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Robust Optimal Control of Artificial Pancreas

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***Abstract*— Type 1 diabetes affects 415 million patients in the world, the treatment of this illness still limited to external injection of insulin. The Artificial Pancreas (AP) inject automatically the needed amount of insulin through the day.**
In the presented work a new method of control of AP is introduced based on Model Predictive Control (MPC).
The result of in silico simulation done on the FDA-accepted UVa\Padova metabolic simulator shows a great improvement in the development of AP by rejecting rapidly the effect of meal intake and avoiding hypoglycemia.

***Keywords*— Artificial Pancreas, Control Algorithm, Biomedical control, MPC, Hypoglycemia.**

I. INTRODUCTION

Type 1 Diabetes Metabolism (T1DM) is auto immune disease results from the pancreas's incapacity to produce enough insulin. When insulin is lacking the level of glucose rise and hyperglycaemia spends a long time and has a big glucose peak which cause a lot of complications. T1DM can only be treated by external insulin injections. Insulin is a hormone that allows glucose absorption in body cells in order produce energy. Artificial Pancreas (AP) is a very effective therapeutic solution to this disease.

The AP system computes and injects the right amount of insulin needed to regulate blood glucose, it is composed from tree components; subcutaneous glucose sensor (CGM), a subcutaneous insulin pump, and a control algorithm. Quite recently, considerable attention has been paid to develop AP system. Some of this research are supported by the Juvenile Diabetes Research Foundation, the European Commission, and the National Institutes of Health (see Refs. [1–9]).

Automatic blood glucose is a complicate tasks given that a lots of challenge exist, for example meal disturbance, big delay in subcutaneous measure and injection and recognition of physical exercises and illness.

The main objectives of the AP is to keep blood glucose in the euglycemic zone (avoiding hypoglycemia and limiting hyperglycemia) the maximum possible, minimize the amount of insulin to inject and emulate the functioning of the natural pancreas.

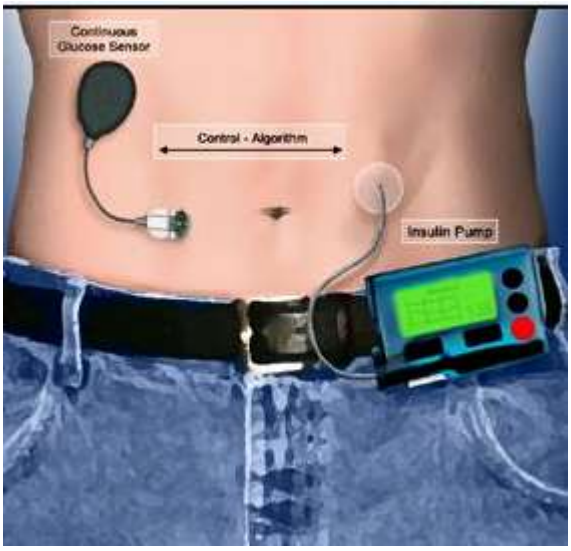

Fig. 1 Image of an Artificial Pancreas

The most important part of the AP is the control algorithm, which is in charge to compute the quantity of insulin to inject in the subcutaneous tissue on the basis of the subcutaneous continuous glucose measurements. The wide used control algorithm in this application is Proportional Integrator Derivative (PID) and the Model Predictive Control (MPC).

PID has been used in 2014 by Jacobs et al. to design a control algorithm that incorporates both fading memory proportional derivative controller (FMPD) and adaptive system for estimating changing sensitivity [11]. In 2015 Huyett et al. realize a fully implantable AP using intra-peritoneal (IP) insulin delivery and glucose sensing [12]. In 2016 TT. Ly et al. determine the feasibility and efficacy of an automated PID with insulin feedback (PID-IFB) controller in overnight closed-loop (OCL) control of children and adolescents [13]. Pinsker et al. compare MPC and PID control for the AP, and indicate that MPC performed particularly well [14].

MPC has been used in 2015 by Jacobs et al. to show how exercise can be automatically detected and use an exercise dosing adjustment algorithm [15]. Del Favero et al. suggest in randomized 2-month study a modular model predictive control (MMPC) managed by a wearable system [16]. In 2016 Resalat et al. introduce a DH-MPC approach that can switch between dual hormone and single hormone [17]. Renard et al. investigate a wearable AP during day and night (D/N-AP) for 1 month under free-living conditions in patients with T1DM. Doyle's group extend the MPC by defining a new cost

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function named zone MPC instead of a set point target in several works described in [19-22].

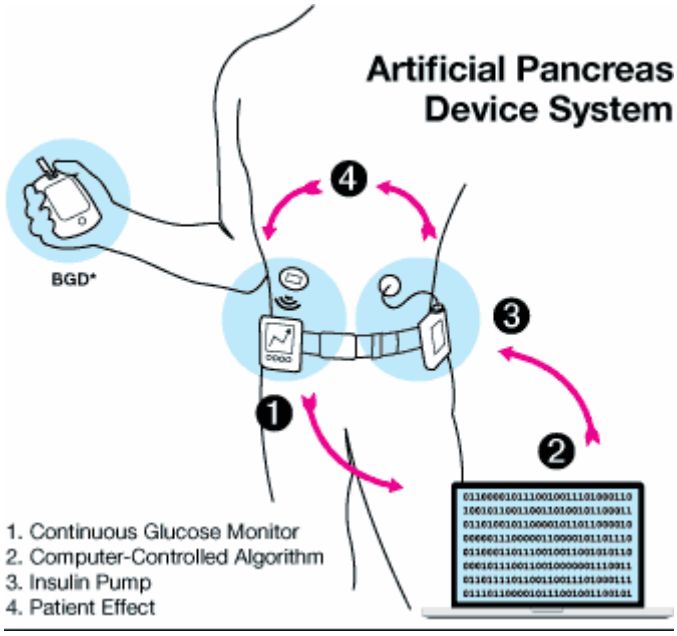

Fig.2 Components of Artificial Pancreas

Based on the approach presented in [23], the purpose of this paper is to design a control algorithm that can overcomes actual challenges in the automatic glucose control. The principle of the new method is to introduce a new formulation of the cost function of MPC that gives a fast controller capable to reject rapidly the effect of meal intake and avoid hypoglycemia.

The remainder of the paper is organized into the followings sections: Section II outlines the modelization phase, section III discusses the design and the tuning of the controller. In silico trials are presented in Section IV, section V concludes the paper.

II. MODELIZATION

A. *Insulin-glucose transfer function*

The model used in this work is a discrete time, linear time-invariant (LTI) system, the sample-period is T = 5 [min], the input of the model is the insulin bolus $U_{IN,i}$ [U] and the plant output is the blood-glucose value $Y_{BG,i}$ [mg/dL]. The model is linearized around a steady-state that leads to an output ys = 110 [mg/dL].
The input and the output can be written as:

$$u_i := U_{IN,i} - U_{BASAL,i} * \frac{T}{60\ min/h} \quad (1)$$

$$y_i = Y_{BG,i} - y_s \quad (2)$$

$Y(Z^{-1})$ is the z-transform of output yi and $U(Z^{-1})$ is the z-transform ui. The transfer function is described as follows:

$$\frac{y(z^{-1})}{u(z^{-1})} = \frac{1800\ Fc}{u_{TDI}} \cdot \frac{z^{-3}}{(1-p_1Z^{-1})(1-p_2Z^{-1})^2} \quad (3)$$

p_1 = 0.98, p_2 = 0.965 are poles, F:=1.5 is the safety factor, U_{TDI} [U] is the subject specific total daily insulin amount, and c is a constant used for unit conversion:

$$c := -60\ (1-p_1)\ (1-p_2)^2 \quad (4)$$

B. *State-space model*

The transfer function can be transformed to the following state space model:

$$x_{i+1} = Ax_i + Bu_i \quad (5)$$

$$y_i = Cx_i \quad (6)$$

$$A := \begin{bmatrix} p_1 + 2p_2 & -p_1p_2 - {p_2}^2 & p_1{p_2}^2 \\ 1 & 0 & 0 \\ 0 & 1 & 0 \end{bmatrix} \in \mathbb{R}^{3\times3}$$

$$B := \frac{1800\ Fc}{u_{TDI}} [1\ 0\ 0]^T \in \mathbb{R}^3$$

$$C := [0\ 0\ 1] \in \mathbb{R}^{1\times3}$$

State-estimation

We need to estimate the first value x_0 in order to predict the other values of the state in the prediction horizon, for that we use a Luenberger observer, the estimator is implemented in this form:

$$\hat{x}_{k+1} = A\hat{x}_k + BU'_k - L(Y'_k - \hat{Y}'_k) \quad (7)$$

$$\hat{Y}'_k = C\hat{x}_k \quad (8)$$

which is a linear time-invariant system with $\hat{x}_k$ representing estimated states of x_k and $\hat{Y}'_k$ representing the estimated BG Y_k. The following equations define the gain L

$$L = K^T \quad (9)$$

$$K = -(CPC^T + \hat{R})^{-1}CPA^T \quad (10)$$

and P satisfies the discrete algebraic Riccati equation:

$$P = APA^T + \hat{Q} - APC^T(CPC^T + \hat{R})^{-1}\ CPA^T \quad (11)$$

Where $\hat{Q} = 1$ and $\hat{R} = 1000$ are positive definite design parameters.

III. CONTROL DESIGN AND TUNING

A. *Controller*

The controller chosen in this work is the MPC because it presents many advantages in control of blood glucose, first the use of constraints on the insulin delivery rate, further it can

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compensate the delay induced by the system by prediction of the evolution of the system then the capacity to include effect of meals, exercise, and other events that are a function of the time of day and it provides the opportunity to integrate many form of cost function.
The principle of MPC is to use a model to predict the effect of control moves on future outputs then to compute the optimal control using an optimization of the cost function. The basic idea is shown in Figure 3 for a constant future set point.

B. Cost function

In the proposed method we apply an exponential penalty on glucose excursions below the desired reference and a quadratic penalty on glucose excursions above the set point in order to get a fast control, the cost function J of the controller is defined as:

$$J'\left(\{U^{k+j}\}_{j=0}^{N-1}\right) = \sum_{j=1}^{P}\|Y_+(k+j)\|^2 + \sum_{j=1}^{P}\exp(a\|Y_-(k+j)\|) + R_+\sum_{j=0}^{N-1}\|U_+(k+j)\|^2 + R_-\sum_{j=0}^{N-1}\|U_-(k+j)\|^2 \quad (12)$$

With $R_+ = 7000$, $R_- = 3000$ (Asymmetric cost function) and $a = 0.16$ are parameters of the command. R and Q are weighting factor, the horizon of prediction is P=9 and N=5 is the horizon of command. The exponential penalty is used to compensate aggressively the hypoglycemia, however using a quadratic penalty on excursions above the reference to maintain a less aggressive response to hyperglycemia.

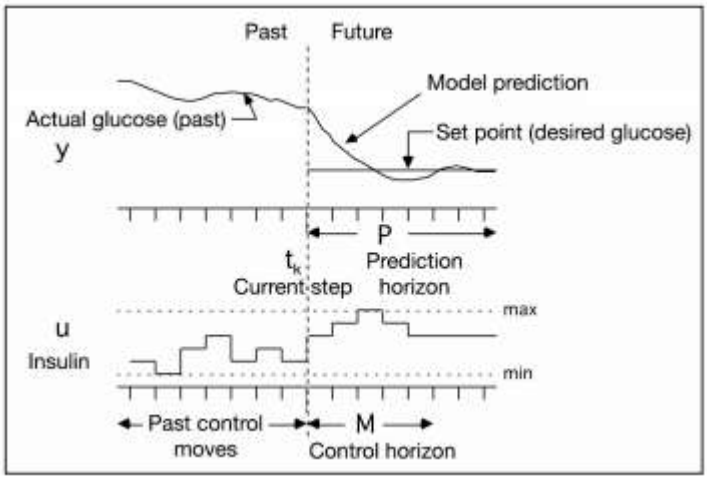

Fig 3. Basic concept of MPC.

C. Speed of command

The two weighting factors Q and R play important role on the tuning of the MPC, they influence directly the performance of the command. Their values can determinate the speed of response of the algorithm to changes in glucose concentration and the aggressively of the control. In order to regulate glycaemia effectively and compensate the delay caused by subcutaneous injection and measure of glycaemia. We accelerate the regulation of glucose by injecting proportionally more insulin on rising and less in the decreasing phase of glycaemia.
When Y is increasing, the cost function is penalized with R(α1) while the penalization is madded by $Q(\alpha 1)$ in the case of glucose decreasing, with α1 is the glucose rate of change.
In Figure 4 we present a comparison of different control settings.

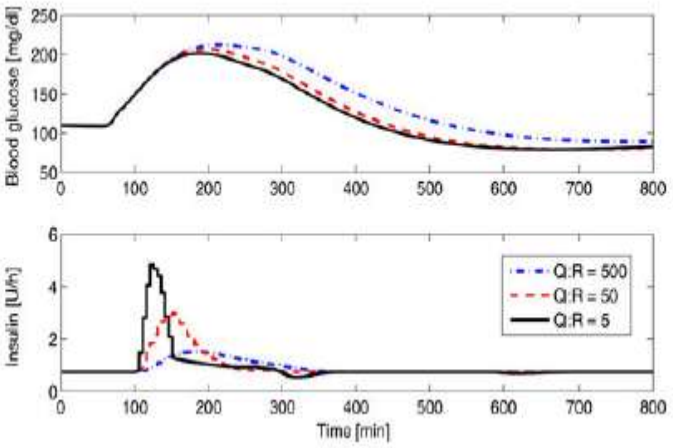

Fig.4 Comparison of different control settings

The optimization function of Matlab used in this work is *fmincon* function to solve constrained problem by applying the following hard constraint (I_D'): $-\text{basal} \leqq I_D' \leqq 72$ U/h.

IV. In Silico Artificial Pancreas Evaluation

In order to evaluate performance of the controller, in silico trials has been done on the US FDA-accepted Universities of Virginia/Padova metabolic simulator which provide trials equivalent to animal test [30].

The protocol of simulation included tree unannounced meals (60g CHO dinner 50g CHO breakfast 65g CHO lunch), in this simulation we compare the aMPC to zone model predictive controller (zMPC) used in [29]. The simulation start at 6:00 PM and finish at 12:00 AM of the second day of simulation.

Figure 5 depicts the mean BG and insulin delivery traces for 30 in silico patients in the UVA/Padova simulator and the insulin profiles to regulate glycemia. Results show that the proposed controller ameliorate required performances in comparison with the other MPC controllers. The time spent in hyperglycemia and its magnitude has significantly down and the acceleration of the command allows to reject rapidly the effect of the disturbance related to meal intake also hypoglycemia was avoided by minimizing the insulin injection in the phase of glycemia decreasing.

Table I shows statistics of simulation results for 30 in silico patients of the UVA/Padova simulator. This statistics confirm

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the robustness and the efficacy of the accelerated-MPC (aMPC) by maximizing the time spent in the safe zone and ameliorating the general mean of glucose values.

Table I: The percentage of time that all 30 patients with T1DM spent in different zone.

Variable	*ZMPC*	*Proposed MPC*
Mean glucose	143.6	145.3
0[80,140]mg/dl	51%	56%
[70,180]mg/dl	63%	68%
>180 mg/dl	37%	30%
<70 mg/dl	0.35%	0.25%
Alarm of Hypos	4	2

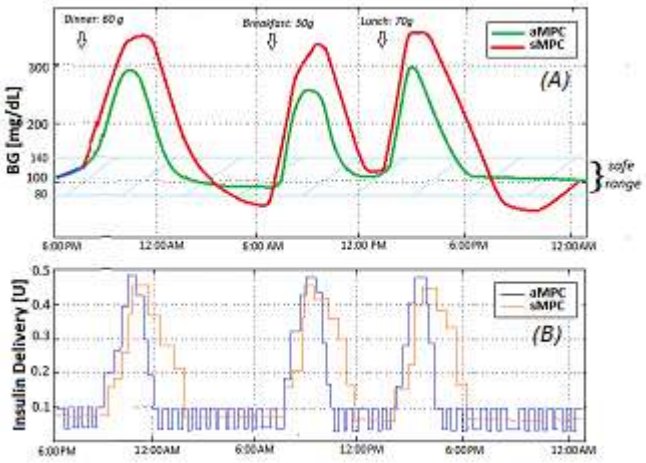

Fig. 5 Mean glucose (A) and insulin (B) traces of 30 in silico subjects controlled by the zMPC and aMPC.

V. CONCLUSION

In conclusion, many problems remain to be solved before an automatic blood glucose control becomes a reality, however a great improvement on the development of the AP has been done until now. This work present a contribution to ameliorate control algorithm for AP by introducing a novel formulation of the MPC which accelerate the speed of command and get satisfactory performance. The efficacy of the controller was validated by in silico test on the FDA-accepted UVa\Padova metabolic simulator.

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