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Implications of Meal Library & Meal Detection to Glycemic Control of Type 1 Diabetes Mellitus through MPC Control

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Abstract: Recent technological progress in insulin pumps and continuous glucose monitors (CGM) are enabling development of an artificial β-cell that will allow superior glycemic control for patients with type 1 diabetes mellitus (T1DM). A control algorithm that is implemented in such system will need to regulate basal insulin as well as to reject unmeasured disturbances, such as meals. A traditional approach is to combine feed-forward control as a means to overcome meal disturbances, where the user informs the controller on a meal and estimates the size of that together with PID control or Model Predictive Control (MPC) to address the regulation problem. This approach fails with T1DM adolescents and children because they often forget to give a pre-meal bolus and are poor at estimating meal sizes. A novel approach to overcome this problem is suggested in this paper by the combination of a meal library and a meal detection algorithm in the framework of Model Predictive Control (MPC). In this work, the challenging problem of an unannounced mixed meal is being addressed using this novel combination.

1. INTRODUCTION

Type 1 diabetes mellitus (T1DM) is an autoimmune disease characterized by the destruction of pancreatic β-cells that are responsible for the production of insulin. As a result, exogenous insulin is required to regulate glucose levels in patients with type 1 diabetes. Currently, glucose sensors and insulin pumps are used independently by paitients in an attempt to maintain normoglycemia. Recent advances in insulin pumps and glucose sensing technology suggest that a closed-loop artificial β-cell for T1DM could soon be available with suitable control algorithms (Hovorka et al. 2006; Gillis et al. 2007). Development of automated control sets a basic requirement: perform at least as well as a patient that uses bolus dosing effectively. The ultimate goal of the automated system is to be able to fully mimic the pancreatic β-cells. The automated closed-loop artificial β-cell is a challenging control problem due to uncertainty in the available data, the difficulty of developing accurate models and the nature of unmeasured disturbances. This challenging problem can be divided into two control objectives, the first is a regulation of basal insulin and the second is disturbance rejection including meals, stress, and physical activity.

Hence, any controller that will be implemented in such a system should address these issues and be conservative with disturbances rejection (such as meals), since overdosing of insulin can drive the patient to severe hypoglycemia and a controller only delivering insulin cannot provide adequate counter-regulation..

A traditional control approach for this kind of problem is to combine a feed-forward controller as a mean to overcome meal disturbances, where the user informs the controller about a meal, together with a PID controller Steil (2006) or Model Predictive Control (MPC) Hovorka (2004) to address the regulation problem. These can be considered reasonable for patients who are able and willing to take control of the disease; however, they are not valid for patients who do not, or cannot, assume this responsibility.

A novel approach to overcome this problem is suggested in this paper by the combination of a meal library and a meal detection algorithm in the framework of MPC. This combination permits flexible control over an extensive range of conditions with minimal user intervention. The performance of the proposed strategy is evaluated using a meal library that allows various meal compositions (e.g. type of carbohydrate, fat, and protein) as well as different meal sizes and serves as in-silico test bed.

The remainder of this paper outline is as follows: Section 2 presents a library of glucose absorption profiles containing

different compositions of mixed meals; Section 3 introduces the meal detection algorithm; Section 4 presents the proposed control strategy; Section 5 presents simulation results; Section 6 concludes the paper and proposes future research.

2. GLUCOSE ABSORPTION MODEL LIBRARY

The modeling of hepatic balance, insulin absorption and the independent/dependent insulin utilization has been extensively investigated for a number of years: Bergman (2003), Cobelli (1982) and Hovorka (2004). However, less is known about intestinal absorption patterns (Dalla Man et al. 2006), which makes the task of developing a general and accurate mathematical model for glucose rate of appearance following mixed meals a challenging task. A practical solution to overcome this difficulty has been presented by the authors in the form of a library of glucose absorption profiles for different types of mixed meals (Herrero et al. 2007).

The library has been constructed based upon a simulation model of the glucose-insulin system in the postprandial state by Dalla Man (2007) together with published data from studies on the effect of the meal composition (e.g. carbohydrate type, fat) on the plasma glucose and insulin concentrations of healthy subjects (Normand et al. 2001; Frost et al. 2003; Galgani et al. 2006).

Simulation model parameters are based on data from a large database of normal subjects who underwent a triple-tracer meal protocol with a fixed meal composition. The library consists of a set of mixed meals represented by the set of parameters corresponding to the glucose absorption sub-model.

The model equations for the glucose absorption sub-model are:

$$\begin{aligned} \dot{q}_{sto1}(t) &= -k_{21}\cdot q_{sto1}(t) + D\delta(t) \\ \dot{q}_{sto2}(t) &= -k_{empt}\cdot q_{sto2}(t) + k_{21}\cdot q_{sto1}(t) \\ \dot{q}_{gut}(t) &= -k_{abs}\cdot q_{gut}(t) + k_{empt}\cdot q_{sto2}(t) \\ R_a(t) &= f\cdot k_{abs}\cdot q_{gut}(t) \end{aligned} \quad (1)$$

where $q_{sto1}(t)$ and $q_{sto2}(t)$ are the amounts of glucose in the stomach (solid and liquid phase, respectively); $\delta(t)$ is the impulse function; D is the amount of ingested glucose; $q_{gut}(t)$ is the glucose mass in the intestine, k_{21} the rate of grinding; k_{empt} the rate of gastric emptying; k_{abs} the rate constant of intestinal absorption; and f the fraction of the intestinal absorption which actually appears in plasma. The nonlinear representation of the gastric empting by Dalla Man (2007) is described in the following equations:

$$k_{empt}(t) = k_{\min} + \frac{k_{\max}-k_{\min}}{2} \left\{\tanh\left[\alpha\left(q_{sto}-b.D\right)\right] - \tanh\left[\beta\left(q_{sto}-c.D\right)\right] + 2\right\} \quad (2)$$

with

$$q_{sto}(t) = q_{sto1}(t) + q_{sto2}(t) \quad , \quad \alpha = \frac{5}{2\cdot D\cdot(1-b)} \quad , \quad \beta = \frac{5}{2\cdot D\cdot c}$$

where $k_{\min}$ and $k_{\max}$ are the minimal and maximal absorption rates respectively, b is the percentage of the dose for which k_{empt} decreases at $(k_{\max} - k_{\min})/2$. Similarly, c is the percentage of the dose for which k_{empt} is back to $(k_{\max} - k_{\min})/2$.

Limited published data on the effect of meal composition on plasma glucose and insulin concentrations for T1DM subjects forced the authors to rely on data from healthy subjects. This can be justified by the fact that the glucose absorption physiology is similar in T1DM and healthy subjects. Furthermore, with healthy subjects, there is less interference since the endogenous glucose production is mostly suppressed in the prandial period.

The parameters of the glucose absorption sub-model ($k_{\max}$, $k_{\min}$, k_{abs}, ,b and d), were fitted for various compositions of mixed meals by the constrained optimization routine *fmincon* (The MathWorks, Inc., Natick, MA), by introducing plasma insulin profiles and carbohydrate amount to the glucose-insulin simulation model. The constrains for such optimization were derived from physiological data.

Fig. 1 presents an example of an absorption profile, which has been developed based on the mixed meal with the composition and nutritional characteristics shown in Table 1. The line with red squares in the top graph represents the measured glucose concentration; the solid green line corresponds to the simulated response with the identified parameters. The bottom figure shows the corresponding glucose absorption profile where the corresponding fitted parameters of the glucose absorption sub-model with their coefficient of variation (CV) values are listed in Table 2, (Cobelli and Carson 2007).

Table 1. - Nutritional characteristics of the identified low glycemic meal consist of : long-grain white rice, low-fat cheese, fructose, pear, bran-cookies and oil (Galgani et al. 2006)

Energy (KJ)	1516±35
Carbohydrates (g)	52.4±1.2
Fat (g)	10.5±0.2
Protein (g)	14.5±0.3
Dietary fiber (g)	2.9±0.1
Energy density (KJ/g)	3.93±0.02
Glycemic load (g)	22±2
Glycemic index (%)	43

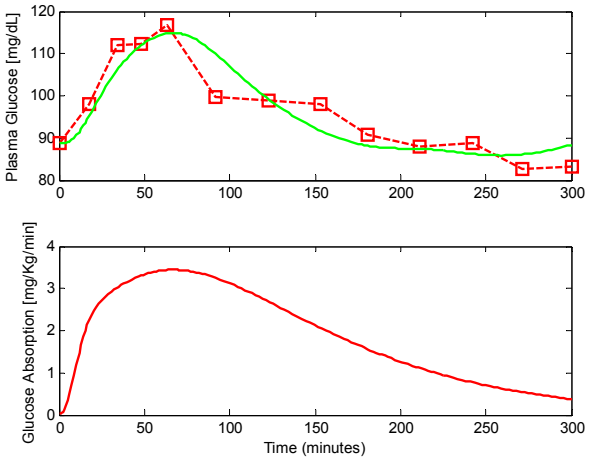

Fig. 1 – Example of plasma glucose and glucose absorption profile of the mixed meal (Table 2); Measured glucose concentration is denoted by red squares, simulated response as a solid green and the corresponding glucose absorption profile as a solid red line.

Table 2. - Indentified parameters

Parameter	k_{max}	k_{min}	k_{abs}	*B*	*D*
Value	0.0516	0.0135	0.0222	0.8203	0.0074
CV (%)	42.5	48.5	75.5	23	52

3. MEAL DETECTION

A meal event is one of the largest disturbances that a control algorithm for an artificial β-cell must manage. However, to achieve a fully automated closed-loop system, we advocate that the controller be informed about the meal event in order t to eliminate the disturbance without causing postprandial hypoglycemic due to excessive insulin delivery. One way to automate the response to a meal event was suggested by Dassau (2007), where the glucose rate of change estimated from CGM data is used to flag a meal. A detailed description of the detection algorithm can be found in (Dassau et al. 2008). For this implementation, a simplified algorithm is implemented to notify the MPC of the upcoming meal. The glucose rate of change is estimated using a three point (current and two previous samples) backward difference calculation with a set of heuristics to filter noise and signal drops. It has been shown that the meal detection algorithm can flag a meal in less than 30 min from the meal onset,when the glucose has increased no more than 30 mg/dL from the base line (pre-meal). This encouraging result permits automated control action in sufficient time to avoid a prolonged post-prandial hyperglycemic event.

4. METHODOLOGY

We propose to use a MPC controller with a meal detection algorithm and a meal library, as a control solution that can cope with unannounced mixed meals in the context of a fully closed loop artificial β-cell. The development environment of Matlab® and Simulink® *(*The MathWorks, Inc., Natick, MA*)* with the Matlab® MPC toolbox were selected for this implementation. We then introduced the aforementioned glucose-insulin simulation model for a T1DM patient (Dalla Man et al. 2007) as an *in silico* "process plant". In particular, subject #2 was selected from the associated database as the plant. The Jacobian of the same model with a different set of parameters (subject #1), was considered as the prediction model for the MPC controller. This mismatch is introduced in order to make the simulations more realistic. Fig. 2 shows the mismatch between the two models for the previously described mixed meal and a same insulin bolus of 3.5U and the corresponding basal insulin infusion. Solid red line and dotted green corresponds to patient 1 and patient 2 respectively.

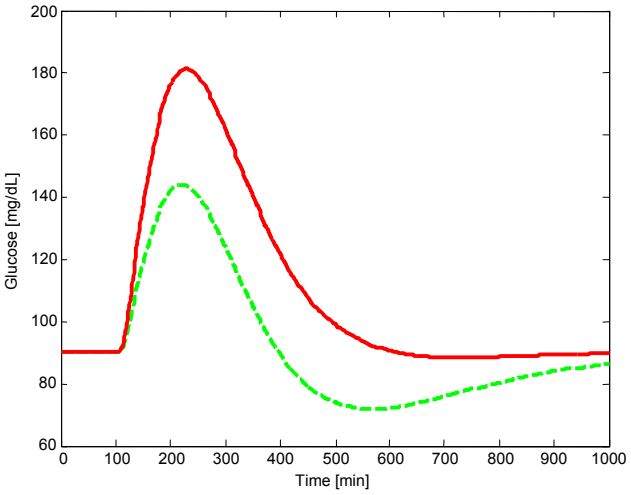

Fig. 2 – Model mismatch between patient #1 denoted as a red solid line and patient #2 as a dashed green line.

A summary of this combined strategy is presented in Fig. 3. Glucose values are conveyed to the meal detection algorithm as soon as a meal is detected, a flag is sent to the controller to: (a) switch from a constant reference (e.g. 90 mg/dL) to a variable one (e.g. trapezoidal, (Hovorka et al. 2004; Ruiz-Velazquez et al. 2004; Bequette 2005) that is a more physiological trajectory that mimics the normal glucose profile to a meal intake. This minimizes the risk of severe hypoglycemic events due to less aggressive control action; (b) a generic glucose absorption profile is introduced to the controller as an additional input (measured disturbance) to improve the controller prediction and performance since the composition and meal size is unknown.

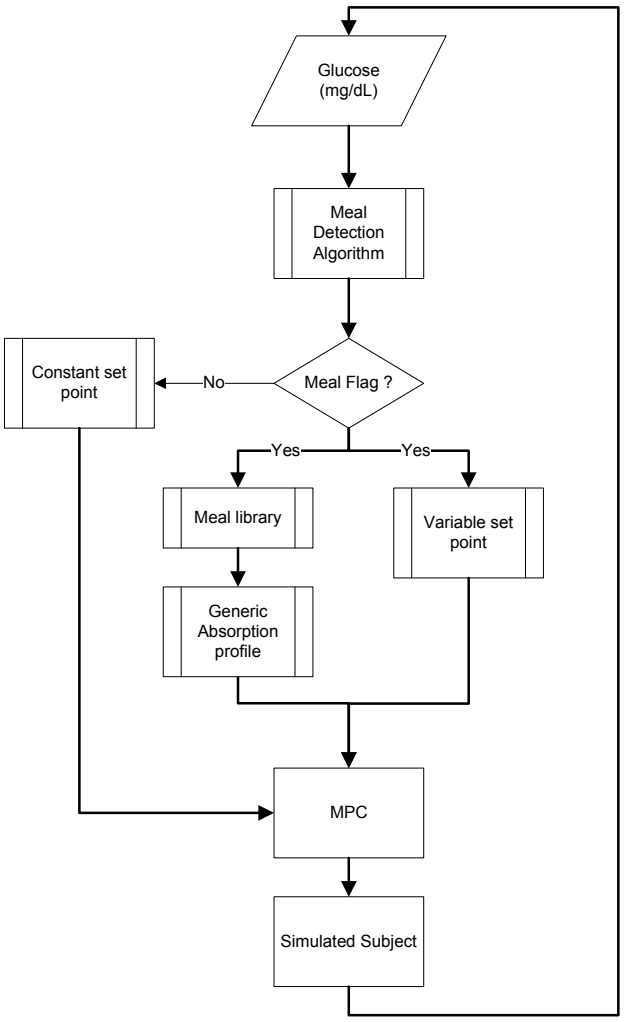

Fig. 3 – Flow diagram of the combined approach of MPC with meal detection and the corresponding detection outputs (a) variable setpoint and (b) absorption profile.

5. RESULTS

In order to evaluate the proposed approach, four different configurations are presented: (1) simple MPC without meal detection (i.e. unannounced meal); (2) MPC with meal detection and variable reference; (3) MPC with meal detection, variable reference and generic glucose absorption profile; (4) MPC with meal announcement, variable reference and generic glucose absorption profile (i.e. user intervention). The last configuration serves to quantify the delay associated with meal detection and its reflection on the controller performance.

All four configurations were challenged with the same mixed meal, previously described Section 2 and with the same MPC tuning.

The MPC prediction and control horizons have been set to 2 hours, and 15 minutes, respectively. No significant improvements were observed for longer horizons. The controller weight were [1,0.01] for the output (W_y) and input (W_u) respectively and the sampling time was set to 5 minutes

As for constraint on the input, the physical constraints of an actual insulin pump were used ([0,72] U/hr). At no time during the *in silico* trials were these constraints violated.

To allow comparisons, a basal glucose level of 90 mg/dL and a meal intake at 100 minutes from time zero were selected for all four scenarios. The following line codes are used: setpoint as a red dotted line; plasma glucose as a blue line; hypoglycemic boundary (70 mg/dL) as a green dashed line, meal flag point as a green circle and controller moves as a black line in the lower plot

5.1 Configuration #1 – Simple MPC (no meal detection)

This configuration represents the results of a simulation when a MPC controller with a constant setpoint of 90 mg/dL needs to reject a meal disturbance. As presented in Fig. 4, the response provided by the controller is completely unacceptable from a clinical point of view, since a severe hypoglycemic state is reached. This is mainly due to the large mismatch between the prediction model and the plant, which is often the case in reality.

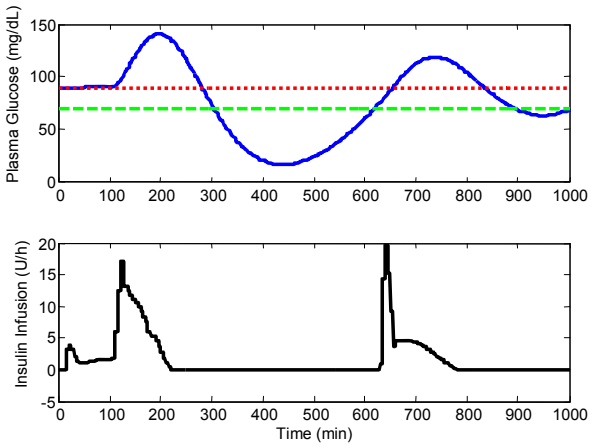

Fig. 4 – Simple MPC with no meal detection. 15 U of insulin were used to cover the meal (lower figure in black), which led to severe hypoglycemia. The setpoint denoted by the red dotted line, plasma glucose with blue solid line, hypoglycemic boundary (70 mg/dL) with green dashed line and controller moves with the black line in the lower plot.

5.2 Configuration #2 - MPC with meal detection and variable reference

As can be seen from Fig. 5, as soon as a meal is detected (~ 12 min from the onset of the meal) a trapezoidal reference is triggered which notably improves the response to this disturbance. Nevertheless, a small hypoglycemic event is observed. As expected, the reference shape notably affects the controller performance to a specific meal event. By selecting a generic shape, an improved level of performance can be observed with respect to a constant setpoint.

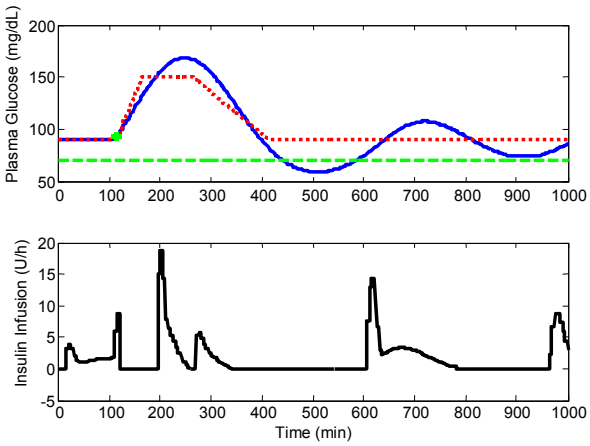

Fig. 5 – MPC with meal detection and variable reference. 11.5 U of insulin were used to cover the meal, which led to a mild hypoglycemia. The setpoint denoted by the red dotted line, plasma glucose with blue solid line, hypoglycemic boundary (70 mg/dL) with green dashed line, meal flag point with the green circle and controller moves with the black line in the lower plot.

5.3 Configuration #3 - MPC with meal detection, variable reference and estimated glucose absorption profile

In this configuration, in addition to the trapezoidal reference, generic meal absorption and sensor noise are introduced. The absorption sub-model from Hovorka et al (2004) is used to generate the profile. As can be seen from Fig. 6, this addition improves the controller performance and its ability to follow the trajectory setpoint regardless of some oscillations, which are perfectly justifiable. Moreover, no postprandial hypoglycemic events were present. The parameter values for the glucose absorption sub-model are: D_g=45g, A_g=0.8 and t_{max}=70.

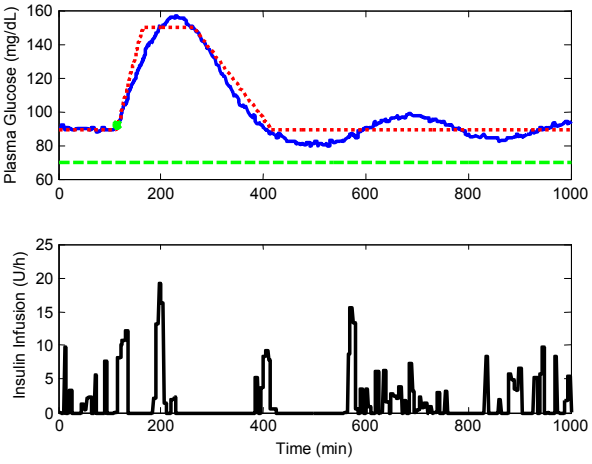

Fig. 6 – MPC with meal detection, variable reference and estimated glucose absorption profile and process noise of ± 3 mg/dL. 11 U of insulin were used to cover the meal. The setpoint denoted by the red dotted line, plasma glucose with blue solid line, hypoglycemic boundary (70 mg/dL) with green dashed line, meal flag point with the green circle and controller moves with the black line in the lower plot.

5.4 Configuration #4 - MPC with meal announcement, variable reference and estimated glucose absorption profile

This configuration is intended to evaluate a scenario in which the user informs the controller of a meal event. The following steps are taken as soon as such information is reveled to the controller: (a) setpoint change (trapezoidal reference) is delayed for 15 minutes from the meal announcement in order to contemplate the glucose absorption delay, (b) a more accurate absorption profile is estimated since, the amount of carbohydrates is considered to be approximately known. The parameter values for the glucose absorption sub-model are: D_g=52g, A_g=0.8 and t_{max}=70.

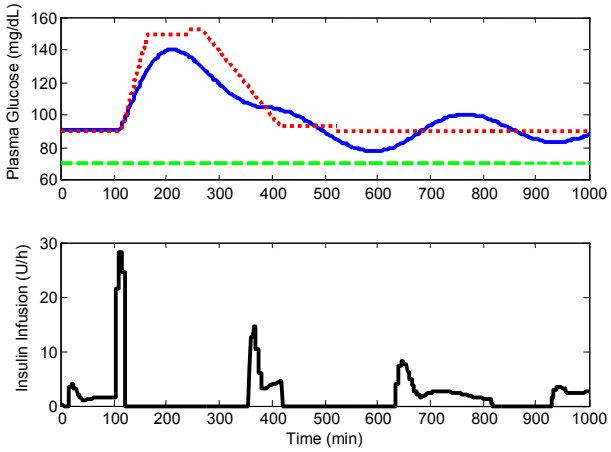

Fig. 7 – MPC with announced meal, variable reference and generic glucose absorption profile. 10 U of insulin were used to cover the meal. The setpoint denoted by the red dotted line, plasma glucose with solid blue line, hypoglycemic boundary (70 mg/dL) with green dashed line and controller moves with the black line in the lower plot.

As was expected, the controller performance for the announced meal case 4 (Fig. 7) is better than the case with meal detection, but only modestly. Hence, the delay introduced by the meal detection algorithm does not affect significantly the performance of the controller.

Table 3. – Clinical results summary

Configuration	1	2	3	4
Insulin units to cover the meal (U)	15	11.5	11	10
Hypo event	Yes - severe	Yes - mild	No	No
Glucose maximum (mg/dL)	140	170	156	141
Glucose minimum (mg/dL)	15	55	80	74
Time for glucose to return to premeal baseline * (min)	700	700	270	690
*Premeal glucose values were between 80 to 100 mg /dL				

6. CONCLUSIONS

A novel approach for glucose control consisting of the combination of a meal detection algorithm together with a

variable setpoint and an absorption profile achieved both the minimization of post-prandial hyperglycemia and postprandial hypoglycemia as can be seen in Table 3. Furthermore, it has been shown that the time delay, which is introduced by the meal detection, has only a minor effect on the controller performance. Hence, this can serve as a fall back to meal announcement. We can conclude that an artificial β-cell incorporating such an approach will allow flexibility and better control performance in uncertain conditions. In the future, clinical evaluations of the simulation results are needed to fully examine the combined approach.

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