Journal of Diabetes Science and Technology
Volume 1, Issue 6, November 2007

SYMPOSIUM

Model Predictive Control of Type 1 Diabetes: An *in Silico* Trial

Lalo Magni, Ph.D.,[1] Davide M. Raimondo, M.S.,[1] Luca Bossi, M.S.,[1] Chiara Dalla Man, Ph.D.,[2] Giuseppe De Nicolao, Ph.D.,[1] Boris Kovatchev, Ph.D.,[3] and Claudio Cobelli, Ph.D.[2]

Abstract

Background:
The development of artificial pancreas has received a new impulse from recent technological advancements in subcutaneous continuous glucose monitoring and subcutaneous insulin pump delivery systems. However, the availability of innovative sensors and actuators, although essential, does not guarantee optimal glycemic regulation. Closed-loop control of blood glucose levels still poses technological challenges to the automatic control expert, most notable of which are the inevitable time delays between glucose sensing and insulin actuation.

Methods:
A new *in silico* model is exploited for both design and validation of a linear model predictive control (MPC) glucose control system. The starting point is a recently developed meal glucose–insulin model in health, which is modified to describe the metabolic dynamics of a person with type 1 diabetes mellitus. The population distribution of the model parameters originally obtained in healthy 204 patients is modified to describe diabetic patients. Individual models of virtual patients are extracted from this distribution. A discrete-time MPC is designed for all the virtual patients from a *unique* input–output-linearized approximation of the full model based on the average population values of the parameters. The *in silico* trial simulates 4 consecutive days, during which the patient receives breakfast, lunch, and dinner each day.

Results:
Provided that the regulator undergoes some individual tuning, satisfactory results are obtained even if the control design relies solely on the average patient model. Only the weight on the glucose concentration error needs to be tuned in a quite straightforward and intuitive way. The ability of the MPC to take advantage of meal announcement information is demonstrated. Imperfect knowledge of the amount of ingested glucose causes only marginal deterioration of performance. In general, MPC results in better regulation than proportional integral derivative, limiting significantly the oscillation of glucose levels.

continued →

Author Affiliations: [1]Dipartimento di Informatica e Sistemistica, University of Pavia, Pavia, Italy; [2]Department of Information Engineering, University of Padova, Padova, Italy; and [3]Department of Psychiatry and Neurobehavioral Science, University of Virginia Health System, Charlottesville, Virginia

Abbreviations: (FHOCP) finite horizon optimal control problem, (HBGI) high blood glucose index, (LBGI) low blood glucose index, (MPC) model predictive control, (PID) proportional integral derivative, (T1DM) type 1 diabetes mellitus

Keywords: artificial pancreas, diabetes, model predictive control, simulation, virtual patients

Corresponding Author: Claudio Cobelli, Ph.D., Department of Information Engineering, University of Padova, Via Gradenigo 6/B, I-35131 Padova, Italy; email address cobelli@dei.unipd.it

Abstract cont.

Conclusions:
The proposed *in silico* trial shows the potential of MPC for artificial pancreas design. The main features are a capability to consider meal announcement information, delay compensation, and simplicity of tuning and implementation.

J Diabetes Sci Technol 2007;1(6):804-812

Introduction

The development of artificial pancreas, e.g., a closed-loop control system for maintaining normoglycemia in type 1 diabetes mellitus (T1DM), has been envisaged and discussed since the 1970s.[1,2] However, devices requiring intravenous blood glucose sampling and intravenous glucose and insulin delivery, such as the Biostator™, were not suitable for outpatient use. Recent technological advancements in subcutaneous continuous glucose monitoring and subcutaneous insulin delivery systems have paved the way to the development of minimally invasive glucose control systems.[2,3]

However, the availability of innovative sensors and actuators, although essential, does not guarantee the achievement of optimal glycemic regulation under all conditions. Closed-loop control of blood glucose levels still poses technological challenges to the automatic control expert.

The principal obstacle to satisfactory closed-loop control is the presence of significant disturbances (i.e., meals and physical activity) and delays in the effect of meals and subcutaneous insulin on glycemia and furthermore from glycemia to measured subcutaneous glucose. Moreover, the control system must satisfy constraints on both plasma glucose levels and insulin delivery rates. These features explain the difficulties encountered when standard proportional integral derivative (PID) controllers are employed. Model predictive control (MPC) is likely to be the most suitable approach to design control systems in the presence of delays and constraints.[4,5] Compensation for delays by means of feed-forward action, as well as constraint handling, is naturally incorporated in the design process. For the possible application of MPC strategies to glucose control in T1DM, the reader is referred elsewhere.[2,6,7]

The comparison of different control algorithms is facilitated greatly by the availability of reliable large-scale simulation models. In fact, *in silico* trials are perhaps the best way to address the robustness of the artificial pancreas against interindividual variability prior to conducting *in vivo* clinical trials. Until recently, the drawback of large-scale computer simulation models was the difficulty of identifying all relevant parameters from plasma concentration measurements. Recently, a new generation *in silico* model of the glucose–insulin system has been developed from the analysis of 204 nondiabetic individuals with various degrees of glucose tolerance who underwent a triple tracer meal protocol.[8] This way, it was possible to obtain glucose and insulin fluxes during a meal independently of the model. Exploiting the knowledge of glucose production, utilization, rate of appearance in plasma, and pancreatic insulin secretion, it is possible to identify the various unit processes of the system through a subsystem forcing function strategy.

In this article, the new *in silico* model is exploited for both design and validation of a linear MPC system. First, the model is modified to provide a good description of the metabolism in T1DM. Then, a linearization of the model around basal values is used to design a linear MPC scheme. A major problem for the artificial pancreas is guaranteeing satisfactory performance under conditions of metabolic disturbance and interindividual variability. In order to validate this aspect, the population distribution of the model parameters of the healthy 204 individuals was modified to obtain the parameter distribution of diabetic patients. Individual models of virtual patients are then extracted from this distribution. The availability of realistic individual models is the basis for conducting an *in silico* trial: the closed-loop control can be tuned individually and then tested on each virtual

patient, possibly injecting disturbances and uncertainties in order to assess robustness of control. The protocol simulates 4 days during which the patient receives breakfast, lunch, and dinner each day. The performance of the MPC system is compared to the performance of a standard PID controller.

Methods

In order to synthesize and test the controller, we used the meal glucose–insulin model.[8] Some modifications have been introduced in order to simulate the metabolic specifics of T1DM.

Model of Glucose–Insulin Dynamics

Glucose Intestinal Absorption. Glucose intestinal absorption was modeled by a recently developed three-compartment model[9]

$$\begin{aligned} Q_{sto}(t) &= Q_{sto_1}(t) + Q_{sto_2}(t) \\ \dot{Q}_{sto_1}(t) &= -k_{gri} Q_{sto_1}(t) + d(t) \\ \dot{Q}_{sto_2}(t) &= -k_{gut}(t, Q_{sto}) Q_{sto2}(t) + k_{gri} Q_{sto_1}(t) \\ \dot{Q}_{gut}(t) &= -k_{abs} Q_{gut}(t) + k_{gut}(t, Q_{sto}) Q_{sto2}(t) \\ Ra(t) &= \frac{f k_{abs} Q_{gut}(t)}{BW} \end{aligned} \quad (1)$$

where Q_{sto} (mg) is the amount of glucose in the stomach (solid, Q_{sto1}, and liquid phase, Q_{sto2}), Q_{gut} (mg) is the glucose mass in the intestine, k_{gri} is the rate of grinding, k_{abs} is the rate constant of intestinal absorption, f is the fraction of intestinal absorption that actually appears in plasma, d (mg/min) is the rate of ingested glucose, BW (kg) is body weight, Ra (mg/kg/min) is the glucose rate of appearance in plasma, and k_{gut} is the rate constant of gastric emptying, which is a time-varying nonlinear function of Q_{sto}

$$k_{gut}(t, Q_{sto}) = k_{\min} + \frac{k_{\max} - k_{\min}}{2}\left\{\tanh\left[\alpha\left(Q_{sto} - b\bar{D}(t)\right)\right] - \tanh\left[\beta\left(Q_{sto} - a\bar{D}(t)\right)\right] + 2\right\}$$

$$\alpha = \frac{5}{2\bar{D}(t)(1-b)}, \beta = \frac{5}{2\bar{D}(t)a}, \bar{D}(t) = Q_{sto}(\bar{t}) + \int_{\bar{t}}^{\bar{t}_f} d(\tau)d\tau$$

where $\bar{t}$ and $\bar{t}_f$ are the initial and final times of the last ingestion, while a, b, k_{max}, and k_{min} are model parameters.

Glucose Subsystem. A two-compartment model is used to describe glucose kinetics[10]

$$\begin{aligned} \dot{G}_p(t) &= EGP(t) + Ra(t) - U_{ii}(t) - E(t) - k_1 G_p(t) + k_2 G_t(t) \\ \dot{G}_t(t) &= -U_{id}(t) + k_1 G_p(t) - k_2 G_t(t) \end{aligned} \quad (2)$$

where G_p (mg/kg) and G_t (mg/kg) are glucose masses in plasma and rapidly equilibrating tissues and in slowly equilibrating tissues, respectively, EGP is endogenous glucose production (mg/kg/min), E (mg/kg/min) is renal excretion, U_{ii} and U_{id} are insulin-independent and -dependent glucose utilizations, respectively (mg/kg/min), and k_1 and k_2 are rate parameters.

Glucose Renal Excretion. Renal excretion, which occurs if plasma glucose exceeds a certain threshold, is modeled as follows[11]

$$E(t) = \begin{cases} k_{e_1}\left[G_p(t) - k_{e_2}\right] & \text{if } G_p(t) > k_{e_2} \\ 0 & \text{if } G_p(t) \le k_{e_2} \end{cases} \quad (3)$$

where k_{e_1} is the glomerular filtration rate and k_{e_2} is the renal threshold of glucose.

Endogenous Glucose Production. EGP comprises a direct glucose signal and a delayed insulin signal[12]

$$EGP(t) = \max\left\{0, k_{p1} - k_{p2} G_p(t) - k_{p3} I_d(t)\right\}, \quad (4)$$

where the delayed insulin signal I_d (pmol/liter) is given by

$$\begin{aligned} \dot{I}_1(t) &= -k_i\left[I_1(t) - I(t)\right] \\ \dot{I}_d(t) &= -k_i\left[I_d(t) - I_1(t)\right] \end{aligned} \quad (5)$$

where I (pmol/liter) is the plasma insulin concentration, k_{p1} is the extrapolated EGP at zero glucose and insulin, k_{p2} is liver glucose effectiveness, k_{p3} is a parameter governing the amplitude of insulin action on the liver, and k_i is the rate parameter accounting for the delay between insulin signal and insulin action.

Glucose Utilization. Glucose utilization consists of two components: an insulin-independent glucose utilization U_{ii}, which represents the glucose uptake by the brain and erythrocytes, and an insulin-dependent component U_{id}, which depends nonlinearly on glucose concentration in the tissues[13]:

$$\begin{aligned} U_{id}(t) &= \frac{V_m(t) G_t(t)}{K_m + G_t(t)} \\ V_m(t) &= V_{m0} + V_{mx} X(t) \\ \dot{X}(t) &= -p_{2U} X(t) + p_{2U}\left[I(t) - I_b\right] \end{aligned} \quad (6)$$

where K_m, V_{m0}, and V_{mx} and are model parameters, X (pmol/liter) is the remote insulin signal, I_b (pmol/liter) is the basal insulin level, and p_{2U} is a rate constant of insulin action on peripheral glucose utilization.

Subcutaneous Insulin Kinetics. This article adopts a variation of a model described in Verdonk *et al.*[13]:

$$\begin{aligned} \dot{S}_1(t) &= -(k_{a1} + k_d) S_1(t) + u(t) \\ \dot{S}_2(t) &= k_d S_1(t) - k_{a2} S_2(t) \end{aligned}, \quad (7)$$

where $u(t)$ (pmol/kg/min) represents the administration (bolus and infusion) of insulin. The first compartment

represents the amount of nonmonomeric insulin in the subcutaneous space, which is partly transformed into monomeric insulin (second compartment) and partly enters the circulation with rate constants of insulin absorption k_{a1} and k_d, respectively; the monomeric insulin is finally absorbed with rate constant k_{a2}.

Insulin Subsystem. The model equations are

$$\begin{aligned} \dot{I}_l(t) &= -(m_1 + m_3)I_l(t) + m_2 I_p(t) \\ \dot{I}_p(t) &= -(m_2 + m_4)I_p(t) + m_1 I_l(t) + k_{a1} S_1(t) + k_{a2} S_2(t)' \end{aligned} \quad (8)$$

where $I_p(t) = V_I I(t)$ (pmol/kg) and I_l (pmol/kg) are insulin masses in plasma and in liver, respectively, V_I (liter/kg) is the body weight-normalized insulin volume, and m_i, $i = 1,...,4$ are model parameters.

Subcutaneous Glucose Kinetics. Subcutaneous glucose concentration G_M (mg/dl) is obtained as

$$\dot{G}_M(t) = -k_{sc} G_M(t) + k_{sc} \frac{G_p(t)}{V_G}, \quad (9)$$

where V_G (dl/kg) is the body weight-normalized glucose volume and k_{sc} is a rate constant.

Virtual Patient Generation. In order to obtain parameter joint distributions in T1DM, the parameters identified in 204 healthy subjects were used as a starting point.[8] Some modification was needed to realistically describe the metabolism of a person with T1DM. The basal glucose concentration was assumed to be on average 50 mg/dl higher than in nondiabetic individuals, the insulin concentration (due to an external insulin pump) was assumed to be on average four times higher than in nondiabetic individuals, endogenous glucose production was assumed to be 35% higher than in nondiabetic individuals, and insulin clearance was assumed to be one-third lower than in nondiabetic individuals. Parameters relating to insulin action on both glucose production and utilization were assumed to one-third lower than in nondiabetic individuals. For all parameters and variables, the same intersubject variability of nondiabetic subjects was maintained. The parameters were assumed to be log-normal distributed to guarantee that they were always positive. A covariance matrix (26 × 26) was calculated using the log-transformed parameters. One hundred subjects were generated using the joint distribution, i.e., 100 realizations of the log-transformed parameter vector were extracted randomly from the multivariate normal distribution with a mean equal to the mean of the log-transformed parameters and a 26 × 26 covariance matrix. Finally, the parameters in the 100 virtual subjects were obtained by antitransformation.

Performance Assessment

Virtual Protocol. The performance of closed-loop glucose control was tested on a 4-day virtual protocol:

- simulation starts at basal value and the first meal is dinner at 7:30 pm of day 1; the patient has breakfast at 9:30 am with 45 grams of glucose, lunch at 1:30 pm with 75 grams of glucose, and dinner at 7:30 pm with 85 grams of glucose
- in the first part of the simulation, the virtual "patient" receives a subcutaneous bolus based on an open-loop strategy, while at 9:30 pm of day 2 the controller is plugged in. Thereafter, the piecewise constant insulin delivery is governed by the closed-loop controller and no further bolus is administrated.

The virtual protocol has been designed so as to reproduce a likely clinical trial conducted on real patients. In particular, the first open-loop phase serves as an observation window during which individual patient information may be collected. Insulin delivery during closed-loop control is piecewise constant and is updated every 30 minutes. Shorter sampling intervals are technologically possible but are not compatible with medical supervision likely to be required in the first clinical trials on real patients.

Performance Indices. Some established indices of glucose control are considered.

- Low blood glucose index (LBGI)[14]: given n samples of plasma glucose concentration $G_p(i)$

$$\text{LBGI} = \frac{1}{n}\sum_{i=1}^{n} rl(G_p(i)/V_G)$$

where $rl(\cdot) = 10(g((ln(\cdot))^a - b))^2$ if $g((ln(\cdot))^a - b) < 0$ and zero otherwise. The positive parameters g, a, and b are such that $rl(70) = rl(280) = 25$ and $rl(50) = r(400)$. This index captures the propensity of the algorithm to overshoot the target and possibly trigger hypoglycemia.

- High blood glucose index (HBGI)[14]: directly linked to LBGI, it captures the propensity of the algorithm to stay above the target range

$$\text{HBGI} = \frac{1}{n}\sum_{i=1}^{n} rh(G_p(i)/V_G),$$

where $rh(\cdot) = 10(g((ln(\cdot))^a - b))^2$ if $g((ln(\cdot))^a - b) > 0$ and zero otherwise.

Coefficients of LBGI and HBGI have been modified with respect to literature values to better suit control performance results.

- Minimum of blood glucose concentration G_p/V_G (Min_Glycemia).
- Maximum of blood glucose concentration G_p/V_G (Max_Glycemia).

In order to allow for the transition from open-loop to closed-loop regulation, all indices are computed for two different periods: *commutation* from 9:30 pm of day 2 to 8:00 am of day 3 and *regulation* after 8:00 am of day 3.

Model Predictive Control

The glucose metabolism model can be rewritten in the following compact way:

$$\begin{aligned} \dot{x}(t) &= f(t, x(t), u(t), d(t)) \\ \dot{y}(t) &= G_M(t) \end{aligned} \tag{10}$$

where $x = [Q_{sto1}, Q_{sto2}, Q_{gut}, G_p, G_t, I_p, X, I_1, I_d, I_l, S_1, S_2, G_M]$, and f is derived from the model equations reported in the previous section. In the following, it is assumed that meal announcement is available, i.e., the disturbance signal d (the meal) is known in advance.

The MPC control law is based on the solution of a finite horizon optimal control problem (FHOCP), where a cost function $J(\bar{x}, u)$ is minimized with respect to the input u subject to the state dynamics of a model of the system. Letting u° be the solution of the FHOCP, according to the receding horizon paradigm, the feedback control law $u = \kappa^{MPC}(x)$ is obtained by applying only the first element of the optimal solution to the system. This way, a closed-loop control strategy is obtained solving an open-loop optimization problem.

Model predictive control laws can be formulated for both discrete- and continuous-time systems. In this article, a discrete-time MPC is derived from a *unique* input–output-linearized approximation of the full model based on the average population values of the parameters.

Given the average basal values of G_p, G_t, and I_p in the population, the associated equilibrium point with $d = 0$ is indicated by $(\bar{x}, \bar{u}, \bar{d}, \bar{y})$. Around this equilibrium point, assuming $k_{gut}(t, Q_{sto}) = (k_{max} - k_{min})/2$, the system is linearized and discretized with sample time $T_s = 30$ minutes, yielding

$$\begin{aligned} \delta x(k+1) &= A_D \delta x(k) + B_{Du} \delta u(k) + B_{Dd} d(k) \\ \delta y(k) &= C_D \delta x(k) \end{aligned}, \tag{11}$$

where $\delta x(k) = x(kT_s) - \bar{x}$, $\delta u(k) = u(kT_s) - \bar{u}$, and $\delta y(k) = y(kT_s) - \bar{y}$. After some passages, including a model reduction step derived through a balanced realization of the linearized system and a truncation of the state vector (the MATLAB Control Systems Toolbox instruction *modred* was used), the system is rewritten in the following state-space (nonminimal) representation

$$\begin{aligned} x_{IO}(k+1) &= A_{IO} x_{IO}(k) + B_{IO} \delta u(k) + M_{IO} d(k) \\ \delta y(k) &= C_{IO} x_{IO}(k) \end{aligned}, \tag{12}$$

where $x_{IO}(k+1) = [\delta y(k+1), \delta y(k), \delta y(k-1), \delta u(k), \delta u(k-1), d(k), d(k-1)]'$, and the matrices A_{IO}, B_{IO}, M_{IO}, and C_{IO} are defined accordingly.

In order to derive the MPC control law, the following quadratic discrete-time cost function is considered

$$\begin{aligned} J(x_{IO}(k), \delta u(\cdot)) = &\sum_{i=0}^{7} \left(q\left(y^0(k+i) - y(k+i)\right)^2 + \left(\delta u(k+i)\right)^2 \right) \\ &+ q\left(y^0(k+8) - y(k+8)\right)^2 \end{aligned}, \tag{13}$$

where q is a positive constant.

The solution of the optimization problem has the following structure:

$$\delta u^o(k) = G_{y^0}(y^0 - \bar{y}) + G_{x_{IO}} x_{IO}(k) + G_D D(k), \tag{14}$$

where y^0 is the future (constant) value of the set point, $D(k) = [d(k), d(k+1), \ldots, d(k+7), d(k+8)]$ is the disturbance signal (meal), and G_{y_0}, $G_{x_{IO}}$, G_D are suitable matrices.

If the calculated insulin rate $u(t)$ is negative, a zero value will be applied to the system. The fulfilment of the state constraints, however, cannot be guaranteed; it is only possible to tune the parameter q so as to improve the regulation performance. The major advantages of this input–output MPC scheme are that an observer is not required (x_{IO} is made of past input and output values) and that it is easily implementable because real-time optimization is avoided.

Model predictive control, in general, has several independent tuning parameters: control and prediction horizon, output and input weights, and terminal penalty. However, as better illustrated in the Results section, the main advantage of the adopted choice is the possibility to achieve satisfactory results tuning only one parameter (the output weight q, which is also equal to the weight in the terminal penalty) in a quite straightforward and intuitive way.

With a relatively small increase of the computational burden it is possible to consider both input and state constraints explicitly by solving a constrained linear quadratic optimization problem. In this article, results

obtained with constrained linear MPC are not reported because they did not show any significant improvement in our experiments. In fact, the explicit consideration of only input constraints does not improve the performance of the unconstrained saturated control law, whereas the fully constrained problem, i.e., also with state constraints, introduces nontrivial feasibility problems as a consequence of the approximation error caused by linearization and model reduction. Further work is required to explore this issue.

At the cost of a significant increase of the computational burden, a nonlinear MPC approach could be pursued. The main advantages would be the possibility to take into account nonlinear dynamics and a more robust fulfilment of state constraints. Of course, this calls for a well-identified patient model. Some preliminary results are presented in Magni and colleagues.[15]

Proportional Integral Derivative Control

In order to assess the performance of the proposed control methodology, comparison with a classical PID control law is considered. The control law in the different experiments has been tuned on either the average patient or individually. In the latter case, only the proportional gain K_p has been modified. Moreover, the PID controller incorporates a feed-forward action in order to take advantage of the knowledge of meal amount. The parameters of the PID are $T_i = 210$ and $T_d = 40$, where T_i and T_d are integral and derivative times, respectively. The feed-forward action from the meal signal to insulin rate is given by a transfer function with gain 0.0022. Both the PID and the feed-forward action have been implemented in discrete time with sampling period $T_s = 30$ minutes. In order to obtain discrete-time implementation, an FOH approximation method was used together with an antiwindup scheme.

Results

Experiment 1: The ingested amount of glucose is exactly as considered in the protocol. One hundred subjects are simulated using an MPC control law synthesized with $q = 0.003$ for all subjects and the set point is 112 mg/dl.

Experiment 2: The same as experiment 1, but this time q has been tuned for each subject.

Experiment 3: The same as experiment 2, but without meal announcement.

Experiment 4: The ingested amount of glucose is varied randomly within ±40% of the nominal value for all 100 patients. The MPC control law has the same parameters as those used for experiment 2 and relies on the nominal glucose dose to decide the feed-forward action.

Experiment 5: The same as experiment 1, but using a PID control law with $K_p = -7.09 \times 10^{-4}$ for all subjects.

Experiment 6: The same as experiment 5, but the gain of the PID is tuned individually.

Experiment 7: The same as experiment 6, but without meal information.

Experiment 8: The same as experiment 4, using a PID control law with meal information.

Experiment Evaluation

Figure 1 shows the scatter plots of Min_Glycemia vs Max_Glycemia during *regulation* for experiments 1–8. In particular, the six panels in **Figure 1** contain the following comparisons: (**A**) experiments 1 and 2, (**B**) experiments 5 and 6, (**C**) experiments 2 and 3, (**D**) experiments 6 and 7, (**E**) experiments 2 and 4, and (**F**) experiments 6 and 8. Note that the panels in the left column (**A**, **C**, and **E**) refer to MPC, whereas the results of PID control are reported in the right column (**B**, **D**, and **F**). Note that in the scatter plot well-regulated patients should stay close to the lower left corner.

Figure 2 shows the effect of a change of the MPC parameter q on the scatter plot (Min_Glycemia, Max_Glycemia) for experiment 2. More precisely, the individually tuned values of q were all scaled by the constant factor 0.8. The corresponding points, before (**full dots**) and after (**star-circle**) scaling, are connected to each other.

In **Figure 3**, the box plots for LBGI and HBGI are reported for experiments 1–8 during both *commutation* ("c") and *regulation* ("r") periods.

In **Figure 4**, the MPC and PID control schemes are compared in subject 36 showing plasma glucose and external insulin evolution. In order to have a global comparison of the relative performance of the two control strategies for all subjects, the scatter plots of Min_Glycemia vs Max_Glycemia in **Figure 5** are reported for experiments 2 and 6.

In reference to the *regulation* period, it is apparent from **Figure 1** that both MPC and PID control achieve good regulation performance even if their design is based only on the average patient model. However, in view of significant interindividual variability, their performance is enhanced considerably if the control parameters (MPC parameter q and PID gain, respectively) are tuned

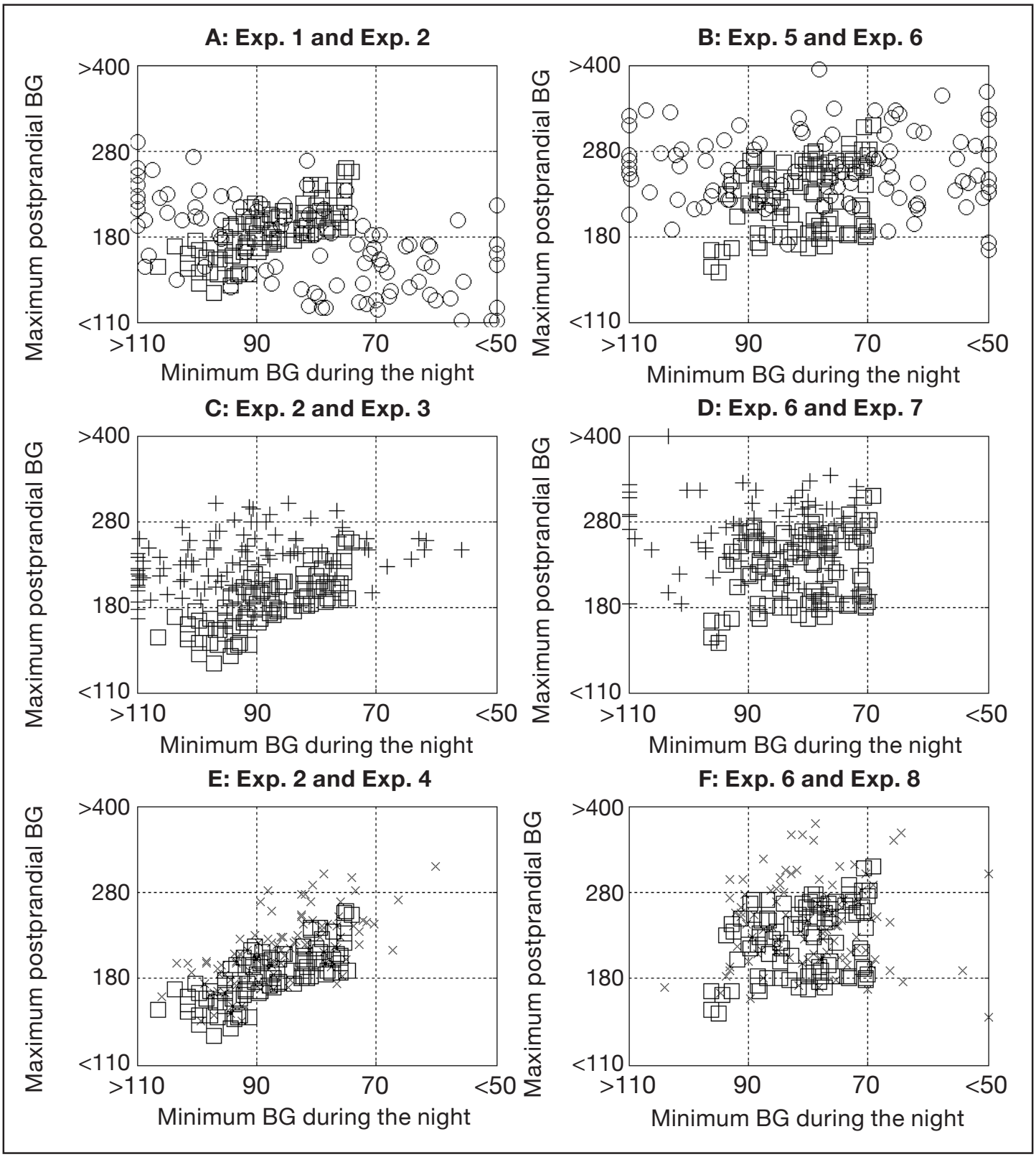

Figure 1. Experiments 1–8: scatter plots of Min_Glycemia vs Max_Glycemia. Each plot compares the results of two experiments. A, C, and E refer to MPC (∘, experiment 1; □, experiment 2; +, experiment 3; ×, experiment 4), whereas B, D, and F refer to PID control (∘, experiment 5; □, experiment 6; +, experiment 7; ×, experiment 8). Well-regulated patients should stay close to the lower left corner.

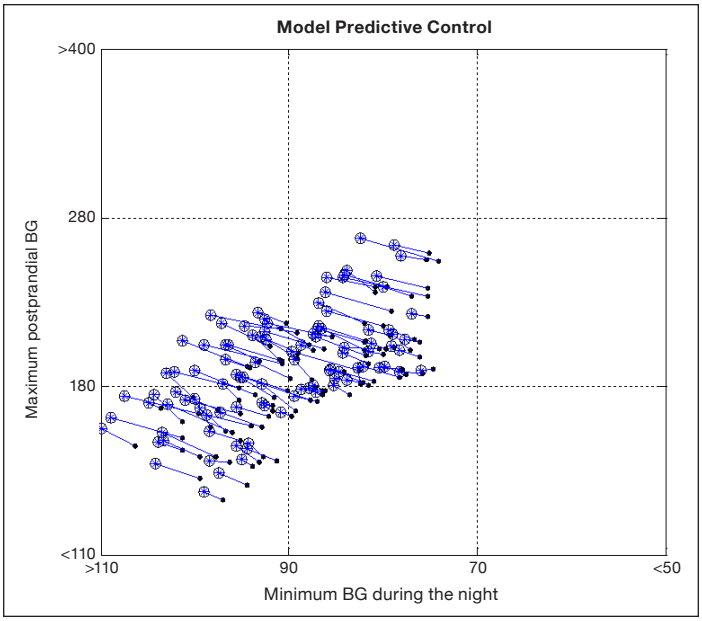

Figure 2. Min_Glycemia vs Max_Glycemia during *regulation* for experiment 2 with the individually tuned values of q (full dot) and with same values of q scaled by the constant factor 0.8 (star-circle).

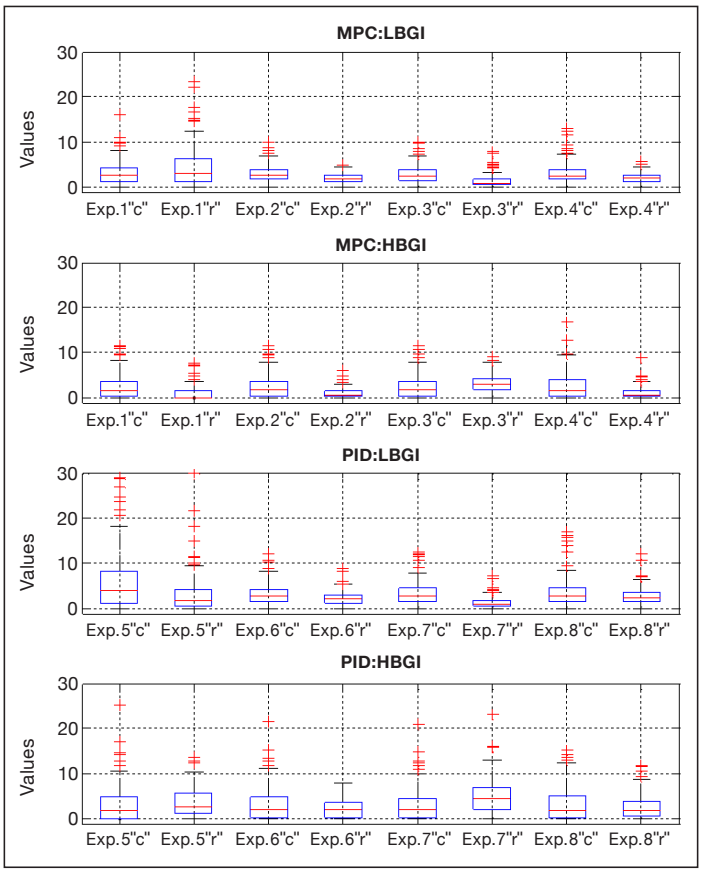

Figure 3. Box plots for LBGI and HBGI for experiments 1–8 during both *commutation* ("c") and *regulation* ("r") periods.

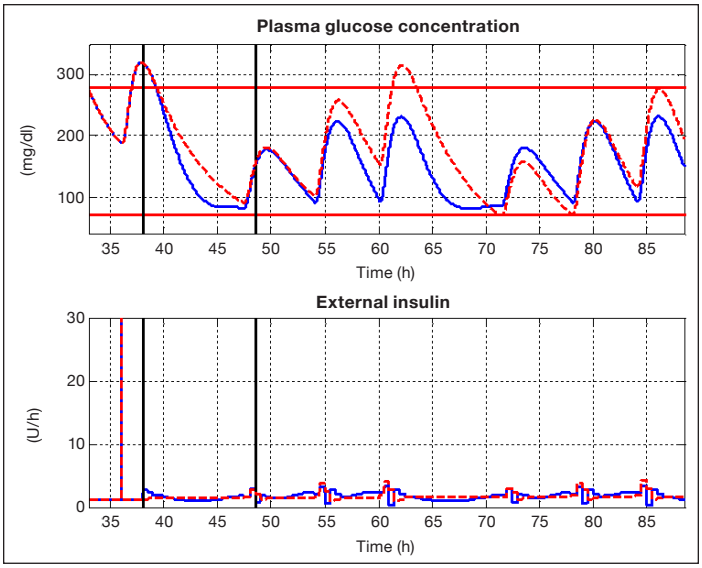

Figure 4. Subject 36: experiment 2 (MPC, continuous line) and experiment 6 (PID, dashed line).

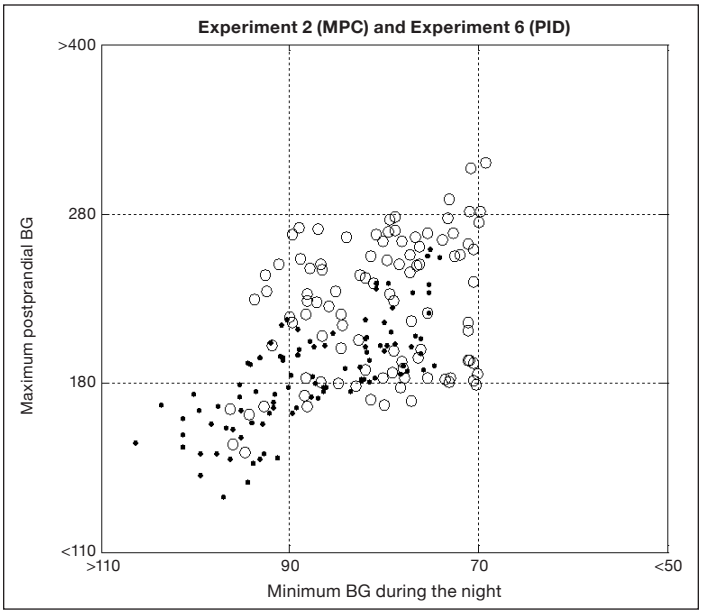

Figure 5. Scatter plots of Min_Glycemia vs Max_Glycemia for experiments 2 (•) and 6 (○).

individually (see **Figures 1A** and **1B**). The tuning of parameter q is straightforward and intuitive: a reduction of q makes the control action less aggressive, thus using less insulin. This implies an increase of both Min_Glycemia and Max_Glycemia, as shown in **Figure 2**. The ability of MPC to take advantage of meal announcement is shown in **Figure 1C**. As seen in **Figure 1D**, there is performance deterioration when meal information is not considered also with PID control. Imperfect knowledge of the amount of ingested glucose (experiments 4 and 8)

causes only a marginal deterioration of performance of the regulator for MPC, whereas a greater deterioration is observed for PID control (**Figures 1E** and **1F**). This difference is also highlighted by the LBGI and HBGI box plots reported in **Figure 3**. Robustness in the face of meal announcement information is essential because the feed-forward action relies on presumed knowledge of meals that are 4 hours ahead. It is remarkable that MPC achieves satisfactory results even with a 40% meal uncertainty.

As evident from **Figure 4**, the MPC controller normalizes glycemia very quickly, even if starting from unfavorable initial conditions. The transient of external insulin shows that the insulin flux increase anticipates the meals. This is because of the predictive ability of MPC that computes the current value of the insulin infusion also based on the future values of the meals (see the vector $D(k)$ in the control law[14]).

Finally, **Figure 5** shows that, using the best implementations (e.g., individual tuning), MPC produces a better regulation than PID, limiting glucose oscillation significantly.

Conclusions

The *in silico* trial has demonstrated that linear output feedback MPC achieves satisfactory glycemic regulation in a population of simulated "type 1 diabetic patients." The proposed scheme is robust with respect to uncertainty in the meal announcement information. Robustness with respect to sensor errors could be investigated by complementing the simulator with a probabilistic model of sensor noise. Another future research direction concerns the development of nonlinear MPC that could take advantage of the knowledge of the nonlinear dynamics described by the large-scale *in silico* model.

Funding:

The authors acknowledge the financial support by the Juvenile Diabetes Research Foundation "Artificial Pancreas Project" at the University of Virginia.

References:

1. Bequette BW. A critical assessment of algorithms and challenges in the development of a closed-loop artificial pancreas. Diabetes Technol Ther. 1998;7:28-47.
2. Hovorka R. Continuous glucose monitoring and closed-loop systems. Diabet Med. 2005;23:1-12.
3. Klonoff DC. The artificial pancreas: how sweet engineering will solve bitter problems. J Diabetes Sci Technol. 2007;1(1):72-81.
4. Mayne DQ, Rawlings JB, Rao CV, Scokaert PO. Constrained model predictive control: stability and optimality. Automatica. 2000;36:789-814.
5. Garcia CE, Prett DM, Morari M. Model predictive control theory and practice–a survey. Automatica. 1989;25(3):335-48.
6. Dua P, Doyle FJ III, Pistikopoulos EN. Model-based blood glucose control for type 1 diabetes via parametric programming. IEEE Trans Biomed Eng. 2006;53:1478-91.
7. Parker RS, Doyle FG 3rd, Peppas NA. A model-based algorithm for blood glucose control in type I diabetic patients. IEEE Trans Biomed Eng. 1999 Feb;46(2):148-57.
8. Dalla Man C, Rizza RA, Cobelli C. Meal simulation model of the glucose-insulin system. IEEE Trans Biomed Eng. 2007;54:1740-9.
9. Dalla Man C, Camilleri M, Cobelli C. A system model of oral glucose absorption: validation on gold standard data. IEEE Trans Biomed Eng. 2006;53:2472-8.
10. Vicini P, Caumo A, Cobelli C. The hot IVGTT two-compartment minimal model: indexes of glucose effectiveness and insulin sensitivity. Am J Physiol. 1997;273:E1024-32.
11. Breda E, Cavaghan MK, Toffolo G, Polonsky KS, Cobelli C. Oral glucose tolerance test minimal model indexes of beta-cell function and insulin sensitivity. Diabetes. 2001;50:150-8.
12. Dalla Man C, Toffolo G, Basu R, Rizza RA, Cobelli C. A model of glucose production during a meal. Proceedings of IEEE-EMBS Conference, New York; 2006.
13. Verdonk CA, Rizza RA, Gerich JE. Effects of plasma glucose concentration on glucose utilization and glucose clearance in normal man. Diabetes. 1981;30:535-7.
14. Kovatchev BP, Clarke WL, Breton M, Brayman K, McCall A. Quantifying temporal glucose variability in diabetes via continuous glucose monitoring: mathematical methods and clinical application. Diabetes Technol Ther. 2005;7:849-62.
15. Magni L, Raimondo DM, Dalla Man C, De Nicolao G, Kovatchev B, Cobelli C. Model predictive control of glucose concentration in subjects with type 1 diabetes: an *in silico* trial. 17th IFAC World Congress; submitted.