Control-Relevant Models for Glucose Control Using *A Priori* Patient Characteristics

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***Abstract*—One of the difficulties in the development of a reliable artificial pancreas for people with type 1 diabetes mellitus (T1DM) is the lack of accurate models of an individual's response to insulin. Most control algorithms proposed to control the glucose level in subjects with T1DM are model-based. Avoiding postprandial hypoglycemia (<60 mg/dl) while minimizing prandial hyperglycemia (>180 mg/dl) has shown to be difficult in a closed-loop setting due to the patient–model mismatch. In this paper, control-relevant models are developed for T1DM, as opposed to models that minimize a prediction error. The parameters of these models are chosen conservatively to minimize the likelihood of hypoglycemia events. To limit the conservatism due to large intersubject variability, the models are personalized using *a priori* patient characteristics. The models are implemented in a zone model predictive control algorithm. The robustness of these controllers is evaluated *in silico*, where hypoglycemia is completely avoided even after large meal disturbances. The proposed control approach is simple and the controller can be set up by a physician without the need for control expertise.**

***Index Terms*—Artificial pancreas, control-relevant modeling, model predictive control (MPC), type 1 diabetes mellitus (T1DM).**

I. Introduction

FOR people with type 1 diabetes mellitus (T1DM), the pancreatic β-cells do not secrete endogenous insulin, which is essential for glycemic control. Treatment with exogenous insulin is needed to avoid extended periods of high glucose levels (hyperglycemia, glucose concentrations >180 mg/dl) that may lead to complications. Intensive treatment with either multiple daily insulin injections or with an external insulin infusion pump is a demanding task for the individuals with T1DM and their families. It requires frequent blood glucose measurements, insulin dose estimation, and estimation of meal sizes. An automated system (an artificial pancreas) for insulin delivery for T1DM has been the focus of research for more than 40 years [1]–[3], both to improve glycemic control and to ease the day-to-day diabetes management. Overviews of more recent work are available [4], [5].

In the artificial pancreas considered here, glucose levels are measured by a subcutaneous continuous glucose monitor (CGM) and insulin is delivered by a continuous subcutaneous insulin infusion (CSII) pump. The insulin dose is calculated by the control algorithm. There is a substantial time delay between insulin delivery and the appearance of insulin in the blood stream with the use of subcutaneous (sc) insulin delivery. This time delay due to sc insulin administration limits the achievable control performance.

While the artificial pancreas is expected to improve glycemic control, closed-loop control introduces certain risks [5]. The main risk is hypoglycemia (glucose concentrations <60 mg/dl) after meal-induced hyperglycemia, caused by overdelivery of insulin. The effect of overdelivery is not immediate due to the time delay, and even if the insulin delivery is turned OFF, hypoglycemia may not be avoidable [5]. One of the problems in the development of reliable closed-loop control algorithms is the lack of accurate models for individual subjects. If an accurate model of a subject's response to insulin is available, the controller design is straightforward. If no accurate models are available, the patient–model mismatch can cause hypoglycemia and will limit control performance.

It is well known that good control performance can be achieved with approximate models, provided that the modeling is linked to the control objective, see, for example, [6] and [7]. In this paper, simple, personalized control-relevant models are developed for T1DM. The goal of this paper is to show that with these control-relevant models, good control performance can be achieved and hypoglycemia can be avoided. The main difference between a control-relevant model and most models that have been used for control in T1DM is that it is developed specifically to achieve the desired control performance, rather than optimized for the prediction of future glucose values.

Data-based models for individual subjects are often inaccurate because clinical data in T1DM are not sufficiently rich to identify accurate models [8], [9]. Autoregressive models can be used to overcome the identifiability issues [10], [11], but

Manuscript received June 17, 2011; revised August 27, 2011; accepted October 27, 2011. Date of publication November 22, 2011; date of current version June 20, 2012. This work was supported by the Juvenile Diabetes Research Foundation under Grant 22-2009-797 and Grant 22-2009-796 and by the National Institutes of Health under Grant DK085628-01. *Asterisk indicates corresponding author.*

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Digital Object Identifier 10.1109/TBME.2011.2176939

they cannot be used for control because they do not contain an exogenous input. Identification methods [12] and protocols that improve the identifiability of the models have been suggested [13]–[17], but the possibilities for experiment design are limited due to strict safety requirements and constraints on clinical protocols.

Average or "population" models, either data based or from first principles, are of limited accuracy due to the large intersubject variability. Personalized models or personalized controller approaches have, therefore, been proposed for control [18]–[23]. A personalized approach corresponds to standard clinical practice. Current treatment for T1DM uses subject-specific basal insulin delivery rates, insulin to carbohydrate (CHO) ratios, and correction factors. However, in the aforementioned studies, hypoglycemia could not be avoided for all subjects; the proportional integral derivative controllers proposed in [24] could not avoid hypoglycemia either.

The use of safety layers and constraints on the delivered insulin has been proposed to avoid hypoglycemia after meal-induced hyperglycemia [25]–[28]. Although a safety system will be part of a final design of the artificial pancreas, it should not replace a safe controller design. A good control algorithm should meet performance specifications and prevent hypoglycemia for normal operating conditions. The control-relevant models proposed in this paper use *a priori* information to maintain robustness margins when there is a mismatch between the model and the patient. The approach is personalized using *a priori* (i.e., easily available) patient characteristics to limit conservatism.

The proposed models can be used to design any controller that is based on a linear model. In this paper, the models are implemented in a zone model predictive control MPC algorithm [29]. *In silico*, experiments on 100 virtual subjects show that good control performance is achieved, while hypoglycemia is avoided even for large meal challenges of up to 160 g of CHO. Designing the proposed zone MPC controller for an individual requires only the subject's total daily insulin (TDI) and an indication from the physician about the accuracy of this value. No time-consuming identification step is needed, and no control expertise is needed to set up the controller.

This paper is organized as follows. In Section II, the T1DM control problem is described and control specifications are given. Personalized control-relevant models are developed in Section III. The implementation of these models in a zone MPC algorithm is described in Section IV. Results of an *in silico* trial for 100 subjects are given in Section V, followed by a discussion and conclusions.

II. Control Specifications

In this *in silico* study, an artificial pancreas that uses CGM measurements and a CSII pump is considered. The sampling period for measurement and control is 5 min. The system is challenged by meal disturbances that are not announced to the controller. No feedforward prandial insulin bolus is given. The control system is required to

1) overcome unannounced meal challenges;
2) minimize postprandial hypoglycemia.

As described in Section I, avoiding postprandial hypoglycemia has shown to be a difficult challenge in both *in silico* and clinical trials. The occurrence of postprandial hypoglycemia in model-based control systems can be explained by a patient–model mismatch. Due to a patient–model mismatch, the designed controller can be either too conservative or too aggressive. If the controller is too conservative, meal challenges will not be overcome as quickly as expected. If the controller is too aggressive, a meal disturbance will cause an excessive corrective response, which explains the low glycemic values following postprandial hyperglycemia. The hypoglycemia is expected to be more severe if the postprandial hyperglycemia was more pronounced, i.e., for larger meal sizes.

III. Personalized Models for Control

Good control performance can be obtained with approximate models, if these models are relevant for control [6], [7], especially if the experimental conditions can be manipulated without constraints. In T1DM, experimental conditions are limited and such identification techniques cannot be applied. However, sophisticated first principle models are available, for example, from [30]. These models cannot be connected directly to individuals with T1DM, but they do provide a description of the dynamics of the insulin–glucose system and the range of the intersubject variability. In the following, this *a priori* information will be used to define control-relevant models for T1DM.

This paper focuses on linear controllers that use a linear model for control design purposes. It is assumed that any designed controller provides acceptable performance and robustness margins in closed loop with the model that it is designed for. If this model is control relevant, this controller will also be safe when applied to an individual with T1DM, i.e., the robustness margins will be preserved in case of a reasonable model–patient mismatch. The trade-off for a robust design without hypoglycemia is in the closed-loop performance.

For robustness, an approximate model needs to be accurate at frequencies around the closed-loop bandwidth. *A priori* information from first principles models [30] will be used to define models that underestimate the robustness margins. If a controller based on this model is applied to an individual with T1DM, the margins will be maintained and hypoglycemia can be avoided. To limit the loss of performance due to the model–patient mismatch, the models are individualized using *a priori* patient characteristics.

In the following, nonparametric models are identified from the UVa/Padova metabolic simulator [30]. These models are used as an indication of the dominant dynamics and the intersubject variability. The expected closed-loop bandwidth is estimated and parametric models are identified to provide a model structure that captures the dynamics around this expected bandwidth. This model structure is then used to define a fixed model that underestimates the robustness margins. The gain of the model is personalized using *a priori* patient characteristics. These personalized models will lead to a safe controller only if the hypothesis that the robustness margins are underestimated is met.

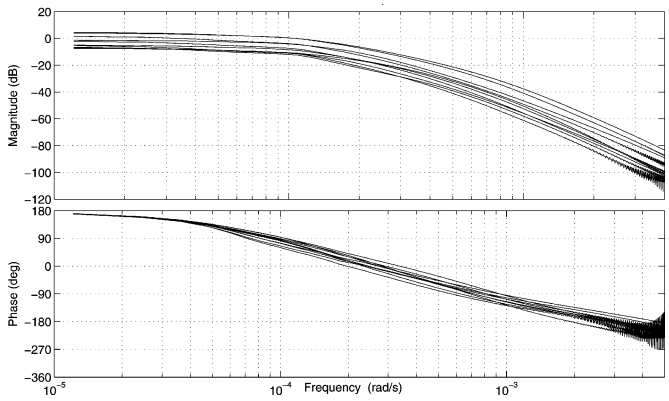

Fig. 1. Bode diagrams of the ETFE for ten subjects of the UVa/Padova metabolic simulator [30], from insulin (pmol/min) to glucose (mg/dl). The maximal frequency shown is 0.005 rd/s.

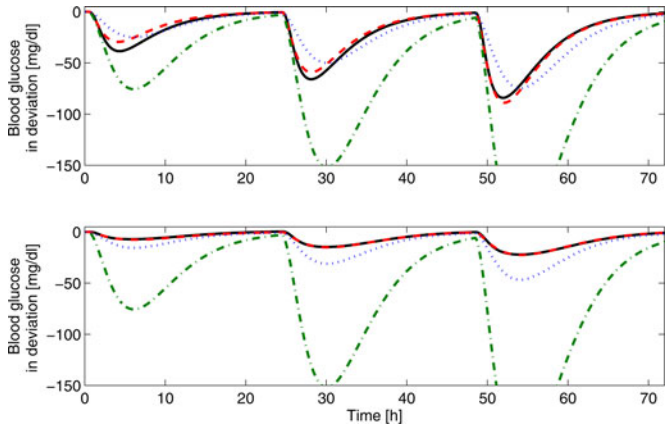

Fig. 2. Deviation from the fasting blood glucose in response to series of insulin boluses as described in the text for two subjects of the UVa/Padova simulator. The first subject is an example of an individual with high insulin sensitivity, and the second subject shows a slow response to insulin. (Black continuous line) Measured response. (Dashed line) Response of identified OE model (partly overlaps the measured response). (Dash-dotted line) Response of M_r. (Dotted line) Response of the personalized model M_i.

Guidelines on how to choose the model are given for clinical indications when violation of this hypothesis can be expected.

Note that even though the proposed approach is based on linear control techniques, the developed control algorithms are evaluated on the nonlinear UVa/Padova metabolic simulator [30]. A population of ten representative subjects from the UVa/Padova metabolic simulator [30] is used to develop the models and design the controllers. In Section V, a different population of 100 *in silico* subjects is used for validation.

A. Control Relevant Models

A frequency response function (FRF) is estimated for each of the ten subjects from an open-loop experiment performed in simulation. A first insulin bolus of one unit is given after the fasting blood glucose corresponding to the subject's basal rate is reached. A second insulin bolus of two units is given 24 h after the first bolus. A third bolus of three units is given after 48 h. The total simulation time is 72 h. The venous blood glucose concentration was available every 5 min for the ten subjects. This protocol cannot be performed clinically, but *in silico* this informative experiment provides the required information, without the additional noise of CGM measurements.

For each subject, an empirical transfer function estimate (ETFE) is calculated [31]. Although the venous blood glucose value does not contain stochastic noise, a window size of $116 = N/4$, where N is the total number of samples, was used to reduce the effect of nonlinearities and truncation. The Bode diagrams of the estimated responses are given in Fig. 1. Note that these models are indicative of the behavior but are by no means an exact representation of the system.

Because an insulin increase leads to a decrease of glucose concentration, the phase of the transfer functions is 180° degrees at low frequencies. The crossover frequency for these open-loop systems is the frequency at which the phase angle curve crosses zero degrees and is situated at approximately 2×10^{-4} rd/s. Since insulin can only be added and cannot be removed in case of overdelivery, the achievable bandwidth is limited. The closed-loop bandwidth is expected to be situated between 5×10^{-5} and 4×10^{-4} rd/s, close to the crossover frequency. These values are verified in Section IV.

Any model structure that captures the dynamics around the expected bandwidth would be appropriate for control purposes. In the following, parametric models are identified that not only capture the dynamics around the bandwidth as required, but also have a time response that resembles the response of glucose to insulin. A parametric model is estimated for each subject using the output-error structure [31]. The input variable to the model is the insulin delivery by the CSII pump, and the output variable is the blood glucose concentration (deviations from the steady state). Note that in a control application, CGM measurements will be used which cause an additional time delay. The estimated time delay for the ten subjects was 2–4 samples. The time delay of the models was, therefore, 2 samples, or 10 min. Third-order models M were defined as

$$M(q^{-1}) = \frac{bq^{-3}}{1 + a_1 q^{-1} + a_2 q^{-2} + a_3 q^{-3}} \tag{1}$$

where q^{-1} is the backward shift operator and $a_1, \ldots, a_3$ and b are the model parameters to be identified. The percentage of the training data that is explained by a model is given by fit:

$$\text{fit} = 100(1 - \|y_p - y\|)/\|y - \bar{y}\| \tag{2}$$

where y is the measured output, y_p is the output predicted by the model, $\|\cdot\|$ is the two-norm, and $\bar{y}$ is the mean value of the measured output. The ten identified models achieve a fit between 89.5% and 98.6% on the training data. The improvement for additional parameters is marginal. The improvement for different time delays is also marginal. Note that no validation data are used because noise-free venous blood glucose levels were used. The model error is mainly due to nonlinearities. The model response to the series of insulin boluses is compared to the actual response for two subjects in Fig. 2. The pole locations of the ten models are given in Table I.

TABLE I
LOCATION OF THE POLES OF THE IDENTIFIED OUTPUT ERROR MODELS FOR THE TEN SUBJECTS

1st pole	2nd pole	3rd pole
0.98 + 0.01i	0.98 + 0.01i	0.92
0.99	0.95 + 0.06i	0.95 + 0.06i
0.96	0.95 + 0.01i	0.95 + 0.01i
0.98	0.94	0.86
0.97 + 0.01i	0.97 + 0.01i	0.93
0.99	0.96	0.92
0.98	0.95	0.89
0.98 + 0.01i	0.98 + 0.01i	0.83
0.99 + 0.01i	0.99 + 0.01i	0.84
0.98	0.95 + 0.02i	0.95 + 0.02i

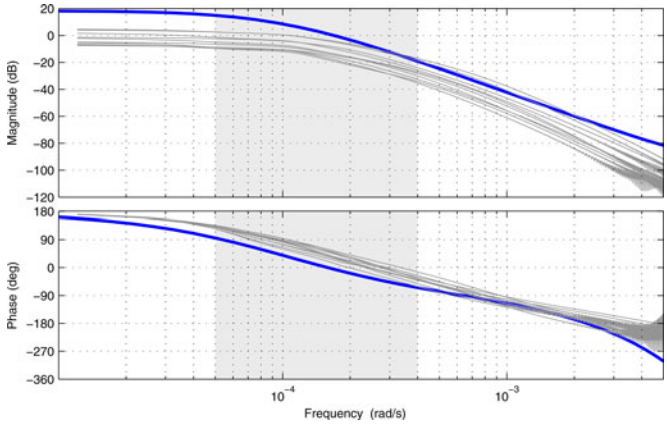

Fig. 3. (Thin lines) Bode diagram of estimated frequency responses of ten subjects of the UVa/Padova simulator, from insulin (pmol/min) to glucose (mg/dl). (Thick line) Bode diagram of M_r (3). The gray band represents the frequency band around the closed-loop bandwidth.

Any model structure that captures the dynamics around the bandwidth is appropriate for control for these nonresonant systems, and the exact structure is of limited importance. Based on the structure of models 2, 3, 4, 6, 7, and 10, a control-relevant model M_r is defined as

$$M_r(q^{-1}) = \frac{Kq^{-3}}{(1-0.98q^{-1})(1-0.965q^{-1})^2} \tag{3}$$

where $K = 2.005 \times 10^{-4}$, when the units for insulin are (pmol/min) and glucose (mg/dl). The Bode diagram of this model in Fig. 3 shows that the phase of the model is lower than the phase angle of the estimated FRF in the frequency region around the expected closed-loop bandwidth, and the gain is overestimated. Consequently, controllers based on this model will tend to be robust. Note that the proposed model is a conservative choice for control for the expected bandwidth, but will not be a conservative choice if the bandwidth of the closed-loop system is, for example, 10^{-3} rd/s.

B. Personalized Models

It will be shown in Section V that an MPC controller designed using the model in (3) causes no hypoglycemia, even for large meal sizes. The trade-off for this robustness is limited controller performance if the patient–model mismatch is large. In the following, personalization of the models using a clinical estimate of the correction factor is proposed to limit this conservatism.

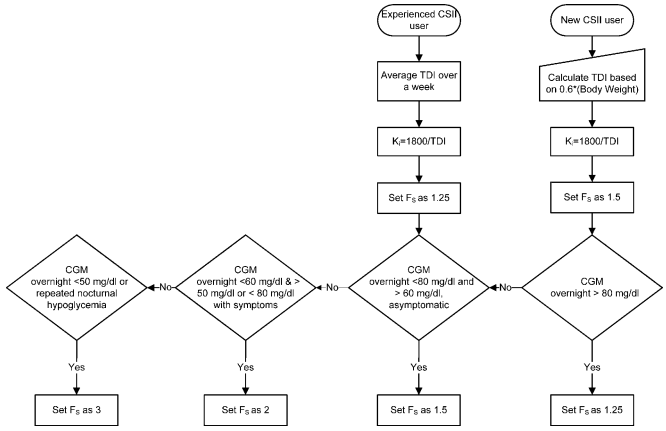

Fig. 4. Guidelines on choosing F_s for individuals with T1DM.

The dynamics of the personalized models are fixed and are based on the control relevant solution described previously. A clinical estimate of the subject's sensitivity to insulin is used to adjust the gain of the model and reduce the conservatism. The personalized models M_i based on *a priori* clinical information are given by

$$M_i(q^{-1}) = \frac{F_s K_i c q^{-3}}{(1-0.98q^{-1})(1-0.965q^{-1})^2} \tag{4}$$

where M_i is the model for subject i, F_s is a safety factor, and K_i is the individualized gain based on the correction factor. It is calculated using the 1800 rule [32] that requires the individual TDI

$$K_i = 1800/\text{TDI}. \tag{5}$$

In (4), c is a constant that depends on the units that are used.

The robustness margins of a controller based on M_i will be preserved when applied to an individual with T1DM if the hypothesis that the margins are underestimated is met. This will be the case if the correction factor is accurate or overestimated. If the correction factor is likely to be underestimated, the safety factor F_s can be adjusted to compensate for the uncertainty. This factor directly affects the gain margin of the system. It can be chosen by the physician and should normally take values ≥ 1. The guidelines shown in Fig. 4 indicate when the correction factor is likely to be underestimated based on clinical parameters and advise how to choose F_s accordingly.

In Fig. 2, the response of the personalized models to the series of insulin boluses is shown for two subjects. Note that the gain of these control-relevant models is not exact, even in simulation. Although the UVa/Padova metabolic simulator contains an exact correction factor, it is not equal to the estimate calculated using the 1800 rule.

IV. IMPLEMENTATION IN ZONE MPC

In MPC, the optimal input sequence that minimizes the predicted control errors is calculated at each time step [33]. A dynamic model is used explicitly to predict future behavior, and the predictions are updated using the latest measurement at

each time step (receding horizon). One of the main advantages of MPC is its ability to deal with constraints.

In the artificial pancreas, insulin cannot be removed from the body and the delivery of insulin is constrained to positive values. This strongly affects the achievable performance of closed-loop control. Delivery is also limited by the CSII pump, as well as by possible time-varying safety constraints. Although no safety constraints are considered in this paper, they will be part of a final design of the artificial pancreas. MPC is, therefore, used to deal with the input constraint and facilitate the future addition of safety constraints. A zone MPC controller has been proposed [29], where the control objective is to control the blood glucose level to the normoglycemic zone. This approach mimics the control strategy of individuals without diabetes, where no clear and invariant glycemic setpoint is present but a euglycemic zone exists (approximately 80–140 mg/dl). Furthermore, if the blood glucose level approaches a steady-state value in the range, the control action is constant, limiting the system's sensitivity to noise.

The estimated disturbance at time k is defined as $\hat{d}(k|k) = y(k) - y_M(k|k-1)$, the error between the output $y(k)$ measured at time k and the predicted model output $y_M(k|k-1)$. The predicted disturbance is modeled as an exponentially decaying function, $\hat{d}(k+i|k) = 0.98^i \hat{d}(k|k)$, where 0.98 corresponds to the slowest time constant in the models M_r and M_i. Note that this simple disturbance prediction is not based on an identified disturbance model.

The predicted output at time $k+1$ is then given by

$$\hat{y}(k+i|k) = y_M(k+i|k) + \hat{d}(k+i|k). \tag{6}$$

The prediction horizon is given by n_p and the control horizon by n_u; therefore, the insulin delivery u can differ from the basal rate for the first n_u samples and is set equal to the basal rate after that. In the following, all measurements and predictions as well as input values are deviations from the point of linearization.

The proposed models are implemented in two MPC controllers: 1) a setpoint MPC that is linear if the constraint is inactive; and 2) a zone MPC controller that is nonlinear. The cost function for the setpoint MPC controller is given by

$$J_{\text{setpoint}}(u) = \sum_{i=1}^{n_p} \hat{y}^2(k+i|k)Q + \sum_{j=0}^{n_u-1} u^2(k+j|k)R \tag{7}$$

where Q and R are the weights used for controller tuning and u is the input signal. Let the upper and lower bounds of the target zone in the zone MPC algorithm be given by y_{ub} and y_{lb}, respectively. The zone MPC control objective is then defined as

$$J_{\text{zone}}(u) = \sum_{i=1}^{n_p} \hat{y}_z^2(k+i|k)Q + \sum_{j=0}^{n_u-1} u^2(k+j|k)R \tag{8}$$

where

$$\hat{y}_z(k+i|k) = \begin{cases} \hat{y}(k+i|k) - y_{ub}, & \text{if } \hat{y}(k+i|k) > y_{ub} \\ 0, & \text{if } y_{lb} \le \hat{y}(k+i|k) \le y_{ub} \\ y_{lb} - \hat{y}(k+i|k), & \text{if } \hat{y}(k+i|k) < y_{lb}. \end{cases} \tag{9}$$

The controller tuning is fixed for all subjects and is based on simulations of the closed-loop system of the model based on a TDI of 30 units and the zone MPC controller. This represents a subject that is relatively sensitive to insulin. Since the Q to R ratio is fixed, this tuning will be more conservative for subjects that are less sensitive to insulin. A typical disturbance resulting from a meal of 60 g of CHO in the UVa/Padova metabolic simulator [30] is added to the output signal. The achieved disturbance rejection is used as the measure of performance for the controller. $y_{lb} = 80$ mg/dl, $y_{ub} = 140$ mg/dl, $n_p = 100$, and $n_u = 5$. The response is shown in Fig. 5 for three different Q to R ratios. Based on these results, a Q to R ratio of 1:50 is chosen, both to avoid having the controller shut down the insulin delivery after larger meals, and to limit the sensitivity of the system to measurement noise.

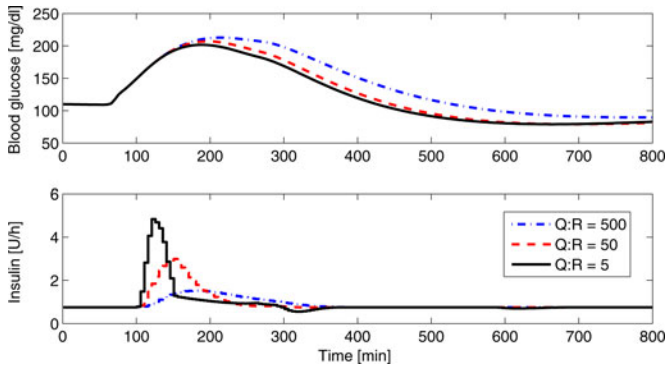

Fig. 5. Comparison of different controller settings. Response of the closed-loop system of the model and the zone MPC controller to a typical meal disturbance of 60-g CHO. TDI = 30 was used both by the controller and the plant. (Dash-dotted line) Q to R of 1:500. (Dashed line) Q to R of 1:50. (Continuous line) Q to R of 1:5. The setting chosen based on these results is a Q to R of 1:50.

The closed-loop bandwidth of the model controlled by a setpoint MPC controller is estimated to verify whether the expected bandwidth used in the model design is achieved. The sensitivity function of the controlled plant is estimated using a multisine disturbance signal. The bandwidth, defined as the frequency where the sensitivity function crosses -3 dB [34], is situated between 6×10^{-5} and 10^{-4} for Q to R ratios of 1:500 and 1:5, respectively.

V. Results

The performance of the controllers presented in Section IV is tested in simulation using 100 *in silico* subjects from the FDA accepted UVa/Padova metabolic simulator [30]. Note that this testing population is different from the population of ten subjects used in Section III.

The nonlinear UVa/Padova metabolic simulator is accepted by the FDA as a substitute for certain animal trials. The following characteristics of this simulator should be taken into consideration while examining these results. The simulator contains

1) 100 subject models with a large intersubject variability;
2) subject-dependent values for the TDI;
3) a subject-dependent correction factor. This correction factor is not equivalent to its estimate K_i based on the 1800 rule;

4) time-invariant subject models, i.e., it does not include diurnal insulin sensitivity variation;
5) an optimal bolus treatment, assuming the exact meal size is known. This treatment is defined per subject model and combines a basal rate with optimal boluses to compensate for meals, for this specific basal rate. If either of these parameters are changed, the programmed treatment is no longer optimal.

The performance is compared to a previously published zone MPC algorithm [35]. This algorithm is similar to the algorithm presented in [29], but an average population model is used rather than identified individual models. For comparison, results for the optimal bolus treatment as implemented in the UVa/Padova metabolic simulator are also given. Note that noise corrupted CGM measurements are used for closed-loop control in all the presented results.

The performance of the controllers is evaluated using two protocols.

Protocol #1 The simulation is started at midnight and the controller is turned ON after 2 h. A single meal of either 75-, 120-, or 160-g CHO is given after 7 h. The total simulation time is 24 h.

Protocol #2 The simulation is started at midnight and the controller is turned ON after 2 h. A 50-g meal is given at 7 h, an 80-g meal at 14 h, and a 60-g meal at 20 h. The next day, 50 g of CHO is given at 7 h, 80 g at 14 h and 60 g at 20 h. The total simulation time is 55 h.

Although protocol #1 is unlikely to happen in reality, it is used to evaluate the safety of the different approaches. In this protocol, any hypoglycemia caused by overdelivery of insulin will be visible, since no second meal is given that can save the subject. Protocol #2 includes two days and two overnight periods.

First, the proposed control strategy is verified using setpoint MPC controllers, where the setpoint is 110 mg/dl and the controller tuning is as described in Section IV. If the meal disturbance is small and the constraints are not active, this controller is linear. If the disturbances are small, the system is approximately linear and the linear control theory that is used in Section III can be assumed valid. The TDI defined in the simulator for the 100 subjects is used to define a personalized model. The accuracy of the estimate of the correction factor is not verified for the different subjects and the default safety factor $F_s = 1.25$ is used for each subject. As expected, no hypoglycemia occurs for any subject, not even for heavy meals with 160-g CHO, both for M_r and for the personalized models M_i. The average responses in Fig. 6 show that, as expected, the solution based on M_r is conservative and the performance of the personalized approach using M_i is superior.

Second, the zone MPC algorithm is evaluated with the two protocols with the following zone settings of $y_{lb} = 80$ mg/dl and $y_{ub} = 140$ mg/dl and the controller tuning is as described in Section IV. The zone MPC algorithm is more aggressive than the setpoint algorithm for this controller tuning. For the 100 *in silico* subjects in the simulator, hypoglycemia occurs for one subject for larger meals if the default safety factor $F_s = 1.25$ is used. The safety factor for this outlier in the simulator is set to $F_s = 3$. For the other 99 subjects, the default value $F_s = 1.25$ is used (note that the correction factor is not verified for these subjects, the estimate can be inaccurate).

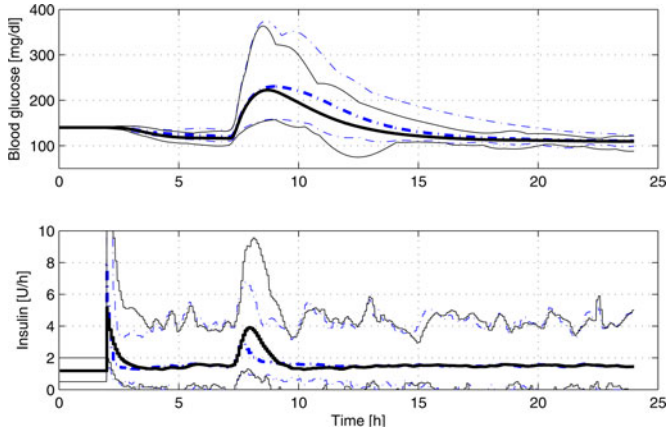

Fig. 6. Average blood glucose responses and average insulin delivery for 100 *in silico* subjects to a 75-g meal, unannounced to the setpoint controller. (Thick continuous line) Setpoint MPC controller based on personalized models M_i (4). (Thick dash-dotted line) Setpoint MPC controller based on M_r (3). The thin lines indicate the envelope of the minimum and maximum responses at each time step for the 100 subjects.

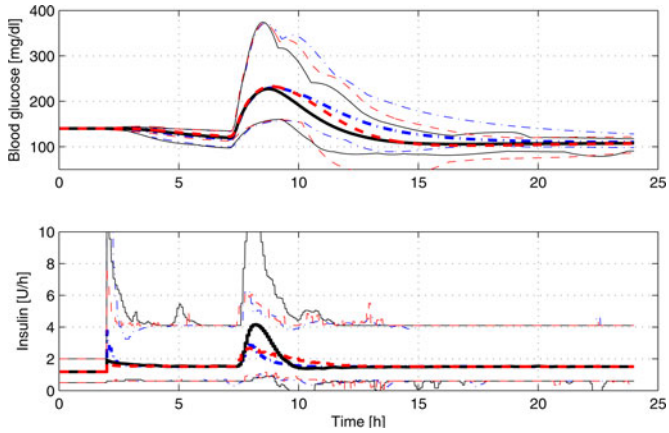

Fig. 7. Average blood glucose responses and average insulin delivery for 100 *in silico* subjects to a 75-g meal, unannounced to the controller. (Continuous line) Zone MPC controller based on personalized models M_i (4). (Dash-dotted line) Zone MPC controller based on M_r (3). (Dashed line) Zone MPC controller using average model as presented in [35]. The thin lines indicate the envelope of the minimum and maximum responses at each time step for the 100 subjects.

In Fig. 7, average time responses are given for protocol #1 with a 75-g meal. The differences in the insulin dosage after 2 h are due to noise in the CGM measurements. The initial blood glucose level is at the upper bound of the zone; therefore the noise has a large effect on the insulin delivery when the controller is turned ON. No hypoglycemia occurs for any of the 100 *in silico* subjects for both models proposed in this paper, M_i and M_r. The approach in [35] leads to hypoglycemia for two subjects. The use of personalized models reduces the conservatism with respect to the use of M_r, as was the case for the setpoint controller. The proposed approach also outperforms the controller in [35], based on an average model.

TABLE II
AVERAGE RESULTS FOR 100 *in silico* SUBJECTS OF THE UVA/PADOVA SIMULATOR FOR PROTOCOL #1, FOR DIFFERENT MEAL SIZES

Meal size	Method	Prandial [mg/dl]	1h Postprandial [mg/dl]	3h Postprandial [mg/dl]	5h Postprandial [mg/dl]	# < 60	# < 70	# < 80
75 g	Proposed approach, setpoint	117 (±5)	208 (±39)	191 (±29)	147 (±21)	0	0	1
	Proposed approach, ZMPC	121 (±7)	211 (±39)	187 (±30)	130 (±22)	0	0	1
	Zone MPC from [35],	123 (±5)	214 (±38)	210 (±31)	145 (±29)	2	3	7
	Optimal bolus treatment	141 (±6)	192 (±30)	151 (±27)	132 (±20)	0	0	0
	70 % of optimal bolus	141 (±6)	204 (±32)	181 (±28)	159 (±21)	0	0	0
	130 % of optimal bolus	141 (±6)	181 (±29)	127 (±27)	112 (±20)	0	1	8
120 g	Proposed approach, setpoint	118 (±5)	266 (±63)	241 (±46)	170 (±31)	0	0	0
	Proposed approach, ZMPC	121 (±8)	269 (±64)	232 (±47)	151 (±31)	0	0	0
	Zone MPC from [35],	124 (±5)	272 (±63)	258 (±50)	151 (±43)	8	10	23
	Optimal bolus treatment	141 (±6)	223 (±46)	159 (±38)	129 (±29)	0	1	5
	70 % of optimal bolus	141 (±6)	241 (±50)	202 (±42)	167 (±32)	0	0	0
	130 % of optimal bolus	141 (±6)	206 (±44)	128 (±35)	102 (±27)	7	14	34
160 g	Proposed approach, setpoint	118 (±4)	319 (±86)	289 (±60)	192 (±41)	0	0	0
	Proposed approach, ZMPC	121 (±8)	322 (±87)	278 (±61)	172 (±42)	0	0	1
	Zone MPC from [35],	124 (±5)	324 (±86)	305 (±68)	156 (±57)	15	29	47
	Optimal bolus treatment	141 (±6)	250 (±61)	169 (±49)	128 (±37)	1	7	10
	70 % of optimal bolus	142 (±6)	275 (±66)	223 (±56)	176 (±41)	0	0	0
	130 % of optimal bolus	141 (±6)	230 (±57)	133 (±44)	97 (±33)	20	40	63

Standard deviations are given in parentheses.

TABLE III
SENSITIVITY TO F_s: AVERAGE RESULTS FOR 100 *in silico* SUBJECTS OF THE UVA/PADOVA SIMULATOR FOR PROTOCOL #1 WITH A MEAL OF 100-g CHO

	Prandial [mg/dl]	1h Postprandial [mg/dl]	3h Postprandial [mg/dl]	5h Postprandial [mg/dl]	# < 60	# < 70	# < 80
$F_s = 0.75$	122.1 (±7.0)	244.6 (±51.8)	189.4 (±39.6)	113.0 (±31.3)	7	14	22
$F_s = 1$	119.6 (±9.9)	242.3 (±54.2)	202.3 (±37.7)	129.4 (±28.4)	1	2	8
$F_s = 1.25$	120.6 (±7.4)	242.9 (±53.5)	210.5 (±38.2)	141.0 (±27.7)	1	2	4
$F_s = 2$	120.0 (±7.2)	242.6 (±52.5)	229.2 (±41.1)	162.0 (±29.9)	0	0	1
$F_s = 3$	117.9 (±6.5)	241.0 (±52.9)	242.5 (±45.4)	177.3 (±32.3)	0	0	0

Standard deviations are given in parentheses. The results are based on zone MPC controllers using M_i.

TABLE IV
AVERAGE RESULTS FOR 100 *in silico* SUBJECTS OF THE UVA/PADOVA SIMULATOR FOR PROTOCOL # 2

	Mean BG [mg/dl]	Max BG [mg/dl]	Min BG [mg/dl]	% of time in [80 140]	% of time in [70 180]	# < 60	# < 70	# < 80
Proposed approach, setpoint	154.1 (±12.9)	240.2 (±44.3)	108.6 (±4.8)	46.1 (±11.8)	77.7 (±12.6)	0	0	0
Proposed approach, ZMPC	147.5 (±10.7)	237.9 (±43.7)	97.8 (±9.3)	51.3 (±10.7)	79.9 (±11.1)	0	1	7
Zone MPC from [35],	154.3 (±11.6)	241.7 (±41.1)	101.5 (±10.9)	43.0 (±11.2)	75.0 (±12.3)	1	2	6
Optimal Bolus Treatment	139.4 (±11.2)	192.1 (±30.1)	113.2 (±11.1)	58.6 (±24.0)	93.7 (±8.4)	0	0	0
70 % of optimal bolus	160.0 (±13.7)	215.7 (±33.9)	132.9 (±9.5)	26.4 (±21.9)	79.5 (±17.6)	0	0	0
130 % of optimal bolus	123.7 (±11.0)	177.9 (±25.6)	93.3 (±13.3)	74.1 (±16.6)	97.1 (±5.1)	1	4	15

Standard deviations are given in parentheses.

In Table II, average results for the 100 *in silico* subjects are given for different meal sizes. For comparison, results for the standard bolus treatment as defined in the simulator are also given. This treatment is effective if the size of the meal is estimated correctly and if the estimate of the subject's insulin to CHO ratio is correct. In practice, the meal size is difficult to estimate and the insulin to CHO ratio is time varying. The effect of a wrongly estimated bolus size is shown by over- and underestimating the meal sizes by 30%. The fasting blood glucose level that corresponds to the basal rate for the optimal bolus treatment is not in the zone. In the closed-loop case, it is assumed that the basal rate corresponds to a fasting blood glucose level in the zone, and the basal rate is chosen accordingly. The resulting average prandial blood glucose levels for zone MPC and for the bolus treatment are therefore different.

The results in Table II indicate that the proposed approach is safe also for large meals. Clearly, the increase in blood glucose after a large meal cannot be avoided when the meal is not announced to the controller. A performance equal to that of an (announced) optimal bolus treatment can therefore not be achieved. Note that all controllers use CGM measurements. The use of noise corrupted measurements can explain why one subject reaches a blood glucose value below 80 mg/dl for a 75-g meal, but does not for a larger meal disturbance.

The sensitivity of the proposed approach to changes in F_s is shown in Table III. The average response to protocol #1 with a large meal of 100 g is given for different safety factors, using zone MPC based on M_i. Note that the safety factor should normally be chosen as $F_s > 1$ and the default value is $F_s = 1.25$, according to the guidelines in Fig. 4. Since changes in F_s and K_i have the same effect on M_i, $F_s = 0.75$ corresponds to a strongly underestimated correction factor. The table clearly shows the trade-off between robustness and performance. One case of hypoglycemia occurred for $F_s = 1.25$, which corresponds to the outlier in the simulator as mentioned previously.

The average results for the 100 *in silico* subjects responses to protocol #2 are given in Table IV. As expected, high blood

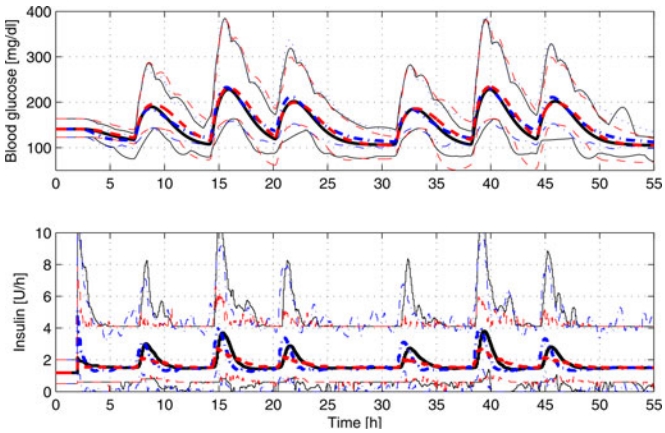

Fig. 8. Average blood glucose responses and average insulin delivery for 100 *in silico* subjects to protocol #2. (Continuous line) Zone MPC controller based on personalized models M_i (4). (Dash-dotted line) Setpoint MPC based on personalized models M_i. (Dashed line) Zone MPC controller using average model as presented in [35]. The thin lines indicate the envelope of the minimum and maximum responses at each time step for the 100 subjects.

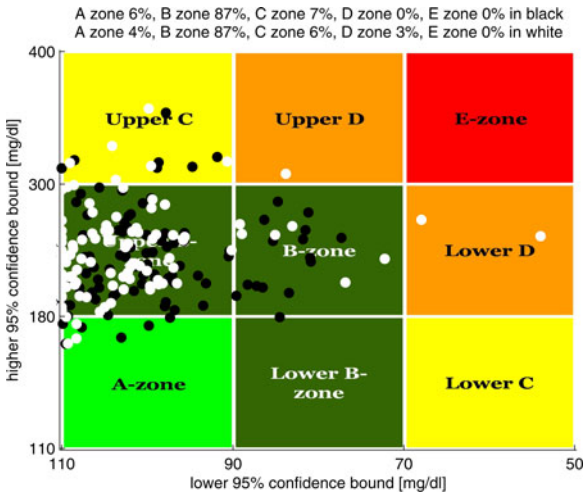

Fig. 9. CVGA [36] of the 100 simulated responses to protocol #2. (Black) Zone MPC controller based on the proposed M_i (4). (White) Zone MPC controller using average model as presented in [35].

glucose values cannot be completely avoided for closed-loop control with unannounced meals and the performance of an optimal bolus treatment cannot be met. However, the use of personalized models limits the conservatism and the average time in the target region of 70–180 mg/dl is 79.9%. The average response for both the setpoint and zone MPC controller based on M_i is shown in Fig. 8. The average response of the zone MPC controller of [35] is given for comparison. The control variability grid analysis (CVGA) plot in Fig. 9 shows the 95% confidence bounds of the maximal and minimal blood glucose values for the 100 *in silico* subjects for the zone MPC controller with M_i and the zone MPC controller in [35]. Low glycemic values are avoided if the approach proposed in this paper is used, without increasing the high values with respect to the approach in [35].

Fig. 10 shows three examples of individual responses to protocol #2. In Fig. 10(a), an example is given of a subject for whom the average response is a good representation of the individual response to insulin. The use of this average model in the controller does not lead to hypoglycemia and is not overly conservative either. The response of the controlled system with the average model is comparable to the response of the controlled system with the proposed personalized model. The total amount of delivered insulin is also comparable. Fig. 10(b) shows an example where the subject's correction factor is lower than average and the average model leads to a conservative controller. The controller based on the proposed personalized model is less conservative and achieves a better time in range for this subject. Fig. 10(c) shows an example of a subject that has higher insulin sensitivity and/or a slower response to insulin than average. For these subjects, the controller based on the average model is potentially unsafe. The proposed approach leads to a safe controller also for this subject.

Fig. 11 shows the average results to protocol #2 for the zone MPC controller using M_i with and without meal announcement. When the meal is announced, an optimal bolus is given at the same time as the meal, the controller uses the information of the given bolus but no meal disturbance model is introduced. The results show that the proposed controllers are safe also if the meals are announced. The use of meal information decreases the postprandial glucose peak as expected.

VI. Discussion

This paper evaluates the proposed control-relevant models using a fixed controller. This approach is personalized since the models are personalized. The current controller design is based on a model for an individual that is sensitive to insulin, and consequently, this controller is conservative for individuals that are less sensitive. A personalized controller tuning could improve the results.

The proposed approach is shown to be safe *in silico* when the meals are not announced to the controller. In this case, the meal-induced hyperglycemia is expected to be large and avoiding hypoglycemia due to overdelivery of insulin is challenging. The *in silico* results in Section V show the possible performance improvement if the meal is announced and the meal information is accurate. In practice, this accurate meal information is rarely available and the development of robust meal announcement is an active field of research.

The UVa/Padova simulator contains a set of time-invariant models. In practice, the behavior of the glucose–insulin system is unpredictable and time varying. The guidelines given for the tuning of the safety factor need to be tested clinically and updated accordingly. A run-to-run approach can be envisioned (see, for e.g., [37]), where the physician initially chooses a large value for safety, and updates it as more information becomes available. A time-varying safety factor could be used to compensate for diurnal variations.

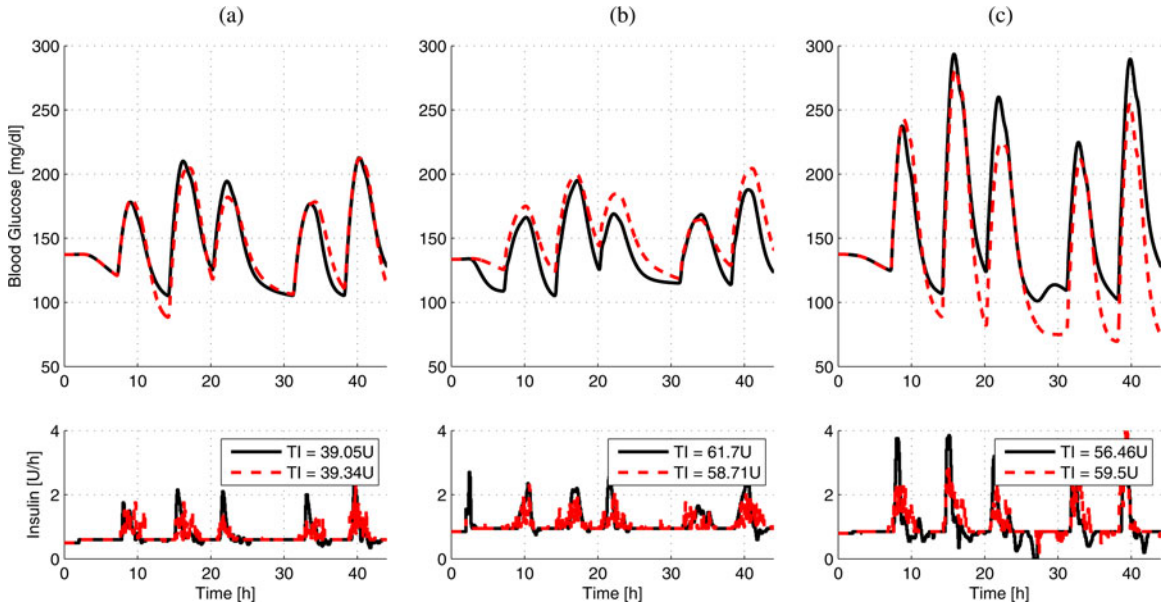

Fig. 10. Representative responses to protocol #2 for three subjects of the UVa/Padova simulator. (Continuous line) Zone MPC with proposed personalized models M_i (4). (Dashed line). Zone MPC with average model from [35]. The total insulin that is delivered in the 44 h of the protocol is indicated in the figure.

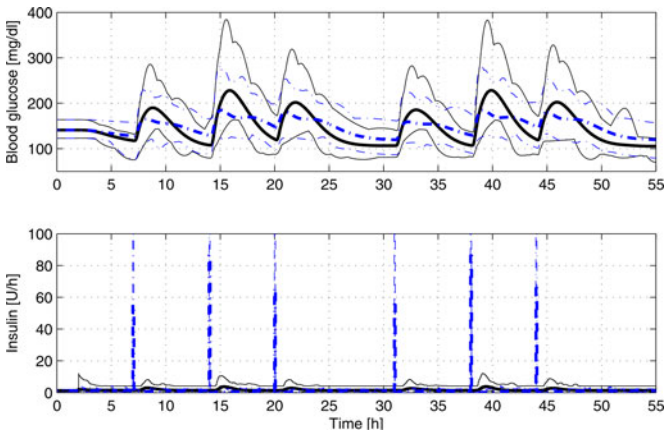

Fig. 11. Comparison of announced and unannounced meals. Average blood glucose responses and average insulin delivery are shown for 100 *in silico* subjects to protocol #2. (Continuous line) Zone MPC controller using M_i and no meal announcement. (Dashed line) Zone MPC controller using M_i with announced meals. (Thin lines) Min and max envelop of the 100 responses.

VII. Conclusion

Control-relevant models for glucose control in T1DM are presented, where the model structure is based on the *a priori* information available in the UVa/Padova metabolic simulator. The gain is personalized using patient characteristics. The approach is tested *in silico* for 100 subjects, without meal announcement or prandial insulin boluses. The robustness of the controllers based on the proposed individualized models is confirmed by the simulation results. No hypoglycemic events occurred for meal disturbances up to 160 g of CHO, and the MPC controller was not overly conservative. The simulation results are promising, but need to be verified clinically.

The personalized models are based on *a priori* patient characteristics; therefore, no time-consuming identification step is needed to develop a model. Minimal control expertise is required to set up the presented zone MPC.

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