. Particularly, at each instant *k,* the steps of the tuning algorithm are as follows.

Step 1. Produce future glucose profile using fixed NMPC control parameters through the minimization of the cost function (10). The calculated insulin infusion rate at this step is not applied to the patient.

Step 2. Check whether the predicted glucose profile, exceeds the limits of the performance envelope, i.e., y^u and y^l. If the limits are not exceeded, go to step 8.

Step 3. Determine the corresponding glucose prediction and the instant at which maximum bound violation occurs. Let this be at instant $k + m$.

Step 4. Calculate the scaled values of the bound violation (A, B), and the glucose change (C) at instant $k + m$.

Step 5. Determine the degree of membership of A, B, and C with respect to membership functions presented in Fig. 2.

TABLE I
BASE RULES OF THE TUNING ALGORITHM

No.	Rule	Result of Γ_u	Result of N_p
R1	If *A* is H and *B* is G	Then μ_Γ is SN	Then μ_{Np} is LP
R2	If *A* is G and *B* is H	Then μ_Γ is LN	Then μ_{Np} is LP
R3	If *A* is G and *B* is G	Then μ_Γ is ZE	Then μ_{Np} is SN
R4	If *A* is H and *C* is P	Then μ_Γ is LN	Then μ_{Np} is SP
R5	If *A* is H and *C* is Z	Then μ_Γ is SP	Then μ_{Np} is SN
R6	If *A* is H and *C* is N	Then μ_Γ is ZE	Then μ_{Np} is ZE
R7	If *B* is H and *C* is P	Then μ_Γ is SN	Then μ_{Np} is ZE
R8	If *B* is H and *C* is Z	Then μ_Γ is SP	Then μ_{Np} is SN
R9	If *B* is H and *C* is N	Then μ_Γ is ZE	Then μ_{Np} is SP

Step 6. Calculate the correction factors $[w_k(N_p), w_k(\Gamma_u)]$.

Step 7. Set the new parameters values as $N_{p,k} = N_{p,\text{previous}} + w_k(N_p)$ and $\Gamma_{u,k} = \Gamma_{u,\text{previous}}(1 + w_k(\Gamma_u))$, where $N_{p,\text{previous}}$ and $\Gamma_{u,\text{previous}}$ are calculated during the previous triggered phase of the tuning algorithm.

Step 8. Compute and apply the sc insulin infusion rate. Proceed to the next instant $k + 1$ and go to step 1.

The initial values of N_p and $\Gamma_u$are set to P_w and Γ_{uw}, respectively. In the presence of a meal disturbance, the control parameters are appropriately updated in order to reduce the overshoot and speed up the closed-loop response. To this end, N_p and Γ_u reset to their initial values whenever a new meal disturbance is applied.

2) Fuzzification: At the fuzzification stage, the scaled values of the bound violation and the glucose change at the instant where maximum violation occurs are fuzzified using the fuzzy sets shown in Fig. 2. Particularly, if upper-bound violation occurs, the scaled value$A$ is specified as

$$A = \frac{y_{NN}(k+m) - y^u}{y^u}. \tag{13}$$

If lower bound is violated, the scaled value$B$ is specified as

$$B = \frac{y^l - y_{NN}(k+m)}{y^l} \tag{14}$$

where $m(N_1 \leq m \leq N_p)$ is the instant at which maximum violation occurs. The definition of $A$and$B$guarantees positive value if the corresponding bound is violated and negative otherwise. The fuzzy set used for the fuzzification of the bound violation is shown in Fig. 2(a), and consists of two membership functions, namely: (G)ood denoted as G and (H)igh denoted as H. Therefore, if the upper bound is violated, then A belongs to H and B to G and vice versa.

The scaled value of glucose change at the instant where the maximum violation occurs is defined as follows:

$$C = \frac{y_{NN}(k+m) - y_{NN}(k+m-1)}{y_{NN}(k+m)}. \tag{15}$$

The scaled value of glucose change is transformed into a member of fuzzy sets, using the fuzzy set shown in Fig. 2(b). This fuzzy set consists of three membership functions: (P)ositive, (Z)ero, and (N)egative.

3) Inference Engine: The base rules governing the tuning guidelines are given in Table I. In this Table, μ_Γ and $\mu_N p$

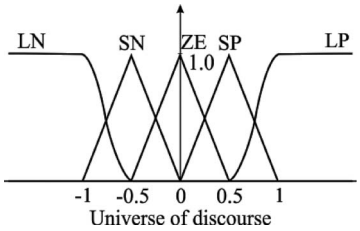

Fig. 3. Fuzzy set for the output of MPC parameters.

represent the rule output for N_p and Γ_u, respectively, while LN (Large Negative), SN (Small Negative), ZE (Zero), SP (Small Positive), and LP (Large Positive), are the output fuzzy sets represented by sigmoid and triangular membership functions as shown in Fig. 3. These functions are denoted as μ_5, μ_4, μ_3, μ_2, and μ_1, respectively. The base rules formulate the general understanding of the effect of parameters N_p and Γ_u in closed-loop response. In general, according to simulation experience [20], increasing N_p at a fixed nonzero value of Γ_u results in a faster response with less overshoot. Furthermore, reduction of Γ_u speeds up the response. We chose to increase N_p for both upper- and lower-bound violation, in order to prevent from large overshoots in glucose response—which may result in hyperglycaemic episodes—while speeding up the glucose response to avoid hypoglycemic episodes. Morever, since reduction of Γ_u speeds up the response, parallel reduction of N_p should be avoided, because this would lead to more aggressive control performance and might result to instability.

4) Defuzzification: At the defuzzification stage, the outputs of the base rules are properly processed in order to produce crisp values, which are used as factors to update the NMPC control parameters. The base rules of Table I, which are in linguistic form, are expressed in mathematical form using a common fuzzy rule operation [20]. Particularly, the AND command is transformed into minimum operation. For example, the results of Rule 1 in Table I can be written as follows:

$$\mu_{4,1}(\Gamma_u) = \min(\mu_H(A), \mu_G(B)) \tag{16}$$

$$\mu_{1,1}(N_p) = \min(\mu_H(A), \mu_G(B)) \tag{17}$$

where $\mu_H(A)$ is the degree of membership of A in the fuzzy set H and $\mu_{j,i}(\bullet)$ denotes the membership degree of $(\bullet)$ to the *j*th output membership function with respect to rule *i*. Therefore, the center of area principle [32] is applied in order to produce the correction factor Γ_u. For the prediction horizon, the correction factor is calculated as

$$w_k(N_p) = \sum_{j=1}^{n_R} \sum_{i=1}^{n_f} \mu_{j,i}(N_p)\delta_i \tag{18}$$

where n_R and n_f represent the number of rules and the number of membership functions, respectively, while δ_i is the value for the center location of the activated output membership function. Since N_p is an integer, the correction factor is rounded to the nearest integer.

III. Results and Discussion

In order to evaluate the performance and the robustness of the designed IIAS, the UVa T1DM simulator [21] has been used. The UVa T1DM simulator incorporates a modified version of the meal model developed by Man *et al.* [22]–[24] to adapt for T1DM subjects and insulin exogenous infusion [22]. In addition to the patient model, the simulator incorporates a sensor-related errors model to account for sensor noise and measurements' errors and a model for the sc insulin pump. The UVa T1DM simulator simulates a sufficiently large cohort of *in silico* subjects in order to cover the wide variability observed among diabetic population and serves as an *in silico* environment for preclinical testing trial. In this paper, the proposed IIAS has been tested with the ten adults' population available in the training version of the UVa simulator. The ten patients are characterized by a wide diversity in their parameters (e.g., body weight and insulin sensitivity) and, therefore, can serve as small population to evaluate the controller [8], [9].

The evaluation of the IIAS is performed in two stages: 1) evaluation of the predictive performance of the personalized glucose–insulin metabolism model; and 2) evaluation of the controller considering several simulation scenarios.

A. Evaluation of the Personalized Glucose–Insulin Metabolism Model

Open-loop experiments were performed in order to generate the data for the training and testing of the personalized glucose–insulin metabolism models. Particularly, each *in silico* subject was fed for one week, with 1) basal rate, which keeps the specific patient at its fasting state (provided by the UVa T1DM simulator), 2) insulin bolus whenever carbohydrates were ingested (provided by the UVa T1DM simulator), and 3) various meal profiles corresponding to breakfast, lunch, dinner, and two snacks. In order to account for patient real life, meal times and amounts values were randomly chosen within the following ranges: {[6–8 A.M.], [12–2 P.M.], [4–4.30 P.M.], [6–8 P.M.], [10–11 P.M.]} and {[40–60 g], [60–80 g], [0–10 g], [70–90 g], and [0–10 g]}, respectively. Data corresponding to the first four days were used for training the model, while the remaining three days were used for its testing. The predictive performance of the glucose–insulin metabolism model was evaluated considering a prediction horizon equal to 30 min with a 5-min resolution.

Root-mean-squared error (RMSE) and correlation coefficient (CC) corresponding to the testing dataset were calculated to evaluate the performance of the glucose–insulin metabolism model in terms of matching the predicted glucose with the original ones. Furthermore, in order to evaluate the clinical accuracy of the glucose predictions and their effects on decisions to avoid hypo- and hyperglycemic events, the continuous error grid analysis [33] has been used. The estimates of point and rate precision are combined in a single accuracy assessment for each of the BG ranges: hypoglycemia, euglycemia, and hyperglycemia. To this end, the point error grid analysis (P-EGA) and the rate error grid analysis (R-EGA) are combined in the three clinically relevant regions of hypoglycemia, euglycemia, and hyperglycemia. Clinically accurate glucose predictions are

TABLE II
ERROR MATRIX COMBINING R-EGA AND P-EGA

		P-EGA										
		Hypoglycemia			Euglycemia			Hyperglycemia				
		A	D	E	A	B	C	A	B	C	D	E
R-EGA	A	69.61	13.26	0.00	75.35	4.99	0.02	38.00	4.80	0.00	0.00	0.00
	B	6.63	1.10	0.00	8.84	1.41	0.00	29.20	5.20	0.00	0.00	0.00
	uC	0.00	2.76	0.00	4.22	1.38	0.07	17.20	0.00	0.00	0.00	0.00
	lC	6.08	0.55	0.00	3.16	0.54	0.01	5.60	0.00	0.00	0.00	0.00
	uD	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	lD	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	uE	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	lE	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	AR	76.24			90.61			77.20				
	BE	6.08			9.29			22.80				
	ER	17.68			0.00			0.00				

AR: Accurate readings, BE: Benign errors, ER: Erroneous errors.

TABLE III
IIAS TUNING

Weighting Coefficients				Prediction, minimum and control horizon		
Γ_{uw}	Γ_L	Γ_H	Γ_e	P_w	N_1	N_c
10	10	1	100	10	1	1
Limits of performance envelop (*mg/dl*)		**Glucose target range (*mg/dl*)**		**Reference glucose (*mg/dl*)**	
y^l	y^u	LG	HG	r	
90	140	70	180	110	

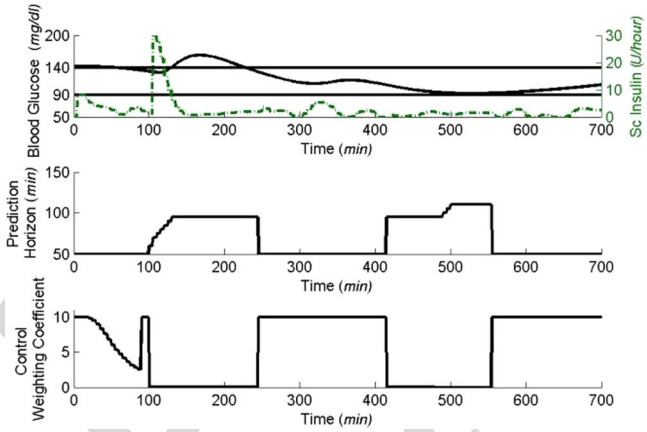

Fig. 4. Upper panel: Adult 5, sc insulin infusion rates (dashed-dotted line), BG data (solid line), limits of performance envelop [90–140 mg/dl] (dashed-line). Middle panel: Prediction horizon. Low panel: control weighting coefficient.

considered to be within the zones A and B on both P-EGA and R-EGA. Clinically benign errors correspond to acceptable point accuracy (i.e., A or B P-EGA zones) and significant errors in rate accuracy (i.e., C, D, or E R-EGA zones), which are unlikely to lead to negative clinical consequences. Clinically significant errors are those that could lead to a negative clinical action and therapeutic consequences.

From both the RMSE (mean $\pm$ standard deviation (SD): 15.67 $\pm$ 6.03) and CC (mean $\pm$ SD: 0.78 $\pm$ 0.16), it is obvious that the predicted glucose profile follows the original one. Moreover, the error matrix combining P-EGA and R-EGA, presented in Table II, shows that erroneous errors are observed in the range of hypoglycemia.

Although the proposed glucose–insulin metabolism model uses CMs for the simulation of sc insulin kinetics and glucose absorption from the gut, similarly with the UVa T1DM simulator, it adopts a completely different approach based on the RNN to map plasma insulin to sc glucose. The latter consists the most essential module of the model. The previously presented prediction accuracy assessment refers to primarily testing the RNN and its effective combination with the CMs. The predictive performance of the glucose–insulin metabolism model has been assessed in a previous study [25], and the superiority of the used RNN over a feedforward neural network (FNN) has been demonstrated [26], using real patient data.

B. IIAS Tuning

The IIAS provides the estimated insulin infusion rates every 5 min. Regarding the performance envelope, lower y^l and upper y^u bounds were chosen to be constant and equal to 90 and 140 mg/dl, respectively, corresponding to a rather narrow target range. Particularly, 90 mg/dl corresponds to the minimum BG level of optimal glucose control [21], while 140 mg/dl is the maximum 2-h postprandial BG level [8]. Moreover, LG and HG were set to 70 and 180 mg/dl, respectively, since, in this paper, BG concentrations between 70 and 180 mg/dl are considered to be within the target range for T1DM. The values of the weighting coefficients Γ_L,Γ_H, and Γ_e were chosen to be 10, 1, and 100, respectively. The rather largeΓ_e value causes quite high insulin infusion rates, which are necessary to prevent hyperglycemic episodes after meal ingestion. Furthermore, $\Gamma_L$is large enough to appropriately penalize for glucose predictions lower than 70 mg/dl and thus preventing from extremely high insulin infusion rates that would lead to hypoglycemic episodes. Parameter P_w is set to 10 corresponding to 50 min in order for the prediction horizon to account for sc insulin action. The control weighting coefficient Γ_{uw} is set to 10, which is high enough to ensure stability of the glucose controller. N_c is set to 1 (its minimum possible value), corresponding to 5 min, in order to minimize on-line computation and $N_1 = 1$ (see Section II-B). Moreover, $u_{\min} = 0$U/h while $u_{\max} = 70$U/h in accordance with the maximum allowable values for patients' safety and pump's hardware limitations [8]. The reference glucose level r is set to 110 mg/dl, which corresponds to the minimum value of the risk index. The numerical values of the parameters are summarized in Table III.

In order to clearly present the evolution of the prediction horizon N_p along with the control weighting coefficient Γ_u over time, the following simulation scenario has been studied: Adult 5 was fed with 50 g at time 100 min. In Fig. 4, BG levels, sc insulin infusion rates along with prediction horizon, and control weighting coefficient are shown. As can be observed, the tuning algorithm does not always enter the triggered phase. It enters the triggered phase whenever there is danger for BG levels to exceed the limits of the performance envelop (90–140 mg/dl), and

TABLE IV
DAILY MEAL PROFILES

Day	1					2		
Meal Time (h)	07:00	12:00	16:00	18:00	23:00	07:30	13:00	18:30
Meal Amounts (g)	45	70 0	5	80	5	40	85	60

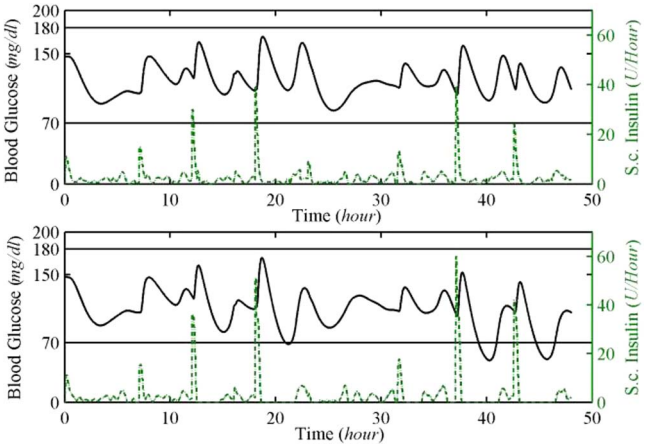

Fig. 5. Control results for Adult 3 under IIAS (upper panel) and fixed parameters NMPC (low panel). Estimated insulin infusion rates (dashed-dotted line), BG data (solid line), glucose target range [70–180 mg/dl].

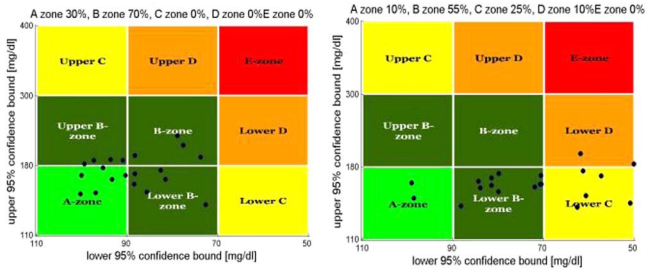

Fig. 6. CVGA for the ten adults of the Uva T1DM simulator. *left:* IIAS (30% in zone A and 70% in zone B). *Right:* NMPC (10% in zone A, 55% in zone B, 25% in zone C, and 10% in zone D).

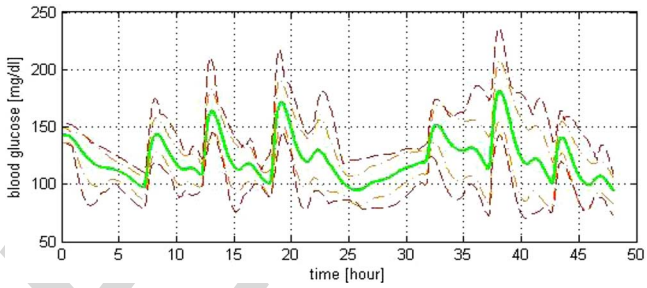

Fig. 7. BG trace for the ten adults of the UVa T1DM simulator when the IIAS is applied. Mean response (solid curve), SD (dashed-dotted curve), and min/max envelop (dashed curve).

appropriately updates the NMPC parameters, managing to reset and maintain glucose levels within the performance envelop.

C. Evaluation of the Controller—Simulation Scenarios

To evaluate IIAS's performance under realistic conditions, several scenarios have been simulated. Particularly, the IIAS has been tested for its ability to handle meal disturbances, fasting conditions, interpatient variability, robustness against erroneous estimation of carbohydrates' amount in ingested meals, and intraday variation in physiological parameters. Furthermore, in order to study the effectiveness of the tuning algorithm, two simulation scenarios have been studied: with (IIAS) and without (fixed parameter NMPC) the tuning algorithm.

1) Evaluation of the IIAS Against Fixed Parameter NMPC: Both controllers have been tested with the ten adults' population. It should be noted that in the case of fixed parameter NMPC, N_p and Γ_e are fixed over time and set both to 10. The simulation scenarios consider a two-day testing period with varying meal timings and amounts (see Table IV).

The superiority of the IIAS over fixed parameter NMPC is shown in Figs. 5 and 6. Fig. 5 presents the estimated sc insulin infusion rates along with the corresponding BG levels, when Adult 3 is fed with the two-day meal protocol and regulated using the IIAS (upper panel) and the fixed parameter NMPC (low panel), respectively. It should be noted that the controllers activate either the basal or the bolus action provided from the insulin pumps and hold the estimated insulin dose constant between sampling instants (per 5 min). As shown in Fig. 5, the application of fixed parameter NMPC caused severe hypoglycaemic episodes, which are defined as BG levels lower than 60 mg/dl [9]. On the other hand, the IIAS managed to maintain BG levels within the target range (70 --180 mg/dl), while achieving less fluctuations over time.

The control variability grid analysis (CVGA) [34], shown in Fig. 6, serves as a tool to evaluate the controllers with the entire population. Each point in the CVGA represents the lower and the upper bound of 95% confidence interval of BG data for one patient during one day. Zones A and B are considered to represent good glucose control. CVGA demonstrates that IIAS provides superior performance over the fixed parameter NMPC, managing to keep all the patients inside the zones A and B. Furthermore, the min/max envelop presented in Fig. 7 indicates that the BG levels for the hard-to-control patients are within the acceptable range 70–236 mg/dl, managing to avoid hypoglycemic episodes and severe hyperglycemic episodes (above 280 mg/dl).

Moreover, numerical metrics of average glycemia, percentage within the target range (70–180 mg/dl), risk associated with extreme glucose deviations [35] (low blood glucose index (LBGI), high blood glucose index (HBGI), and total risk index), are used to provide more details about the controller performance. In Table V, the obtained numerical results, when the IIAS is applied on all 10 patients, are presented. It can be seen that most of the time, BG levels are kept within the target range, while the risk indices (LBGI, HBGI, and total risk index) have low values, showing that tight glycemic control is achieved.

2) Robustness to Meal Estimation Errors: Since the proposed IIAS is informed about the carbohydrates amount of the upcoming meal, its ability to handle meal estimation errors is of utmost importance. To this end, the IIAS has been tested

TABLE V
CONTROL PERFORMANCE OF THE IIAS AND THE OPEN-LOOP PREADJUSTED TREATMENT

Simulation scenario	mean BG Mean (±SD)	Pre meal BG Mean (±SD)	Post meal BG Mean (±SD)	% below target Mean (±SD)	% above target Mean (±SD)	% within target Mean (±SD)	LBGI Mean (±SD)	HBGI Mean (±SD)	risk index Mean (±SD)
Accurate meal announcement (IIAS)	122.25 (9.06)	114.27 (12.31)	139.78 (9.19)	0 (0)	2.51 (2.76)	97.49 (2.76)	0.35 (0.35)	1.09 (0.64)	1.45 (0.66)
40% OEE (IIAS)	117.54 (7.91)	105.57 (8.99)	132.26 (12.68)	1.01 (1.51)	2.40 (3.13)	96.58 (2.83)	0.72 (0.34)	0.92 (0.62)	1.64 (0.66)
40% UEE (IIAS)	120.28 (10.61)	110.11 (11.13)	137.44 (14.30)	5.15 (5.07)	4.36 (4.43)	90.48 (6.66)	0.99 (0.71)	1.27 (0.86)	2.26 (1.10)
Intraday variation in physiological parameters (IIAS)	122.47 (7.58)	128.25 (15.79)	133.31 (15.42)	0.66 (0.87)	3.41 (3.25)	95.91 (3.61)	0.4 (0.27)	1.2 (0.65)	1.6 (0.71)
Open loop preadjusted treatment	130.50 (6.92)	124.4 (6.65)	145.16 (10.80)	1.14 (3.61)	3.68 (3.78)	95.17 (5.59)	0.30 (0.48)	1.65 (0.69)	1.96 (0.91)

against overestimation errors (OEE) and underestimation errors (UEE) up to 40%. Table V demonstrates the mean values and the SDs of the numerical metrics over the results obtained for the ten adults. Although certain hypoglycemic and hyperglycemic episodes occurred, none of them was severe. It is noteworthy that the IIAS is able to handle meal estimation errors and regulate properly insulin infusion rate, in order to keep glucose within the target range most of the time.

3) Robustness Against Intraday Variation in Physiological Parameters: One of the critical challenges for a glucose control algorithm is robustness against intraday variation in physiological parameters. In order to represent diurnal metabolic variations, time variation of the *in silico* patient-specific physiological parameters was considered, as drawn from a normal distribution with SD of 10%. This distribution was chosen to capture the expected variation in insulin sensitivity [36]. In Table V, the obtained numerical results over the ten adults are presented. The IIAS achieved good glucose control, managing to maintain BG levels within the acceptable range for 95.17% of the total time, avoiding severe hypoglycemic and hyperglycemic episodes. Furthermore, the risk indices are low, proving the IIAS' ability to handle intraday variation in physiological parameters.

D. Comparison of the IIAS With Other Glucose Controllers

In order to prove the efficacy of the IIAS, its performance has been compared with that of other open-loop and closed-loop glucose controllers.

1) Open-Loop Preadjusted Treatment: The open-loop preadjusted treatment is supported by the UVa T1DM simulator. The ten *in silico* adults of the simulator followed a protocol of meals presented in Table IV. A matching insulin bolus and a basal rate were provided by the UVa T1DM simulator for each *in silico* adult and the results obtained by applying the open-loop preadjusted treatment are presented in Table V. It can be observed that the IIAS achieves better glucose control.

2) Adaptive Basal Therapy: Since the basal rate provided by the UVa T1DM simulator is nonoptimal, the IIAS has been compared with adaptive basal therapy [37]. The latter suggests adaptation of the basal rate as a gain multiplier based on the current CGM glucose value and its rate of change. Identical meals used in [37] provided input to the ten *in silico* adults, which were regulated by the IIAS. In particular, the ten *in silico* adults followed a one-day meal scenario of 40, 75, 60 g of carbohydrates at 7:00 A.M., 12:00 A.M., and 6:00 P.M., respectively. Results obtained from the application of the IIAS and the adaptive basal therapy are presented in Table VI in terms of hyperglycemia and severe hypoglycemia (<60 mg/dl) along with risk indices. It can be observed that the IIAS provides better glucose control performance.

TABLE VI
COMPARISON OF THE IIAS WITH THE ADAPTIVE BASAL THERAPY [37]

Controller	Hypo-percent (<60mg/dl)	Hyper-percent	Safe percent	risk index
IIAS	0.00 ± 0.00	0.60 ± 1.52	99.40 ± 1.52	0.99 ± 0.43
Adaptive Basal Therapy	0.5 ± 0.01	1.3 ± 0.03	98.2 ± 0.03	1.7 ± 0.59

3) Artificial Pancreatic β-Cell Based on Zone-MPC: In order to justify the use of the proposed nonlinear approach to improve glucose control, the IIAS has been compared with an artificial pancreatic β-cell based on zone-MPC that uses mapped-input data and is adjusted automatically by linear difference personalized models [38]. The ten *in silico* adults followed the three meal scenario used in [38]—consisting of 75, 75, and 50 g of carbohydrates at 7 A.M., 1 P.M., and 8 P.M., respectively—and were regulated by the IIAS. The obtained results are presented in Table VII. It should be noted that no severe hypoglycemic (<60 mg/dl) and hyperglycemic episodes (>280 mg/dl) have been observed during the operation of the IIAS- and zone-MPC-based glucose controllers. As discussed in [38], a single severe hypoglycemic event occurred during the operation of the MPC with set point at 110 mg/dl. When the *in silico* adults were regulated by the IIAS, the mean glucose value was closer to the desired glucose level, while the average SD of the mean glucose value was lower, indicating lower variability in glucose control performance among the *in silico* adults. Furthermore, lower

TABLE VII
COMPARISON OF THE IIAS WITH THE ARTIFICIAL PANCREATIC B-CELL [38]

Controller	Mean Glucose	Hyper- percent
IIAS	117.61 ± 7.11	0.81 ± 2.05
Zone-MPC (bounds: 80-140 *mg/dl*) (Experiment 5 in [38])	152.00 ± 28.00	27.99 ± 20.51
Zone-MPC (bounds: 100-120 *mg/dl*) (Experiment 6 in [38])	141.00 ± 29.00	20.75 ± 19.45
MPC (set-point 110 *mg/dl*) (Experiment 7 in [38])	136.00 ± 29.00	17.54 ± 18.58

percentage of hyperglycemia was observed during the operation of the IIAS. The obtained improved glucose control performance is related to higher on-line computation.

Summarizing, the use of a data-driven model for the simulation of the blood glucose–insulin kinetics (real-time self-adaptive NN) permits personalization of the system and efficient handling of a changing environment. It is important to note that the incorporation of the RNN makes the model capable of simulating glucose–insulin kinetics taking into account patient specific information related to ingested carbohydrates, sc insulin infusion rate, and glucose records from CGMS that are usually available in clinical practice. The metabolic behavior of a specific patient is captured through the real-time update of the RNN's weights. Whenever a new glucose measurement is applied to the model, the RNN's weights are appropriately adapted in order to adjust to the new metabolic behavior. According to above, the RNN consists the most essential module of the personalized glucose–insulin metabolism model. Thus, the similarities of the latter with the UVa T1DM simulator regarding the use of CMs for the sc insulin kinetics and the glucose absorption from the gut do not limit the reliability of the presented assessment of the IIAS performance. This is of particular importance since the IIAS has demonstrated robustness against intraday variation in physiological parameters. Moreover, the tuning algorithm for the real-time update of the NMPC control parameters greatly improved controller's performance, demonstrating its importance toward the tuning of glucose controllers based on MPC.

Clinical evaluation of the IIAS on real T1DM patients is in progress. Future research activities are focused on the optimization of the proposed IIAS and its complete integration into a telecommunication platform for the efficient management and treatment of patients with T1DM [39].

IV. CONCLUSION

A novel IIAS based on NMPC has been proposed in order to estimate optimal insulin infusion rates. The proposed approach introduces 1) a personalized model based on the combined use of CMs and an RNN for the simulation of glucose–insulin metabolism and 2) an automatic algorithm for the on-line adaptation of NMPC parameters. The performance of the IIAS has been *in silico* evaluated using the ten adults' population, available in the training version of the UVa T1DM simulator. The obtained results demonstrate that the proposed IIAS is robust with respect to its ability to handle various conditions characterized by sensor errors, lags, meal disturbances, large meal estimation errors, interpatient variability, and intraday variation in physiological parameters.

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An Insulin Infusion Advisory System Based on Autotuning Nonlinear Model-Predictive Control

Konstantia Zarkogianni, Andriani Vazeou, Stavroula G. Mougiakakou, *Member, IEEE*, Aikaterini Prountzou, and Konstantina S. Nikita*, *Senior Member, IEEE*

***Abstract*—This paper aims at the development and evaluation of a personalized insulin infusion advisory system (IIAS), able to provide real-time estimations of the appropriate insulin infusion rate for type 1 diabetes mellitus (T1DM) patients using continuous glucose monitors and insulin pumps. The system is based on a nonlinear model-predictive controller (NMPC) that uses a personalized glucose–insulin metabolism model, consisting of two compartmental models and a recurrent neural network. The model takes as input patient's information regarding meal intake, glucose measurements, and insulin infusion rates, and provides glucose predictions. The predictions are fed to the NMPC, in order for the latter to estimate the optimum insulin infusion rates. An algorithm based on fuzzy logic has been developed for the online adaptation of the NMPC control parameters. The IIAS has been *in silico* evaluated using an appropriate simulation environment (UVa T1DM simulator). The IIAS was able to handle various meal profiles, fasting conditions, interpatient variability, intraday variation in physiological parameters, and errors in meal amount estimations.**

***Index Terms*—Artificial pancreas (AP), autotuning model-predictive control, personalized model, type I diabetes mellitus (T1DM).**

I. Introduction

INSULIN-dependent diabetes mellitus is a metabolic disorder, characterized by the disability of the body to regulate blood glucose (BG) levels. Particularly, it is an autoimmune disease in which the β-cells of the pancreas are destroyed, resulting in the absence of insulin secretion. Chronic elevation of BG level leads to damage of blood vessels (angiopathy), resulting in serious long-term complications, such as blindness, neuropathy, heart disease, and kidney failure. According to the diabetes control and complications trial [1], the aforementioned complications can be reduced by intensive glycemic control, which involves regular glucose measurements and exogenous insulin administration. Latest advances in technology have led to the development of continuous glucose monitors (CGMs) that provide subcutaneous (sc) glucose measurements at a high frequency [2], and insulin pumps for continuous sc insulin infusion.

The experience with CGMs and insulin pumps, along with advances in computational algorithms for the automatic estimation and adjustment of appropriate insulin infusion rates makes the development of a wearable artificial pancreas (AP) feasible [3]. Closed-loop glucose control systems can be categorized according to the way mealtime insulin delivery is handled. In "fully closed-loop" mode, insulin is delivered without information about the time or size of the meal. In "semiclosed-loop" control, the controller is provided with information regarding the meal size and generates advice on prandial insulin. A significant benefit to controller performance can be obtained, when meal information is provided. Although a wide range of algorithms have been proposed [4], the most common approaches are based on proportional integral derivative controller [5], [6], and model-predictive controller (MPC) [7]–[16]. MPC (linear and nonlinear) seems to be the most appropriate for the development of AP, since it is able to handle problems related to 1) high nonlinearity of the glucose–insulin metabolism, caused by saturation and inhibition effects evidenced by chemical substrates and hormones involved in enzyme dynamics and hormonal control effects, 2) time delays in sc–sc route due to the delayed effect of infused sc insulin and food intake to the blood and, consequently, of glucose diffusion from the blood to the sc space, and the lag time between sc glucose value and glucose sensor (in the case of sensors based on microdialysis or microperfusion), and 3) noise to the sc glucose measurements. The models used to develop glucose controllers based on linear MPC are usually discrete linearized state-space models obtained from the average original nonlinear patient's model, which serves as the *in silico* T1DM patient for the evaluation of the glucose controllers [7], [8], [12]. However, such an approach would suffer from the lack of personalization [4] and from dependences between the predictive model integrated in the glucose controller and the *in silico* patient model, thus limiting the reliability of the *in silico* evaluation of the controller. A model-predictive iterative learning control has been proposed based on

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a data-driven linear autoregressive exogenous model (ARX) [9]. Although this model cannot describe accurately the real relationship between glucose and insulin in T1DM, the proposed control law performed well, especially in the case of repetitive diets. Meal detection and meal size estimation algorithms have been developed to improve meal glucose disturbance rejection when incoming meals are not announced [11]. Furthermore, several attempts have been made toward the development of glucose controllers based on nonlinear model-predictive control (NMPC), [10], [13] [14] and the effectiveness of the NMPC over the linear MPC has been studied [14]. The models used to develop glucose controllers based on NMPC are usually derived by compartmentalizing the various physiological components involved in the human metabolic process [10], [14]. The fact that some of the endocrine processes affecting glucose metabolism are still not fully understood may limit the effectiveness of these controllers. Moreover, experiments on real patients using NMPC have been performed [14]–[16]. Clinical trials have been conducted to investigate whether the closed-loop insulin delivery could control overnight BG [17], [18].

A very important issue toward the implementation of MPC is its tuning. Traditionally, the MPC has a set of tuning parameters, which add flexibility and influence its performance and stability. Usually, their values are adjusted either via trial and error procedures or by following general tuning guidelines [19]. Because of the overlapping effect of the MPC parameters, trial and error is a rather cumbersome task [20]. Furthermore, systematic approaches following tuning guidelines cannot be implemented online by control operators because the glucose metabolism is subject to severe disturbances and changing operating conditions. In order to overcome the aforementioned problems, an on-line adaptive strategy for MPC based on fuzzy logic has been proposed [20], which enables automatic tuning of the parameters and results in good control performance.

To account for the highly nonlinear nature of the glucoregulatory system, this study aims at the design, development, and evaluation of a novel Insulin Infusion Advisory System (IIAS) based on NMPC, which makes use of a new personalized model for the simulation of glucose–insulin metabolism in type 1 diabetes mellitus (T1DM). To address the day-to-day variability in the glucose dynamics of a T1DM individual and the interpatient variability, the proposed personalized approach incorporates a data-driven model, able to capture the glucose metabolic behavior taking into account patient specific information. Moreover, an automatic algorithm for the adaptation of the NMPC's control parameters over time is introduced. The IIAS has been evaluated using the UVa-type T1DM simulator [21], which has been approved by the Food and Drug Administration as a substitute for animals' trial in preclinical testing of closed-loop AP control algorithms.

II. Methodology

The proposed IIAS comprises two modules: 1) the personalized glucose–insulin metabolism model; and 2) the NMPC. These modules along with the automatic algorithm for on-line tuning of NMPC control parameters are described in the following.

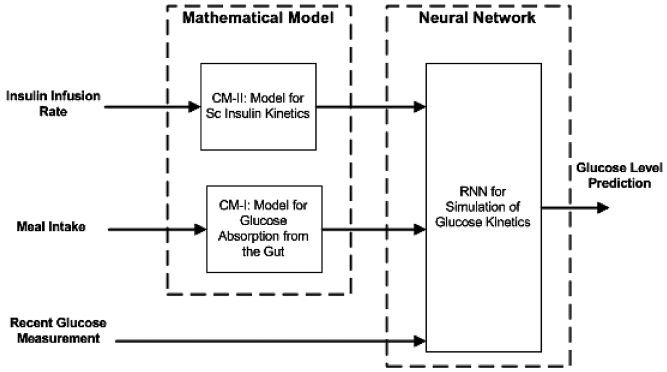

Fig. 1. Outline of the personalized glucose–insulin metabolism model used by the IIAS.

A. Personalized Glucose–Insulin Metabolism Model

In order to provide the controller with glucose predictions ahead in time, a personalized glucose–insulin metabolism model (see Fig. 1) has been developed. The model is based on the combined use of a mathematical model (MM) module and a neural network (NN) module. The MM module consists of two Compartmental Models (CMs), which simulate sc insulin kinetics and glucose absorption into the blood from the gut, respectively, while the NN module incorporates a recurrent neural network (RNN), which models the patient's glucose kinetics. Information regarding recent sc insulin infusion rate and meal intake are fed to the MM module. CMs' outputs along with the recent sc glucose measurement are applied to the RNN that provides glucose predictions.

1) CM for sc Insulin Kinetics: Following an sc insulin injection, the rate of appearance of insulin in plasma $[R_i(t)]$ is described by a linear CM [22]:

$$\dot{I}_{sc1}(t) = -(k_d + k_{a1}) \cdot I_{sc1}(t) + u(t), \quad I_{sc1}(0) = I_{sc1ss} \tag{1}$$

$$\dot{I}_{sc2}(t) = k_d \cdot I_{sc1}(t) - k_{a2} \cdot I_{sc2}(t), \quad I_{sc2}(0) = I_{sc2ss} \tag{2}$$

$$R_i(t) = k_{a1} \cdot I_{sc1}(t) + k_{a2} \cdot I_{sc2}(t) \tag{3}$$

where I_{sc1} and I_{sc2} represent the amount of nonmonomeric and monomeric insulin in the sc space, respectively, $u(t)$(pmol/kg/min) is the exogenous insulin infusion rate, $k_d(0.0164\,\text{min}^{-1})$ is the rate constant of insulin dissociation, and $k_{a1}(0.0018\,\text{min}^{-1})$ and $k_{a2}(0.0182\,\text{min}^{-1})$ are the rate constants of nonmonomeric and monomeric insulin absorption, respectively.

2) CM for Glucose Absorption From the Gut: The physiological model of glucose intestinal absorption is a three-compartment nonlinear model with two compartments representing the stomach (solid and liquid phases) and the third compartment representing the intestine [22], [24]. The model assumes a constant rate of the intestinal absorption

but describes gastric emptying rate to be dependent on the total amount of nutrient in the stomach. Following a meal, the appearance rate of glucose in plasma, Ra (in mg/kg/min), is estimated by the following differential equations:

$$Q_{\mathrm{sto}}(t) = Q_{\mathrm{sto1}}(t) + Q_{\mathrm{sto2}}(t), \quad Q_{\mathrm{sto}}(0) = 0 \tag{4}$$

$$\dot{Q}_{\mathrm{sto1}}(t) = -k_{\mathrm{gri}} \cdot Q_{\mathrm{sto1}}(t) + D \cdot d(t), \quad Q_{\mathrm{sto1}}(0) = 0 \tag{5}$$

$$\dot{Q}_{\mathrm{sto2}}(t) = -k_{\mathrm{empt}}(Q_{\mathrm{sto}}) \cdot Q_{\mathrm{sto2}}(t) + k_{\mathrm{sto}} \cdot Q_{\mathrm{sto1}}(t),$$
$$Q_{\mathrm{sto2}}(0) = 0 \tag{6}$$

$$\dot{Q}_{\mathrm{gut}} = -k_{\mathrm{abs}} \cdot Q_{\mathrm{gut}}(t) + k_{\mathrm{empt}}(Q_{\mathrm{sto}}) \cdot Q_{\mathrm{sto2}}(t),$$
$$Q_{\mathrm{gut}}(0) = 0 \tag{7}$$

$$Ra(t) = \frac{f \cdot k_{\mathrm{abs}} \cdot Q_{\mathrm{gut}}(t)}{BW}, \quad Ra(0) = 0 \tag{8}$$

where Q_{sto}(in mg) is the amount of glucose in the stomach (Q_{sto1}, solid and Q_{sto2}, liquid phase), Q_{gut}(in mg) is the glucose mass in the intestine, k_{gri}(0.0558 min^{-}1) is the rate of griding, $k_{\mathrm{empt}}(Q_{\mathrm{sto}})$ (min^{-}1) is the rate constant of gastric emptying, which is a nonlinear function of Q_{sto} [22], and k_{abs}(0.057 min^{-}1) is the rate constant of intestinal absorption. Moreover, f(0.90), D(in mg) and *BW* (in kg) represent the fraction of intestinal absorption which appears in plasma, the amount of ingested glucose, and the body weight, respectively.

3) RNN: The use of the RNN toward the development of glucose–insulin metabolism model has been studied and its ability to accurately simulate glucose kinetics taking into account previous insulin and meal intakes, along with recent glucose levels, has been proven [25].

The RNN used in the proposed personalized glucose–insulin metabolism model is a fully connected multilayered perceptron NN with two recurrent loops, whose initial weights are set to unity [27], [28]. Subcutaneous glucose levels are considered as the state variable, while the rate of appearance of insulin in plasma and the glucose absorption into the blood from the gut as external inputs. Future glucose predictions are calculated as

$$y_{NN}(k+1) = y_{NN}(k) + RNN(y_{NN}(k), R_{\alpha}(k+1), R_i(k)) \tag{9}$$

where $y_{NN}(k+1)$ and $y_{NN}(k)$ are the sc glucose level predictions at instant *k*+1 and *k*, respectively. The RNN is trained using the Real-Time Recurrent Learning (RTRL) algorithm [29]. RTRL is a sequential, error-correction learning-based algorithm, which allows the RNN to update the weights while operating. The teacher-force version of the RTRL [29] has been applied, according to which the RNN replaces the previous glucose level prediction with the corresponding glucose level value, when available, in order to produce future predictions. During the operation of the IIAS, the RNN's weights are updated based on the RTRL algorithm, whenever a new glucose measurement is applied. This effectively enables the adaptation of the glucose–insulin metabolism model to the special characteristics of the patient and to the diurnal variation of the glucose metabolism. Thus, the on-line training of the RNN ensures its stable performance for the entire input space.

B. NMPC

As already mentioned, the NMPC uses a model that provides estimates of the future outputs of the system to be controlled. The NMPC is based on an optimizer, which computes at each sample time future control movements based on the minimization of an appropriate cost function. Particularly, at each instant: 1) future outputs $y_{NN}(k+i), i = N_1, ..., N_p$ are generated by the prediction model; 2) a cost function of the future control movements is minimized providing a set of future control signals; and 3) only the first element of the suggested control sequence is applied to the system. The procedure is repeated at the next instant.

The definition of the cost function is critical to controller's performance. The cost function used in this paper [see (10)], consists of the standard MPC formulated cost function [30] and one penalty term [31]. Particularly, in (10), first and second terms represent the deviations of the glucose predictions from the reference glucose level r, and the changes in future insulin infusion rates, respectively, while the third term consists of two penalty terms, which add soft constraints ($LG \leq y_{NN}(k+i) \leq HG$) to the optimization problem. The penalty terms increase the cost function whenever the glucose predictions are outside the acceptable range determined by the lowest (*LG*) and the highest (*HG*) desired glucose level. In (10), N_p is the prediction horizon, N_1 is the minimum prediction horizon, N_c is the control horizon, and Γ_e and Γ_u are the prediction and control weighting coefficients, respectively, while Γ_L, Γ_H are penalty coefficients:

$$J = \Gamma_e \sum_{i=N_1}^{N_p} (y_{NN}(k+i) - r)^2 + \Gamma_u \sum_{j=0}^{N_c} \Delta u^2(k+j)$$
$$+ \sum_{i=N_1}^{N_p} \Big[\Gamma_L [\min(0, y_{NN}(k+i) - LG)]^2$$
$$+ \Gamma_H [\min(0, HG - y_{NN}(k+i))]^2 \Big] \tag{10}$$

where

$$\Delta u(k) = u(k) \quad u(k\,1). \tag{11}$$

The cost function is minimized, subject to the constraints

$$u_{\min} \leq u(k) \leq u_{\max}. \tag{((12))}$$

Regarding the values of the aforementioned parameters, N_p is usually chosen to encompass all the response, which is significantly affected by the current control signal (sc insulin infusion). If there is no evidence about the dead time, $N_1 = 1$. The choice of N_c is usually based on a compromise between good glucose control performance and minimization of on-line computation. Furthermore, the selection of $r, LG, HG, \Gamma_L,$ and Γ_H is based on a compromise between ability to handle high glucose levels (caused by meal disturbances) and simultaneously prevent high values of insulin infusion rates, which would cause severe hypoglycaemic episodes.

In this paper, an automatic tuning algorithm, similar to the one proposed in [20], is adopted for the on-line update of the parameters N_p andΓ_u. These parameters play an important role

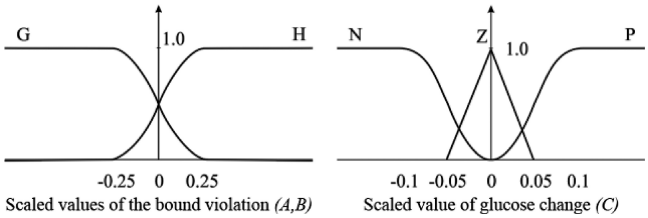

Fig. 2. Fuzzy sets for (a) bound violation and (b) bound violation rate.

to the controller's performance and stability. Although the time to the peak action of sc insulin is considered to be 50 min, the prediction horizon of 50 min is not always optimal, especially in the presence of meal disturbances where glucose levels change rapidly. This is of particular importance, since the sc glucose measurements are subject to inaccuracies and there are lags between the sc and the BG levels. The prediction weighting coefficient Γ_e is chosen to be constant in order to avoid simultaneous increase of N_p and Γ_e, which would increase on-line computation for the minimization of the cost function (10).

C. On-Line Tuning Algorithm of the NMPC Control Parameters

In order for the IIAS to rapidly reject meal disturbances and maintain postprandial glucose levels within the acceptable range, an automatic tuning algorithm has been developed. The tuning technique adapts on-line the NMPC control parameters in order to steer the closed-loop glucose response to satisfy preset time-domain specifications, which are provided by the user in the form of vectors of upper and lower bounds y^u and y^l, respectively. The new values of the NMPC control parameters are determined by fuzzy logic rules.

1) Overview of the Adaptation Algorithm: The proposed tuning method consists of two phases: the observation phase and the triggered phase. In the former, the future glucose profile is predicted, through the minimization of (10), by applying fixed values to the prediction horizon P_w and the control weighting coefficient Γ_{uw}. The obtained glucose profile is checked against the performance envelope. In case a bound violation occurs, the algorithm enters the triggered phase, otherwise the calculated insulin infusion rate is applied to the system and the whole procedure is repeated at the next instant. Particularly, at each instant *k,* the steps of the tuning algorithm are as follows.

Step 1. Produce future glucose profile using fixed NMPC control parameters through the minimization of the cost function (10). The calculated insulin infusion rate at this step is not applied to the patient.

Step 2. Check whether the predicted glucose profile, exceeds the limits of the performance envelope, i.e., y^u and y^l. If the limits are not exceeded, go to step 8.

Step 3. Determine the corresponding glucose prediction and the instant at which maximum bound violation occurs. Let this be at instant $k + m$.

Step 4. Calculate the scaled values of the bound violation (A, B), and the glucose change (C) at instant $k + m$.

Step 5. Determine the degree of membership of A, B, and C with respect to membership functions presented in Fig. 2.

TABLE I
BASE RULES OF THE TUNING ALGORITHM

No.	Rule	Result of Γ_u	Result of N_p
R1	If *A* is H and *B* is G	Then μ_Γ is SN	Then μ_{Np} is LP
R2	If *A* is G and *B* is H	Then μ_Γ is LN	Then μ_{Np} is LP
R3	If *A* is G and *B* is G	Then μ_Γ is ZE	Then μ_{Np} is SN
R4	If *A* is H and *C* is P	Then μ_Γ is LN	Then μ_{Np} is SP
R5	If *A* is H and *C* is Z	Then μ_Γ is SP	Then μ_{Np} is SN
R6	If *A* is H and *C* is N	Then μ_Γ is ZE	Then μ_{Np} is ZE
R7	If *B* is H and *C* is P	Then μ_Γ is SN	Then μ_{Np} is ZE
R8	If *B* is H and *C* is Z	Then μ_Γ is SP	Then μ_{Np} is SN
R9	If *B* is H and *C* is N	Then μ_Γ is ZE	Then μ_{Np} is SP

Step 6. Calculate the correction factors $[w_k(N_p), w_k(\Gamma_u)]$.

Step 7. Set the new parameters values as $N_{p,k} = N_{p,\text{previous}} + w_k(N_p)$ and $\Gamma_{u,k} = \Gamma_{u,\text{previous}}(1 + w_k(\Gamma_u))$, where $N_{p,\text{previous}}$ and $\Gamma_{u,\text{previous}}$ are calculated during the previous triggered phase of the tuning algorithm.

Step 8. Compute and apply the sc insulin infusion rate. Proceed to the next instant $k + 1$ and go to step 1.

The initial values of N_p and $\Gamma_u$are set to P_w and Γ_{uw}, respectively. In the presence of a meal disturbance, the control parameters are appropriately updated in order to reduce the overshoot and speed up the closed-loop response. To this end, N_p and Γ_u reset to their initial values whenever a new meal disturbance is applied.

2) Fuzzification: At the fuzzification stage, the scaled values of the bound violation and the glucose change at the instant where maximum violation occurs are fuzzified using the fuzzy sets shown in Fig. 2. Particularly, if upper-bound violation occurs, the scaled value$A$ is specified as

$$A = \frac{y_{NN}(k+m) - y^u}{y^u}. \tag{13}$$

If lower bound is violated, the scaled value$B$ is specified as

$$B = \frac{y^l - y_{NN}(k+m)}{y^l} \tag{14}$$

where $m(N_1 \leq m \leq N_p)$ is the instant at which maximum violation occurs. The definition of $A$and$B$guarantees positive value if the corresponding bound is violated and negative otherwise. The fuzzy set used for the fuzzification of the bound violation is shown in Fig. 2(a), and consists of two membership functions, namely: (G)ood denoted as G and (H)igh denoted as H. Therefore, if the upper bound is violated, then A belongs to H and B to G and vice versa.

The scaled value of glucose change at the instant where the maximum violation occurs is defined as follows:

$$C = \frac{y_{NN}(k+m) - y_{NN}(k+m-1)}{y_{NN}(k+m)}. \tag{15}$$

The scaled value of glucose change is transformed into a member of fuzzy sets, using the fuzzy set shown in Fig. 2(b). This fuzzy set consists of three membership functions: (P)ositive, (Z)ero, and (N)egative.

3) Inference Engine: The base rules governing the tuning guidelines are given in Table I. In this Table, μ_Γ and $\mu_N p$

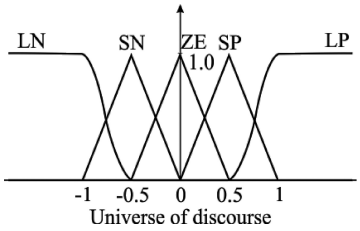

Fig. 3. Fuzzy set for the output of MPC parameters.

represent the rule output for N_p and Γ_u, respectively, while LN (Large Negative), SN (Small Negative), ZE (Zero), SP (Small Positive), and LP (Large Positive), are the output fuzzy sets represented by sigmoid and triangular membership functions as shown in Fig. 3. These functions are denoted as μ_5, μ_4, μ_3, μ_2, and μ_1, respectively. The base rules formulate the general understanding of the effect of parameters N_p and Γ_u in closed-loop response. In general, according to simulation experience [20], increasing N_p at a fixed nonzero value of Γ_u results in a faster response with less overshoot. Furthermore, reduction of Γ_u speeds up the response. We chose to increase N_p for both upper- and lower-bound violation, in order to prevent from large overshoots in glucose response—which may result in hyperglycaemic episodes—while speeding up the glucose response to avoid hypoglycemic episodes. Morever, since reduction of Γ_u speeds up the response, parallel reduction of N_p should be avoided, because this would lead to more aggressive control performance and might result to instability.

4) Defuzzification: At the defuzzification stage, the outputs of the base rules are properly processed in order to produce crisp values, which are used as factors to update the NMPC control parameters. The base rules of Table I, which are in linguistic form, are expressed in mathematical form using a common fuzzy rule operation [20]. Particularly, the AND command is transformed into minimum operation. For example, the results of Rule 1 in Table I can be written as follows:

$$\mu_{4,1}(\Gamma_u) = \min(\mu_H(A), \mu_G(B)) \tag{16}$$

$$\mu_{1,1}(N_p) = \min(\mu_H(A), \mu_G(B)) \tag{17}$$

where $\mu_H(A)$ is the degree of membership of A in the fuzzy set H and $\mu_{j,i}(\bullet)$ denotes the membership degree of $(\bullet)$ to the *j*th output membership function with respect to rule *i*. Therefore, the center of area principle [32] is applied in order to produce the correction factor Γ_u. For the prediction horizon, the correction factor is calculated as

$$w_k(N_p) = \sum_{j=1}^{n_R} \sum_{i=1}^{n_f} \mu_{j,i}(N_p)\delta_i \tag{18}$$

where n_R and n_f represent the number of rules and the number of membership functions, respectively, while δ_i is the value for the center location of the activated output membership function. Since N_p is an integer, the correction factor is rounded to the nearest integer.

III. Results and Discussion

In order to evaluate the performance and the robustness of the designed IIAS, the UVa T1DM simulator [21] has been used. The UVa T1DM simulator incorporates a modified version of the meal model developed by Man *et al.* [22]–[24] to adapt for T1DM subjects and insulin exogenous infusion [22]. In addition to the patient model, the simulator incorporates a sensor-related errors model to account for sensor noise and measurements' errors and a model for the sc insulin pump. The UVa T1DM simulator simulates a sufficiently large cohort of *in silico* subjects in order to cover the wide variability observed among diabetic population and serves as an *in silico* environment for preclinical testing trial. In this paper, the proposed IIAS has been tested with the ten adults' population available in the training version of the UVa simulator. The ten patients are characterized by a wide diversity in their parameters (e.g., body weight and insulin sensitivity) and, therefore, can serve as small population to evaluate the controller [8], [9].

The evaluation of the IIAS is performed in two stages: 1) evaluation of the predictive performance of the personalized glucose–insulin metabolism model; and 2) evaluation of the controller considering several simulation scenarios.

A. Evaluation of the Personalized Glucose–Insulin Metabolism Model

Open-loop experiments were performed in order to generate the data for the training and testing of the personalized glucose–insulin metabolism models. Particularly, each *in silico* subject was fed for one week, with 1) basal rate, which keeps the specific patient at its fasting state (provided by the UVa T1DM simulator), 2) insulin bolus whenever carbohydrates were ingested (provided by the UVa T1DM simulator), and 3) various meal profiles corresponding to breakfast, lunch, dinner, and two snacks. In order to account for patient real life, meal times and amounts values were randomly chosen within the following ranges: {[6–8 A.M.], [12–2 P.M.], [4–4.30 P.M.], [6–8 P.M.], [10–11 P.M.]} and {[40–60 g], [60–80 g], [0–10 g], [70–90 g], and [0–10 g]}, respectively. Data corresponding to the first four days were used for training the model, while the remaining three days were used for its testing. The predictive performance of the glucose–insulin metabolism model was evaluated considering a prediction horizon equal to 30 min with a 5-min resolution.

Root-mean-squared error (RMSE) and correlation coefficient (CC) corresponding to the testing dataset were calculated to evaluate the performance of the glucose–insulin metabolism model in terms of matching the predicted glucose with the original ones. Furthermore, in order to evaluate the clinical accuracy of the glucose predictions and their effects on decisions to avoid hypo- and hyperglycemic events, the continuous error grid analysis [33] has been used. The estimates of point and rate precision are combined in a single accuracy assessment for each of the BG ranges: hypoglycemia, euglycemia, and hyperglycemia. To this end, the point error grid analysis (P-EGA) and the rate error grid analysis (R-EGA) are combined in the three clinically relevant regions of hypoglycemia, euglycemia, and hyperglycemia. Clinically accurate glucose predictions are

TABLE II
ERROR MATRIX COMBINING R-EGA AND P-EGA

		P-EGA										
		Hypoglycemia			Euglycemia			Hyperglycemia				
		A	D	E	A	B	C	A	B	C	D	E
R-EGA	A	69.61	13.26	0.00	75.35	4.99	0.02	38.00	4.80	0.00	0.00	0.00
	B	6.63	1.10	0.00	8.84	1.41	0.00	29.20	5.20	0.00	0.00	0.00
	uC	0.00	2.76	0.00	4.22	1.38	0.07	17.20	0.00	0.00	0.00	0.00
	IC	6.08	0.55	0.00	3.16	0.54	0.01	5.60	0.00	0.00	0.00	0.00
	uD	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	ID	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	uE	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	IE	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	AR	76.24			90.61			77.20				
	BE	6.08			9.29			22.80				
	ER	17.68			0.00			0.00				

AR: Accurate readings, BE: Benign errors, ER: Erroneous errors.

TABLE III
IIAS TUNING

Weighting Coefficients				Prediction, minimum and control horizon		
Γ_{uw}	Γ_L	Γ_H	Γ_e	P_w	N_1	N_c
10	10	1	100	10	1	1
Limits of performance envelop (*mg/dl*)		**Glucose target range (*mg/dl*)**		**Reference glucose (*mg/dl*)**	
y^l	y^u	LG	HG	r	
90	140	70	180	110	

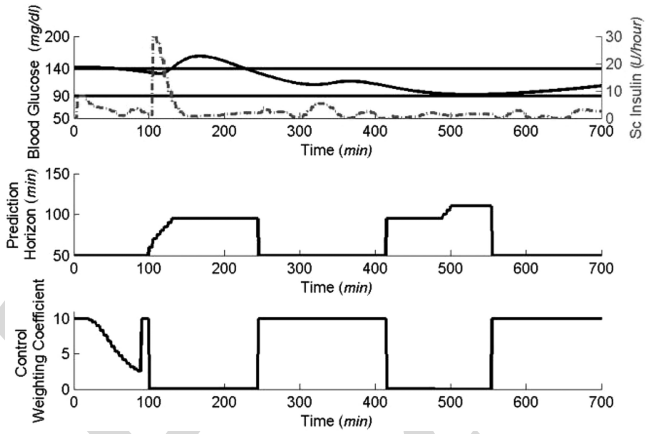

Fig. 4. Upper panel: Adult 5, sc insulin infusion rates (dashed-dotted line), BG data (solid line), limits of performance envelop [90–140 mg/dl] (dashed-line). Middle panel: Prediction horizon. Low panel: control weighting coefficient.

considered to be within the zones A and B on both P-EGA and R-EGA. Clinically benign errors correspond to acceptable point accuracy (i.e., A or B P-EGA zones) and significant errors in rate accuracy (i.e., C, D, or E R-EGA zones), which are unlikely to lead to negative clinical consequences. Clinically significant errors are those that could lead to a negative clinical action and therapeutic consequences.

From both the RMSE (mean $\pm$ standard deviation (SD): 15.67 $\pm$ 6.03) and CC (mean $\pm$ SD: 0.78 $\pm$ 0.16), it is obvious that the predicted glucose profile follows the original one. Moreover, the error matrix combining P-EGA and R-EGA, presented in Table II, shows that erroneous errors are observed in the range of hypoglycemia.

Although the proposed glucose–insulin metabolism model uses CMs for the simulation of sc insulin kinetics and glucose absorption from the gut, similarly with the UVa T1DM simulator, it adopts a completely different approach based on the RNN to map plasma insulin to sc glucose. The latter consists the most essential module of the model. The previously presented prediction accuracy assessment refers to primarily testing the RNN and its effective combination with the CMs. The predictive performance of the glucose–insulin metabolism model has been assessed in a previous study [25], and the superiority of the used RNN over a feedforward neural network (FNN) has been demonstrated [26], using real patient data.

B. IIAS Tuning

The IIAS provides the estimated insulin infusion rates every 5 min. Regarding the performance envelope, lower y^l and upper y^u bounds were chosen to be constant and equal to 90 and 140 mg/dl, respectively, corresponding to a rather narrow target range. Particularly, 90 mg/dl corresponds to the minimum BG level of optimal glucose control [21], while 140 mg/dl is the maximum 2-h postprandial BG level [8]. Moreover, LG and HG were set to 70 and 180 mg/dl, respectively, since, in this paper, BG concentrations between 70 and 180 mg/dl are considered to be within the target range for T1DM. The values of the weighting coefficients Γ_L,Γ_H, and Γ_e were chosen to be 10, 1, and 100, respectively. The rather largeΓ_e value causes quite high insulin infusion rates, which are necessary to prevent hyperglycemic episodes after meal ingestion. Furthermore, $\Gamma_L$is large enough to appropriately penalize for glucose predictions lower than 70 mg/dl and thus preventing from extremely high insulin infusion rates that would lead to hypoglycemic episodes. Parameter P_w is set to 10 corresponding to 50 min in order for the prediction horizon to account for sc insulin action. The control weighting coefficient Γ_{uw} is set to 10, which is high enough to ensure stability of the glucose controller. N_c is set to 1 (its minimum possible value), corresponding to 5 min, in order to minimize on-line computation and $N_1 = 1$ (see Section II-B). Moreover, $u_{\min} = 0$U/h while $u_{\max} = 70$U/h in accordance with the maximum allowable values for patients' safety and pump's hardware limitations [8]. The reference glucose level r is set to 110 mg/dl, which corresponds to the minimum value of the risk index. The numerical values of the parameters are summarized in Table III.

In order to clearly present the evolution of the prediction horizon N_p along with the control weighting coefficient Γ_u over time, the following simulation scenario has been studied: Adult 5 was fed with 50 g at time 100 min. In Fig. 4, BG levels, sc insulin infusion rates along with prediction horizon, and control weighting coefficient are shown. As can be observed, the tuning algorithm does not always enter the triggered phase. It enters the triggered phase whenever there is danger for BG levels to exceed the limits of the performance envelop (90–140 mg/dl), and

TABLE IV
DAILY MEAL PROFILES

Day	1					2		
Meal Time (h)	07:00	12:00	16:00	18:00	23:00	07:30	13:00	18:30
Meal Amounts (g)	45	70	0 5	80	5	40	85	60

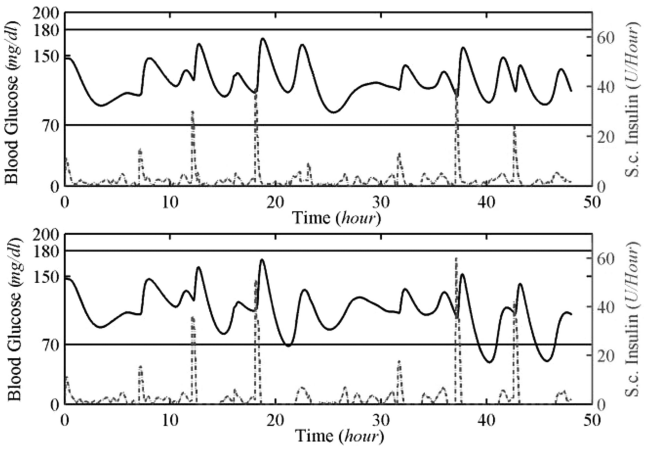

Fig. 5. Control results for Adult 3 under IIAS (upper panel) and fixed parameters NMPC (low panel). Estimated insulin infusion rates (dashed-dotted line), BG data (solid line), glucose target range [70–180 mg/dl].

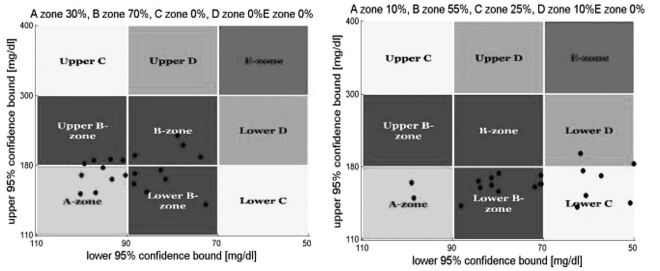

Fig. 6. CVGA for the ten adults of the Uva T1DM simulator. *left:* IIAS (30% in zone A and 70% in zone B). *Right:* NMPC (10% in zone A, 55% in zone B, 25% in zone C, and 10% in zone D).

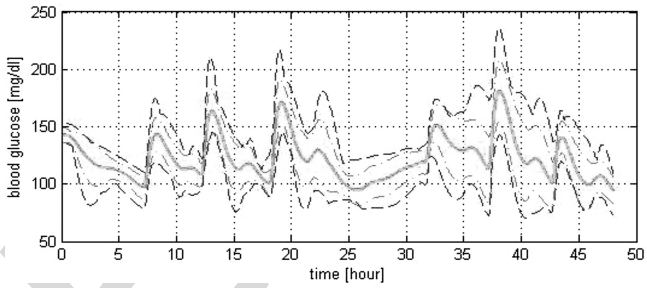

Fig. 7. BG trace for the ten adults of the UVa T1DM simulator when the IIAS is applied. Mean response (solid curve), SD (dashed-dotted curve), and min/max envelop (dashed curve).

appropriately updates the NMPC parameters, managing to reset and maintain glucose levels within the performance envelop.

C. Evaluation of the Controller—Simulation Scenarios

To evaluate IIAS's performance under realistic conditions, several scenarios have been simulated. Particularly, the IIAS has been tested for its ability to handle meal disturbances, fasting conditions, interpatient variability, robustness against erroneous estimation of carbohydrates' amount in ingested meals, and intraday variation in physiological parameters. Furthermore, in order to study the effectiveness of the tuning algorithm, two simulation scenarios have been studied: with (IIAS) and without (fixed parameter NMPC) the tuning algorithm.

1) Evaluation of the IIAS Against Fixed Parameter NMPC: Both controllers have been tested with the ten adults' population. It should be noted that in the case of fixed parameter NMPC, N_p and Γ_e are fixed over time and set both to 10. The simulation scenarios consider a two-day testing period with varying meal timings and amounts (see Table IV).

The superiority of the IIAS over fixed parameter NMPC is shown in Figs. 5 and 6. Fig. 5 presents the estimated sc insulin infusion rates along with the corresponding BG levels, when Adult 3 is fed with the two-day meal protocol and regulated using the IIAS (upper panel) and the fixed parameter NMPC (low panel), respectively. It should be noted that the controllers activate either the basal or the bolus action provided from the insulin pumps and hold the estimated insulin dose constant between sampling instants (per 5 min). As shown in Fig. 5, the application of fixed parameter NMPC caused severe hypoglycaemic episodes, which are defined as BG levels lower than 60 mg/dl [9]. On the other hand, the IIAS managed to maintain BG levels within the target range (70 --180 mg/dl), while achieving less fluctuations over time.

The control variability grid analysis (CVGA) [34], shown in Fig. 6, serves as a tool to evaluate the controllers with the entire population. Each point in the CVGA represents the lower and the upper bound of 95% confidence interval of BG data for one patient during one day. Zones A and B are considered to represent good glucose control. CVGA demonstrates that IIAS provides superior performance over the fixed parameter NMPC, managing to keep all the patients inside the zones A and B. Furthermore, the min/max envelop presented in Fig. 7 indicates that the BG levels for the hard-to-control patients are within the acceptable range 70–236 mg/dl, managing to avoid hypoglycemic episodes and severe hyperglycemic episodes (above 280 mg/dl).

Moreover, numerical metrics of average glycemia, percentage within the target range (70–180 mg/dl), risk associated with extreme glucose deviations [35] (low blood glucose index (LBGI), high blood glucose index (HBGI), and total risk index), are used to provide more details about the controller performance. In Table V, the obtained numerical results, when the IIAS is applied on all 10 patients, are presented. It can be seen that most of the time, BG levels are kept within the target range, while the risk indices (LBGI, HBGI, and total risk index) have low values, showing that tight glycemic control is achieved.

2) Robustness to Meal Estimation Errors: Since the proposed IIAS is informed about the carbohydrates amount of the upcoming meal, its ability to handle meal estimation errors is of utmost importance. To this end, the IIAS has been tested

TABLE V
CONTROL PERFORMANCE OF THE IIAS AND THE OPEN-LOOP PREADJUSTED TREATMENT

Simulation scenario	mean BG Mean (±SD)	Pre meal BG Mean (±SD)	Post meal BG Mean (±SD)	% below target Mean (±SD)	% above target Mean (±SD)	% within target Mean (±SD)	LBGI Mean (±SD)	HBGI Mean (±SD)	risk index Mean (±SD)
Accurate meal announcement (IIAS)	122.25 (9.06)	114.27 (12.31)	139.78 (9.19)	0 (0)	2.51 (2.76)	97.49 (2.76)	0.35 (0.35)	1.09 (0.64)	1.45 (0.66)
40% OEE (IIAS)	117.54 (7.91)	105.57 (8.99)	132.26 (12.68)	1.01 (1.51)	2.40 (3.13)	96.58 (2.83)	0.72 (0.34)	0.92 (0.62)	1.64 (0.66)
40% UEE (IIAS)	120.28 (10.61)	110.11 (11.13)	137.44 (14.30)	5.15 (5.07)	4.36 (4.43)	90.48 (6.66)	0.99 (0.71)	1.27 (0.86)	2.26 (1.10)
Intraday variation in physiological parameters (IIAS)	122.47 (7.58)	128.25 (15.79)	133.31 (15.42)	0.66 (0.87)	3.41 (3.25)	95.91 (3.61)	0.4 (0.27)	1.2 (0.65)	1.6 (0.71)
Open loop preadjusted treatment	130.50 (6.92)	124.4 (6.65)	145.16 (10.80)	1.14 (3.61)	3.68 (3.78)	95.17 (5.59)	0.30 (0.48)	1.65 (0.69)	1.96 (0.91)

against overestimation errors (OEE) and underestimation errors (UEE) up to 40%. Table V demonstrates the mean values and the SDs of the numerical metrics over the results obtained for the ten adults. Although certain hypoglycemic and hyperglycemic episodes occurred, none of them was severe. It is noteworthy that the IIAS is able to handle meal estimation errors and regulate properly insulin infusion rate, in order to keep glucose within the target range most of the time.

3) Robustness Against Intraday Variation in Physiological Parameters: One of the critical challenges for a glucose control algorithm is robustness against intraday variation in physiological parameters. In order to represent diurnal metabolic variations, time variation of the *in silico* patient-specific physiological parameters was considered, as drawn from a normal distribution with SD of 10%. This distribution was chosen to capture the expected variation in insulin sensitivity [36]. In Table V, the obtained numerical results over the ten adults are presented. The IIAS achieved good glucose control, managing to maintain BG levels within the acceptable range for 95.17% of the total time, avoiding severe hypoglycemic and hyperglycemic episodes. Furthermore, the risk indices are low, proving the IIAS' ability to handle intraday variation in physiological parameters.

D. Comparison of the IIAS With Other Glucose Controllers

In order to prove the efficacy of the IIAS, its performance has been compared with that of other open-loop and closed-loop glucose controllers.

1) Open-Loop Preadjusted Treatment: The open-loop preadjusted treatment is supported by the UVa T1DM simulator. The ten *in silico* adults of the simulator followed a protocol of meals presented in Table IV. A matching insulin bolus and a basal rate were provided by the UVa T1DM simulator for each *in silico* adult and the results obtained by applying the open-loop preadjusted treatment are presented in Table V. It can be observed that the IIAS achieves better glucose control.

2) Adaptive Basal Therapy: Since the basal rate provided by the UVa T1DM simulator is nonoptimal, the IIAS has been compared with adaptive basal therapy [37]. The latter suggests adaptation of the basal rate as a gain multiplier based on the current CGM glucose value and its rate of change. Identical meals used in [37] provided input to the ten *in silico* adults, which were regulated by the IIAS. In particular, the ten *in silico* adults followed a one-day meal scenario of 40, 75, 60 g of carbohydrates at 7:00 A.M., 12:00 A.M., and 6:00 P.M., respectively. Results obtained from the application of the IIAS and the adaptive basal therapy are presented in Table VI in terms of hyperglycemia and severe hypoglycemia (<60 mg/dl) along with risk indices. It can be observed that the IIAS provides better glucose control performance.

TABLE VI
COMPARISON OF THE IIAS WITH THE ADAPTIVE BASAL THERAPY [37]

Controller	Hypo-percent (<60mg/dl)	Hyper-percent	Safe percent	risk index
IIAS	0.00 ± 0.00	0.60 ± 1.52	99.40 ± 1.52	0.99 ± 0.43
Adaptive Basal Therapy	0.5 ± 0.01	1.3 ± 0.03	98.2 ± 0.03	1.7 ± 0.59

3) Artificial Pancreatic β-Cell Based on Zone-MPC: In order to justify the use of the proposed nonlinear approach to improve glucose control, the IIAS has been compared with an artificial pancreatic β-cell based on zone-MPC that uses mapped-input data and is adjusted automatically by linear difference personalized models [38]. The ten *in silico* adults followed the three meal scenario used in [38]—consisting of 75, 75, and 50 g of carbohydrates at 7 A.M., 1 P.M., and 8 P.M., respectively—and were regulated by the IIAS. The obtained results are presented in Table VII. It should be noted that no severe hypoglycemic (<60 mg/dl) and hyperglycemic episodes (>280 mg/dl) have been observed during the operation of the IIAS- and zone-MPC-based glucose controllers. As discussed in [38], a single severe hypoglycemic event occurred during the operation of the MPC with set point at 110 mg/dl. When the *in silico* adults were regulated by the IIAS, the mean glucose value was closer to the desired glucose level, while the average SD of the mean glucose value was lower, indicating lower variability in glucose control performance among the *in silico* adults. Furthermore, lower

TABLE VII
COMPARISON OF THE IIAS WITH THE ARTIFICIAL PANCREATIC B-CELL [38]

Controller	Mean Glucose	Hyper- percent
IIAS	117.61 ± 7.11	0.81 ± 2.05
Zone-MPC (bounds: 80-140 *mg/dl*) (Experiment 5 in [38])	152.00 ± 28.00	27.99 ± 20.51
Zone-MPC (bounds: 100-120 *mg/dl*) (Experiment 6 in [38])	141.00 ± 29.00	20.75 ± 19.45
MPC (set-point 110 *mg/dl*) (Experiment 7 in [38])	136.00 ± 29.00	17.54 ± 18.58

percentage of hyperglycemia was observed during the operation of the IIAS. The obtained improved glucose control performance is related to higher on-line computation.

Summarizing, the use of a data-driven model for the simulation of the blood glucose–insulin kinetics (real-time self-adaptive NN) permits personalization of the system and efficient handling of a changing environment. It is important to note that the incorporation of the RNN makes the model capable of simulating glucose–insulin kinetics taking into account patient specific information related to ingested carbohydrates, sc insulin infusion rate, and glucose records from CGMS that are usually available in clinical practice. The metabolic behavior of a specific patient is captured through the real-time update of the RNN's weights. Whenever a new glucose measurement is applied to the model, the RNN's weights are appropriately adapted in order to adjust to the new metabolic behavior. According to above, the RNN consists the most essential module of the personalized glucose–insulin metabolism model. Thus, the similarities of the latter with the UVa T1DM simulator regarding the use of CMs for the sc insulin kinetics and the glucose absorption from the gut do not limit the reliability of the presented assessment of the IIAS performance. This is of particular importance since the IIAS has demonstrated robustness against intraday variation in physiological parameters. Moreover, the tuning algorithm for the real-time update of the NMPC control parameters greatly improved controller's performance, demonstrating its importance toward the tuning of glucose controllers based on MPC.

Clinical evaluation of the IIAS on real T1DM patients is in progress. Future research activities are focused on the optimization of the proposed IIAS and its complete integration into a telecommunication platform for the efficient management and treatment of patients with T1DM [39].

IV. CONCLUSION

A novel IIAS based on NMPC has been proposed in order to estimate optimal insulin infusion rates. The proposed approach introduces 1) a personalized model based on the combined use of CMs and an RNN for the simulation of glucose–insulin metabolism and 2) an automatic algorithm for the on-line adaptation of NMPC parameters. The performance of the IIAS has been *in silico* evaluated using the ten adults' population, available in the training version of the UVa T1DM simulator. The obtained results demonstrate that the proposed IIAS is robust with respect to its ability to handle various conditions characterized by sensor errors, lags, meal disturbances, large meal estimation errors, interpatient variability, and intraday variation in physiological parameters.

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