# A DECISION SUPPORT SYSTEM BASED ON A CLOSED LOOP PFC APPLIED FOR TYPE I DIABETES.

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Abstract: —A predictive functional controller (PFC) for closed-loop control of glucose using subcutaneous (SC) tissue and intravenous (IV) glycemia measurement and SC and IV infusion of monomeric insulin analogs was developed and evaluated in a simulation study. This analysis is implemented on a generalized rigorous model which can simulate the interaction between glucose-insulin for Type 1 Diabetes Mellitus (T1DM) or `normal subjects`. According to the simulation results, stable control is achievable for unknown or variable time delays as well as for slow time variations of the controlled system. Therefore model together with PFC could be an useful tool for developing an extra corporeal artificial pancreas prototype and/or as a decision support technique for defining the proper insulin dosage for each patient and for education purposes. Several simulation results are presented for the sake of comparison with other well known models and predictive control strategies. 

Keywords: Insulin-glucose model PFC strategy decision support diabetes care

## 1. INTRODUCTION

An estimate of the global cost of diabetes, based on epidemiological studies conducted by the World Health Organization, revealed that diabetes may account for 23% of the total health care budget in every country (Jonsson; 1998). In this context, since many years ago, a vigorous research has been stimulated on implantable SC sensors, insulin pumps with SC access, support the idea of important improvements on SC closed-loop control strategies for insulin-dependent diabetes therapy (Bellazzi et al.; 2001) .

This work focus on modeling and predictive functional control in order to complement earlier control approaches and application of computers in diabetes care . Up to now the authors of this article did not find any PFC application on glucoregulatory problems.

The PFC technique is the third generation of a family of Model Algorithmic Control (MAC), developed by Richalet and coworkers during the last decades (see Richalet, 1993). It resides on representing the process with a linear impulse response model, generate the control algorithm for one or more coincidence points with the reference trajectory, solve it and apply the calculated input action through the named base functions. The manipulated variable can be constrained on its maximum and minimum values and its rate of variation.

In particular, the development of the control strategy includes the following steps: 1) implementation of a

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mathematical model for the simulation of a patient with T1DM; 2) development of system identification for obtaining the internal (predictive) model; 3) design the PFC by defining the parameters and 4) performing numerical experiments on closed-loop control and compare with previous results. The system has been assessed by simulation, using both SC and IV routes for insulin delivery and blood glucose measurement

## 2- CASE STUDY: GLUCOSE-INSULIN INTERACTION MODEL FOR TYPE I DIABETES

The mathematical model for glucose regulation chosen for this study is based on a compartmental one analogous to that given by Carson et all. (1983) which belongs to the class of theoretically rigorous models. However, in order to simulate the dynamic effect of exogenous glucose and insulin relating to the different typical tests or meal intake, the model is implemented combined with transfer functions. In this context, the complete model can be considered as a hybrid one. Another assumption was consider that patients with T1DM endogenous insulin secretion was suppressed whereas insulin and glucagon kinetics have been assumed to be normal. Note that these considerations are valid for patients with T1DM without defective glucose counter regulation. The model shown in Figure 1 includes a single glucose compartment representing the extra cellular fluids, three insulin compartments (liver and portal plasma insulin, plasma insulin, and insulin in the interstitial fluids), and a glucagon compartment. The considered unit processes are net hepatic glucose balance, renal excretion of glucose, and insulin-independent glucose utilization. The model equations used in the simulations and a list of symbols are given in the Appendix. In order to cover with the same model a great number of patients' glucose behavior the original equations are modified. The differential equation referred to glucose balance ($x_1$) is affected by modifying the insulin secretion and the "initial condition" for each patient according to its basal level of blood glucose early in the morning before breakfast. In Figure 2 are presented several curves of blood glucose according to each patient characteristics and for a healthy person when the same oral glucose tolerance test (OGTT) is performed. The computational implementation was done in Matlab-Simulink. For simulating the OGTT a solution of 75gr of glucose in 375ml of water is given orally to an adult patient. For accounting the effect on the dynamic behaviour in blood glucose a second order transfer function given by:

$$H(s) = \frac{K}{\left(w_n^2.s^2 + 2.\xi.w_n.s + 1\right)} \qquad (1)$$

setting the damping coefficient $\xi = 1{,}03$ ; and natural frequency $w_n = \pm 19{,}36\left(\frac{rad}{seg}\right)$; with a gain of $K = 1{,}2$ is included for modelling the glucose input to the endocrine system. This transfer function can be modified in order to adjust properly for each particular patient.

In addition the model is useful for simulating the effect when intravenous glucose tolerance test IVGTT is done. In Figure 3 is shown the model prediction and the real data of a normal subject of 70 Kg of weight under an IVGTT consisted on receiving 30,4 mmol/l of a glucose solution during 2 minutes at time = 500 min and sampling blood glucose during 182 min. taken from Cobelli, C. and Bergman (1981).

Besides, the model can estimate the blood glucose time evolution for a well known equivalent carbohydrates consumption during specific gut. This information was taken from Hejlesen et al. (1998), for testing the Diabetes Advisory System (DIAS) predictions (Andreassen et al.; 1994). In Figure 4a is shown the quantity of carbohydrates present in the gut and the moments when they are fed to the healthy volunteer. In Figure 4b is shown the blood glucose concentration varying, indirectly dependent of meal intake given above.

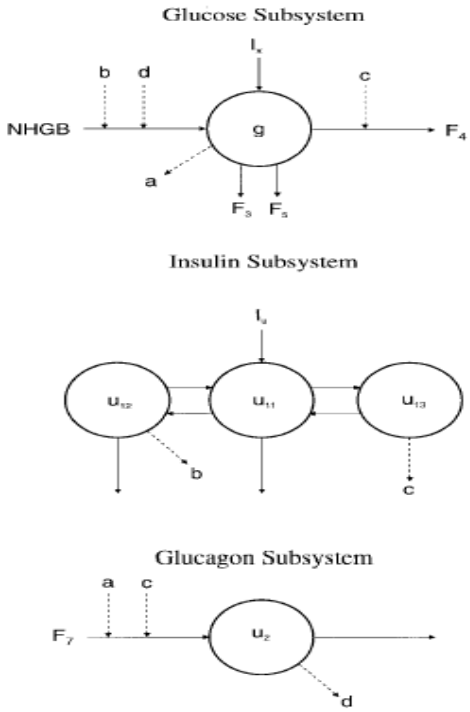


Fig. 1 Mathematical model adopted from the literature and adjusted to diabetic state used in the numerical experiments.

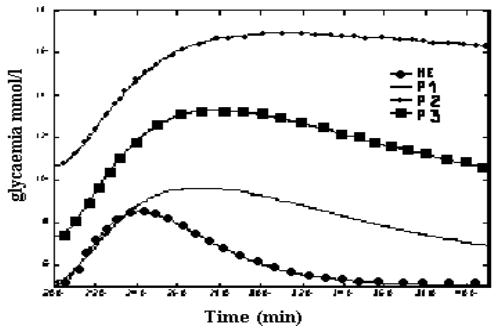


Fig. 2: dynamic behaviour of blood glucose for different patients (Pj) and healthy volunteer (HE) after an OGTT.

Intravenous (IV) and subcutaneous (SC) routes for monomeric insulin analogs delivery can be simulated as well. Determination of transfer rates between plasma and SC compartment is adjusted as a linear, first-order system with the transfer function in the frequency domain (Laplace transform of the impulse response) .

$$g_{sc}(s) = \frac{K_{sc}}{(1 + t_{sc}.s)}.e^{-t_m.s} \qquad (2)$$

where: $K_{sc} = 0,9$ , $t_{sc} = 5\,\text{min}$ , $t_m = 10\ \text{min}$ , is the time delay due to the tubing in an *ex vivo* monitoring system, it can be ranged between 0-20 minutes (Trajanoski and Wach , 1998).

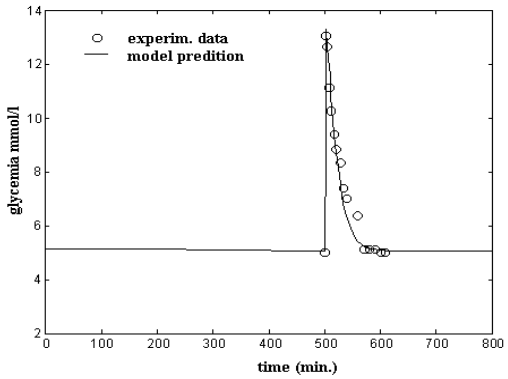


Fig. 3: glycemia time evolution for a healthy person after an IVGTT

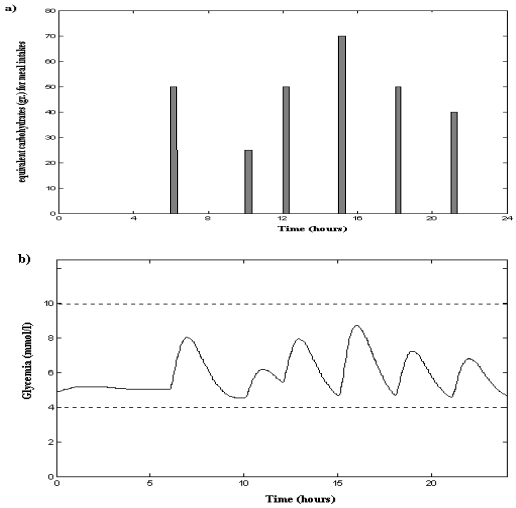


Fig. 4: a) daily carbohydrate diet b) model predictions of the effect on blood glucose concentration for a `normal subject`.

In the next sections several simulation results of applying PFC for decision supporting on insulin IV and SC dosages are shown. Therefore, because of the overall aspects included in the model it is named "generalized".

## 3. MATHEMATICAL CALCULATIONS FOR PFC DESIGN

PFC is applied to enhance insulin delivery at normal glucose levels and to attenuate insulin delivery when glucose falls even at hyperglycaemic levels.

For PFC the structure of the model and its parameters are estimated by any identification algorithm available which exploits the data collected during specific step test experiments. The model is used to predict the future process output and to compute the control action in order to satisfy a given target (C) for the process variable (PV).

PFC basically consists of the same elements as can be seen in Figure 5: the dynamic model; a reference trajectory $y_r(n)$ which describes the smooth transition of the target variable from its current value to the future set point profile within a prediction horizon that corresponds to the end of the coincidence horizon. This trajectory can be interpreted as the desired behavior of the closed loop system. The future error between the reference trajectory and the predicted output over the coincidence horizon [$H_1$, $H_2$] is estimated. A self compensation is done accounting the actual mismatch between real data and model output. For estimating the future error at coincidence horizon by specific kind of extrapolation allows to improve the model prediction For the application study analyzed here only one coincidence point and a constant set point C is assumed. It will be developed the control law for first order with time delay on both "process" (Gmi) and perturbation model (Gdi). In this case the "process" refers to the relationship between insulin infusion (manipulated variable) and blood glucose (controlled variable). Meanwhile, the glucose entering to the system in any standard way such as OGTT, IVGTT or meal intake are considered as typical disturbances. Therefore, Gdi represents the transfer function between glucose as independent variable and blood glucose.

$$Gmi(s) = Gmi.\frac{1}{1 + \tau_{mi}.s} \qquad (3)$$

$$Gdi(s) = Gdi.\frac{1}{1 + \tau_{di}.s} \qquad (4)$$

Applying the Z-transform results

$$\begin{cases} Gmi\ (z) = Gmi\ \dfrac{(1 - \alpha_m)}{(z - \alpha_m)} \\ \alpha_m = e^{\left(-\frac{Ts}{\tau_{mi}}\right)} \end{cases} \qquad (5)$$

$$\begin{cases} Gdi\ (z) = Gdi\ \dfrac{(1 - \alpha_d)}{(z - \alpha_d)}, \alpha_d = e^{\left(-\frac{Ts}{\tau_{di}}\right)} \end{cases} \qquad (6)$$

In the canonic form,

$$\begin{cases} x_m(k+1) = \alpha_m.x_{mi}(k) + \alpha_d.x_{md}(k) + Gmi.(1-\alpha_m).u(k) + \\ \qquad Gdi.(1-\alpha_d).d(k) \\ y_m(k) = x_m(k) \end{cases} \qquad (7)$$

Accounting the inputs of manipulated variable *u(k)* and a perturbation *d(k)*, the system response at (n+H) point becomes

$$\begin{aligned} & y(n+H) = \alpha_m^{\,H}.x_{mi}(n) + \alpha_d^{\,H}.x_{md}(n) + \\ & \sum_{j=0}^{H-1} \alpha_m^{\,H-1-j}.Gmi.(1-\alpha_m).u(j+n) + \\ & \sum_{j=0}^{H-1} \alpha_d^{\,H-1-j}.Gdi.(1-\alpha_d).d(j+n) \end{aligned} \qquad (8)$$

The model output can be expressed as a sum of free (L) and forced (F) terms

$$y_m(n+H) = y_F(n+H) + y_L(n+H) \quad (9)$$

$$y_m(n+H) = \alpha_m^H . y_{mi}(n) + \alpha_d^H . y_{md}(n) + Gmi.(1-\alpha_m^H).u(n) + Gdi.(1-\alpha_d^H).d(n) \quad (10)$$

Therefore the control equation is obtained by the following steps $\varepsilon(n+H) = \varepsilon(n).\lambda^H$ (11)

$$\lambda = e^{-\frac{3Ts}{TRBF}} \quad (12)$$

$\alpha_m^H . y_{mi}(n)$ :

$\rightarrow$ Free responses

$\alpha_d^H . y_{di}(n)$ :

$Gmi.(1-\alpha_m^H).u(n)$ :

$\rightarrow$ Forced responses

$Gdi.(1-\alpha_d^H).d(n)$ :

$$\begin{cases} \varepsilon(n) = c(n) - y_p(n) \\ \varepsilon(n+H) = c(n) - y_R(n+H) \end{cases} \quad (13)$$

$$\Rightarrow c(n) - y_R(n+H) = \lambda^H.(c(n) - y_p(n))$$

and considering

$$\Delta_p(H) = (c(n) - y_p(n)).(1-\lambda^H) \quad (14)$$

$$\begin{cases} \Delta_p(H) = \Delta_m(H) \\ (c(n) - y_p(n)).(1-\lambda^H) = y_m(n+H) - y_m(n) \end{cases} \quad (15)$$

then,

$$(c(n)-y_p(n)).(1-\lambda^H) = \alpha_m^H y_{mi}(n) + \alpha_d^H y_{md}(n) + Gmi(1-\alpha_m^H)u(n) + Gdi(1-\alpha_d^H)d(n) - y_m(n) \quad (16)$$

The control algorithm is given by

$$u(n) = K_0.\varepsilon(n) + K_1.y_{mi}(n) + K_2.y_{md}(n) + K_3.d(n) + K_4.y_m(n) \quad (17)$$

where

$$K_0 = \frac{(1-\lambda^H)}{Gmi.(1-\alpha_m^H)} \qquad K_1 = \frac{-\alpha_m^H}{Gmi.(1-\alpha_m^H)}$$

$$K_2 = \frac{-\alpha_d^H}{Gmi.(1-\alpha_m^H)} \qquad K_3 = \frac{-Gdi.(1-\alpha_d^H)}{Gmi.(1-\alpha_m^H)} \quad (18)$$

$$K_4 = \frac{1}{Gmi.(1-\alpha_m^H)}$$

Finally, if it is assumed that $d(n) = y_{md}(n) = 0$

$$\frac{U(z)}{\varepsilon(z)} = \frac{K_0.(z-\alpha_m)}{(z-1)} \quad (19)$$

As can be seen from (19) the controller transfer function has an implicit integrator which guarantees zero tracking error for step inputs.

The forced response is calculated by assuming the input to the system is related to base functions as are shown in Fig. 6. Typically these functions are steps $B_1(i) = 1$; ramps $B_2(i) = i$ or parabolas $B_3(i) = i^2$. The choice of the basis functions defines the input profile and can assure a predetermined behavior.

$$u(n+i) = \sum_{K=1}^{Nb} \mu_K(n) UB_K(i) \quad (20)$$

For system with delay it must be estimated the error between real data system and model estimations at instant (n-Tdm) as is shown in Figure 7. There, Tdm is the time delay.

Hence the predicted output of the plant is given by

$$\hat{y}_p(n) = y_m(n) + e_{0\,RET}(n) \quad (21)$$

$$e_{0ret} = y_{Pret} - y_{Mret} \quad (22)$$

where

$$\hat{\varepsilon}(n) = (c(n) - \hat{y}_P(n)) \quad (23)$$

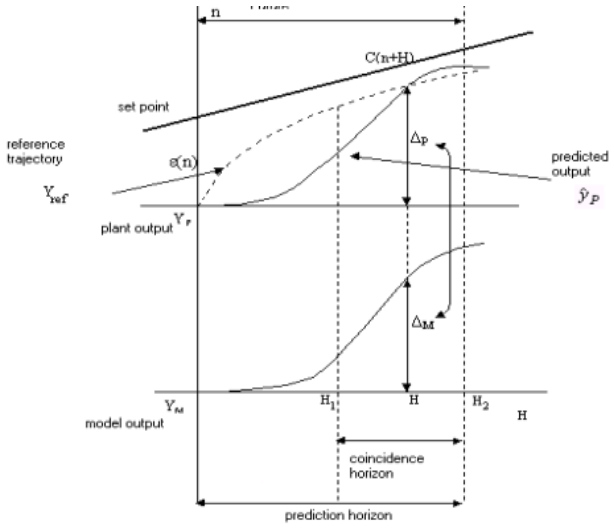


Fig. 5. PFC principles for design for one coincidence point.

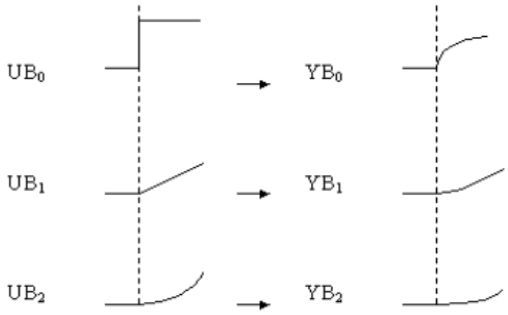


Fig. 6. base function for input and forced output calculations

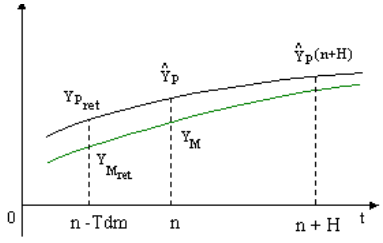


Fig. 7 prediction of the delayed response

Accounting considerations (21) to (23) the control algorithm for the system with delay is given by

$$u(n) = K_0.\hat{\varepsilon}(n) + K_1.y_{mi}(n) + K_2.y_{md}(n) + K_3.d(n) + K_4.y_m(n) \quad (24)$$

The parameters to be tuned for these controllers are: *coincidence point (H)* [sec]. C*losed loop time response* [TRBF, sec] of the reference trajectory. If control zone is applied *low and high* TRBF must be defined. The high value is applied when controlled

variable is exactly at the set point. If it is going far from the set point but it is inside the allowed zone TRBF decreases linearly up to the limit of the zone. There it reaches the lowest value in order to drive the controlled variable inside the zone as quickly as possible. By using a control zone the parameter TRBF is moving linearly between those two extremes (low and high values).

*Transition zone* [%] set the allowed zone for the controlled variable expressed as ± n% with respect to set point value, c*onstraints to manipulated variable* are also included fixing maximum, minimum and variations for it.

## 4. APPLICATION RESULTS

The dynamic interaction between plasma insulin and blood glucose concentration in an T1DM during an OGTT for both SC and IV glycemia measurements are presented in this section. The objective is that PFC be capable of regulating the blood glucose at 5mmol/l without violating the allowable band for the patient.

The large number of tuning parameters adds flexibility to the tuning procedure, but simultaneously, it makes proper tuning more difficult. However it is considered that PFC strategy is very intuitive for selecting the parameters and the same criteria used for industry applications can give reasonable results.

In Table 1 are summarized the chosen parameters for 75gr-OGTT using vein-to-vein route where PFC simulates a Biostator algorithm. In Table 2 the same test is performed but implementing subcutis-to subcutis route. In both cases one coincidence point was adopted, the starting point for coincidence horizon is 120 and the end point is 1000 and the sampling time was 0,1.

Table 1: PFC parameters for an OGTT and vein-to-vein route

| Zone control | Constrains to the manipulated variable |
|---|---|
| $T_{rbf\_L} = 10$ | $U_{min} = 0$ |
| $T_{rbf\_H} = 15$ | $U_{máx} = 50$ |
| Delta = 20 | $\Delta U/\Delta t = 0{,}5$ |
| Model Insulin-glycemia | Model exog. glucose-glycemia |
| $G_{mi} = -0{,}6$ | $G_{di} = 5$ |
| $\tau_{mi} = 150$ | $\tau_{di} = 110$ |
| $\tau_{mmi} = 3$ | $\tau_{mdi} = 20$ |

The main difference in transfer functions is done on the important time delay involved for the second case. In Figure 8 are presented both glucose dynamic behavior for SC and IV routes showing normoglycemia at every time after the 75gr-OGTT. The vein-to-vein route out performs the subcutis-to-subcutis route. These results demonstrate a clear advantage with respect to those presented by Trajanoski Z and Wach (1998) applying a neural predictive control.

Additionally, a specific meal intake, shown in Figure 4a, is tested and PFC acts like a decision support technique for solving the problem of determining the insulin dosage analogously to AIDA (Lehmann et al.; 1994) or DIAS models. The PFC parameters are the same given in Table 2 and in Figure 9 are presented the application results. From Figure 9a can be seen that the insulin dosage provided by the controller guarantees all the day the patient with normoglycemia. These results represent a demonstration that PFC suggests reasonable SC insulin dosage for the specific T1DM patient.

Table 2: PFC parameters for an OGTT subcutis-to subcutis route

| Zone control | Constrains to the manipulated variable |
|---|---|
| $T_{rbf\_L} = 10$ | $U_{min} = 0$ |
| $T_{rbf\_H} = 15$ | $U_{máx} = 50$ |
| Delta = 20 | $\Delta U/\Delta t = 0{,}5$ |
| Model Insulin-glycemia | Model exog. glucose-glycemia |
| $G_{mi} = -0{,}32$ | $G_{di} = 4.25$ |
| $\tau_{mi} = 140$ | $\tau_{di} = 125$ |
| $\tau_{mmi} = 30$ | $\tau_{mdi} = 25$ |

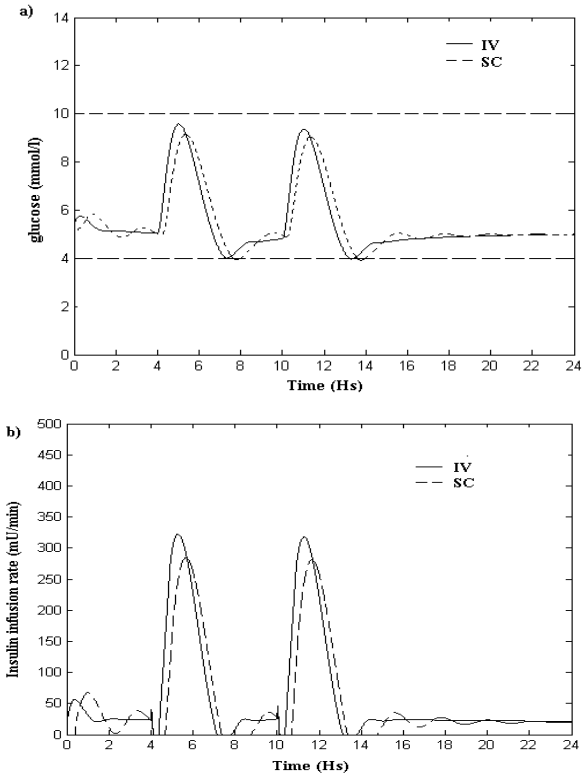


Fig. 8 a) comparison of glucose dynamic for an OGTT at 4 and 10 hours via the SC and IV routes b) comparison of SC. and IV insulin infusion and intravenous insulin infusion

## 5. CONCLUSIONS

The simulation results of the present study demonstrate that the developed generalized model gives good predictions working in an open-loop way. In addition, closed-loop PFC offers a new alternative option for helping on computer diabetes care. PFC potentiality resides on the benefits of MPC philosophy adding a more intuitive tuning parameters rules. Comparisons with other well known strategies give confidence on the technique used here and imply greater acceptability and practicability for patients and health care staff.

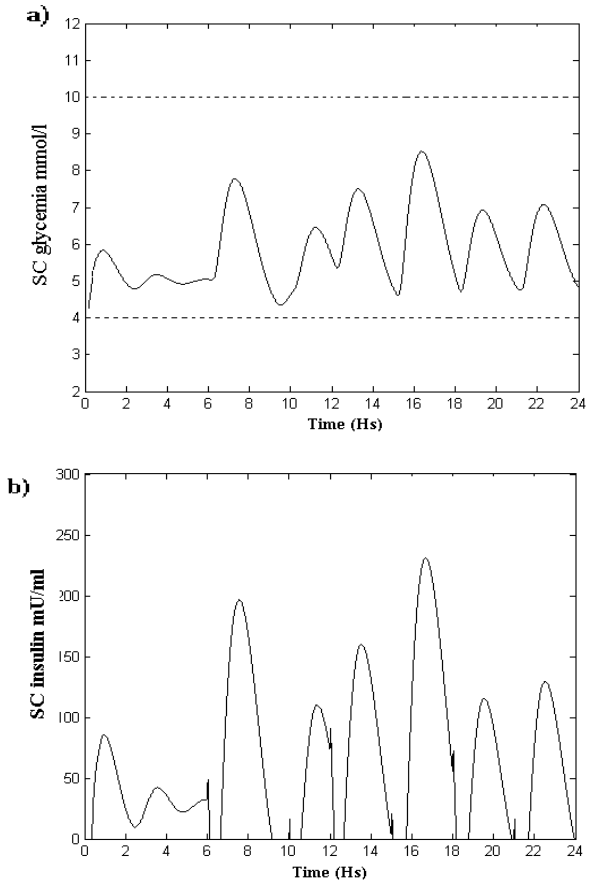


Fig. 9: a) SC blood glucose dynamic for carbohydrates intake shown in Figure 4a b) SC insulin infusion suggested to the patient.

## REFERENCES


Andreassen S, Benn J, Hovorka R, Olesen KG, and Carson ER (1994) *Aprobabilistic approach to glucose prediction and insulin dose adjustment: Description of metabolic model and pilot evaluation study*. Comput Methods Programs Biomed 41: 153-165.

Bellazzi1 R., Nucci G. and Cobelli C. (2001) *The Subcutaneous Route to Insulin-Dependent Diabetes Therapy* IEEE Eng. Med. and Biology January/February pp. 54-64

Carson E. R, C. Cobelli, and L. Finkelstein (1983), *The Mathematical Modeling of Metabolic and Endocrine Systems.* New York: Wiley.

Cobelli, C. and Bergman, R. N. (Eds) (1981).*Carbohydrate metabolism: Cuantitative Physiology and Mathematical Modelling*, Wiley, Chichester.

Hejlesen OK, Andreassen S, Frandsen NE, Sorensen TB, Sando SH, Hovorka R, and Cavan DA (1998) *Using a double blind controlled clinical trial to evaluate the function of a diabetes advisory system: A feasible approach*. Comput Methods Programs Biomed 52: 165-173.

Jonsson B (1998).*The economic impact of diabetes*. Diabetes Care 21 (Suppl. 3): C7-C10.

Lehmann ED, Deutsch T, Carson ER, and Sonksen PH (1994). *AIDA: An interactive diabetes advisor*. Comput Methods Programs Biomed 41: 183-203,

Richalet J., (1993) *Pratique de la Commande Prédictive*, Editorial Hermès, Paris-France.

Trajanoski Z and Wach P (1998) *Neural Predictive Controller for Insulin Delivery using the Subcutaneous Route.* IEEE Trans Biomed Eng 45: 1122-1134.


## APPENDIX

Mathematical Model for the Glucose Dynamics

$$\dot{x}_1(t) = \left(NHGB(x_1, u_{12}, u_2) - F_3(x_1) - F_4(x_1, u_{13}) - F_5(x_1) + I_x(t)\right). \quad \text{(A1)}$$

$x_1(0) = x_{10}$ (initial condition)

$$\dot{u}_{1p}(t) = -k_{12}.u_{1p} + k_{12}.u_{2p} + w(x_1) \quad \text{(A2)}$$

$$\dot{u}_{2p} = k_{12}.u_{1p} - [k_{12} + k_{02}(x_1)].u_{2p} \quad \text{(A3)}$$

$$\dot{u}_{11}(t) = -(m_{01} + m_{21} + m_{31}).u_{11} + m_{12}.u_{12} + m_{13}.u_{13} + I_u(t) \quad \text{(A4)}$$

$$\dot{u}_{12}(t) = -(m_{02} + m_{21}).u_{12} + m_{12}.u_{11} + k_{02}(x_1).u_{2p} \quad \text{(A5)}$$

$$\dot{u}_{13}(t) = -m_{13}.u_{13} + m_{31}.u_{11} \quad \text{(A6)}$$

$$NHGB = F_1(x_1, u_{12}, u_2) - F_2(x_1, u_{12}) \quad \text{(A7)}$$

System output

$y_1 = \frac{x_1}{V_1}$ :plasma glucose conc. (mmol/l) (A8)

$y_2 = \frac{u_{11}}{V_{11}}$ : plasma insuline conc. (μU/ml) (A9)

$y_5 = \frac{u_2}{V_2}$ : blood glucagon conc. (mg/ml) (A10)

NHGB Net hepatic glucose balance

$x_1$: glucose in plasma and extracelular fluids(mmol)

$u_{1p}$: pancreatic stored insulin (μU /kg)

$u_{2p}$: Glucagon, (μU /kg)

$u_{11}$: Plasma insulin, (μU/kg)

$u_{12}$: Liver insulin, (μU /kg)

$u_{13}$: Interstitial insulin, (μU /kg)

$w$ and $F_1$ to $F_7$ : are nonlinear monotonic functions with sigmoidal characteristics dependent on the control variables

$Ix$ e $Iu$: Test inputs, (mg/kg min) and (μU/kg) respectively.

$m_{ij}$, Concentration of monomeric insulin U ml

$h_{ij}$ y $k_{ij}$: constants

$k_{02}$ depent of $x_1$

$V_1$, $V_{11}$ and $V_2$ are distribution volumes of the various compartments (percentage of bodyweight in appropriate dimensions, i.e., dl /kg , l /kg , and ml/kg. The measurable (plasma) variables are $y_1$ (mmol/ l ), $y_2$ (mU/ l ), and $y_3$(mg /ml).