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Multilevel model based glucose control for type-1 diabetes patients

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Abstract— **Diabetes is a disease that involves alterations at multiple biological levels, ranging from intracellular signalling to organ processes. Since glucose homeostasis is the consequence of complex interactions that involve a number of factors, the control of diabetes should be based on a multilevel analysis. In this paper, a novel approach to design of closed-loop glucose controllers based on multilevel models is presented. A control scheme is proposed based on combining a pharmacokinetic/pharmacodynamic model with an insulin signal transduction model for type 1 diabetes mellitus patients. Based on this, an insulin feedback control schemes is designed. Two main advantages of explicitly utilizing information at the intracellular level were obtained. First, significant reduction of hypoglycaemic risk by reducing the undershoot in glucose levels in response to added insulin. Second, robust performance for inter-patient changes, demonstrated through application of the multilevel control strategy to a well established *in silico* population of diabetic patients.**

I. Introduction

Type 1 diabetes mellitus is a multilevel disease characterized by an inability to maintain glucose homeostasis, i.e., regulate blood glucose levels within a normal range, usually due to destruction of insulin producing cells in the pancreas. Individuals with type 1 diabetes mellitus (T1DM) have little or no endogenous insulin production, usually in combination with insulin resistance. The goal of insulin therapy is to achieve glucose homeostasis while avoiding hyperglycaemic and hypoglycaemic events, since poor glucose control leads to short-term and long-term diseases. Patients with T1DM must receive insulin, either in the form of boluses or from continuous insulin infusion pumps. Artificial pancreas replaces conventional therapy by an automated insulin delivery system in the form of closed-loop glucose control. The development of a closed-loop artificial pancreas, which would use continuous glucose monitoring signals and adjust the infusion rate of continuous subcutaneous insulin infusion pumps, is a major research thrust by a number of groups throughout the world. However, most of the considered control approaches are based on a high-level input-output, i.e., insulin/meal-glucose, analysis without consideration of the multilevel interplay. These control schemes use a pharmacokinetic/pharmacodynamic (PKPD) point of view to describe the glucoregulatory system, e.g., the Cobelli-Dalla Man model [1]. Nevertheless, it is well known that glucose homeostasis results from complex interactions between the cellular insulin receptor sensitivity, hormones, metabolic subsystems and organ processes [2]. Systems biology is aimed at analysing biological functions and processes from a systems perspective, i.e., with a focus on the role of interactions in generating functions and dynamic behaviors [3]. Mathematical modeling of the system dynamics is central and deals with organ, intercellular as well as intracellular network models. Multilevel models describe systems and their interactions at different levels of organization and abstraction. In a systems biology context, the aim is not limited to derivation of models that describe the time-varying concentrations of various substances and their effect on the desired biological output, as is the case with PKPD models. Rather, a key objective in systems biology is to consider the interaction of variables at the intracellular level and their interactions with higher level processes and functions. One of the main areas of system biology focus on modelling signal transduction processes and how changes in these signalling networks affect the transmission of information about extracellular conditions to intracellular processes. Insulin signalling is a key factor in the glucoregulatory process, because it transfers information concerning the extracellular insulin concentration to the protein transcription processes within the cell nucleus, thereby modifying the glucose uptake in the cells and stimulating the translocation of the glucose transporter GLUT4 from intracellular sites to the cell surfaces [4]. A physiologic insulin delivery with insulin feedback, which employs a insulin pharmacokinetic model, is developed in [5]. A multilevel model combining an insulin signalling model [6] with a PKPD model [1] was proposed in [7] and a model predictive control based on that multimodel model was designed. The results elucidated how knowledge of the multilevel nature of diabetes diseases can be utilized to develop improved glucose control in an artificial pancreas framework. Following the same idea, this paper shows that even if a simple control strategy is used, a significant improvement is achieved when intracellular information is considered in the control design.

II. Glucose closed-loop scheme

In order to highlight the advantages of using multilevel information for glucose control, an insulin feedback controller (IFB) was designed. The IFB controller is relatively simple, consisting of a simple proportional-derivative controller combined with an inner cascade loop to account for intracellular dynamics. The main motivation behind the control scheme is to illustrate the advantages of using multilevel information without blurring it with the use of complex control schemes. The insulin feedback controller is based on a combination of an insulin pharmacokinetics model and an intracellular model relating the insulin action to the glucose uptake. This information is used to dynamically counteract the insulin

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infusion by the pump, acting as an inner negative insulin feedback loop. The external feedback loop regulates the glucose value provided by a continuous glucose monitor system. The IFB controller is a model-based control scheme, see Fig. 1, which includes a PK model $G_1(s)$ and an insulin signal transduction model $G_2(s)$. The function of the inner loop is essentially avoidance of temporal over-infusion of insulin that would produce a hypoglycaemic event due to the delay of the insulin action on the glucose measure at the interstitial tissue. The function of the outer loop is to regulate changes in glucose values produced by meals, disturbances or errors in the actions of the inner loop using glucose measures. IFB uses a proportional control to regulate the fast dynamics of the inner loop, thereby supporting the regulation of the main controlled output, glucose. For the external feedback loop, any type of controller can in principle be used. Here a simple proportional-derivative (PD) controller will be considered for the reasons given above.

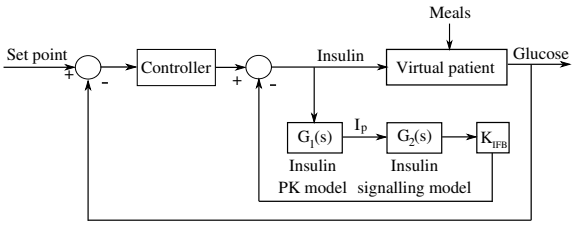

Fig. 1. Insulin feedback control scheme. The controller used is proportional-derivative and the inner negative feedback is based on an insulin PK model plus an intracellular model.

1) PK model: The insulin pharmacokinetics (PK) model describes the plasma insulin response to an exogenous insulin input. The plasma insulin absorption of a bolus of insulin can be modelled using a two-compartment subcutaneous insulin model [8]. This model is based on the assumption that insulin diffuses and is cleared from the body in proportion to its concentration. It can be represented by the transfer function

$$G_1(s) = \frac{I_p(s)}{u(s)} = \frac{K_1}{(\tau_1 s + 1)(\tau_2 s + 1)} \qquad (1)$$

where τ_1 and τ_2 are time constants defining how fast the insulin profile changes and K is the gain in the insulin absorption process associated with the insulin clearance. I_p is the estimation of is the insulin concentration at the interstitial fluid and u is the insulin infusion. This model, which is used to estimate the plasma insulin, has been validated in a population of 8 patients [9]. The correlation coefficient (R^2) between the insulin measured and the estimated plasma-insulin with this model was 0.730 $\pm$ 0.067 [9]. Data shows that the kinetics observed is well described by the model. Figure 2 shows the comparison of the model (1) with the plasma insulin response of two experimental data sets. They were taken from Mudaliar et al. [10] and Dallan Man et al. [1]. The approximated model shows a good fit to the experimental data for the purpose of controller design.

2) Insulin signalling model: The second model required to design the IFB controller is the description of the insulin

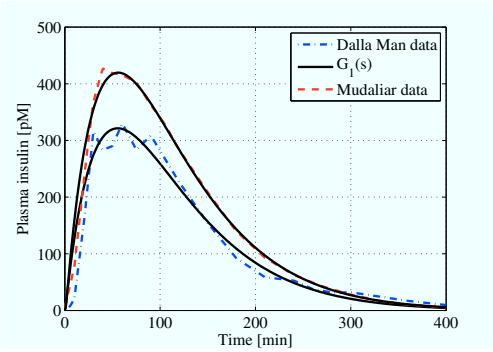

Fig. 2. Comparison between the plasma insulin from the insulin PK model (G_1(s)) and both Dalla Man and Mudaliar experimental data.

signaling ($G_2(s)$ in Fig. 1). The schematic of the components involved in the glucose uptake by adipose tissue are shown in Fig. 3. Here I_p is the insulin concentration at the interstitial fluid, IR is the insulin receptor, IR_p is the phosphorylated IR, IRS is the insulin receptor substrate, IRS_p is the phosphorylated IRS; PKB is the protein kinase B, PKB_p is the phosphorylated PKB; $GLUT4$ is the glucose transporter 4 and $GLUT4_{pm}$ is $GLUT4$ translocated to the plasma membrane. The model structure relates the insulin effects

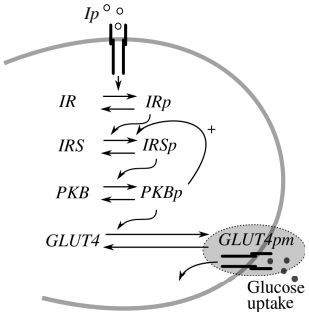

Fig. 3. Schematic outline of insulin signaling pathways. Arrows relates intracellular signaling flow of insulin, from insulin receptor to glucose transporter 4 translocated on the plasma membrane.

on glucose uptake through the insulin signalling cascade inside the cells. The states of the model (2) are the simulated signalling proteins that are either non-phosphorylated or phosphorylated (subscript p). The model parameter values are those presented in [6], obtained by fitting the model to experimental data while imposing certain output constraints.

$$\begin{aligned}
\dot{IR} &= k_{1b} IR_p - k_{1f} IR\, I_p - k_{1basal} IR \qquad (2)\\
\dot{IR}_p &= -k_{1b} IR_p + k_{1f} IR\, I_p + k_{1basal} IR\\
\dot{IRS} &= k_{2b} IRS_p - k_{2f} IRS\, IR_p\\
\dot{IRS}_p &= -k_{2b} IRS_p - k_{2f} IRS\, IR_p\\
\dot{PKB} &= k_{3b} PKB_p - k_{3f} PKB\, IRS_p\\
\dot{PKB}_p &= -k_{3b} PKB_p + k_{3f} PKB\, IRS_p\\
\dot{Glut4} &= k_{4b} Glut4_{pm} - k_{4f} Glut4\, PKB_p\\
\dot{Glut4}_{pm} &= -k_{4b} Glut4_{pm} + k_{4f} Glut4\, PKB_p
\end{aligned}$$

In order to obtain a lower-order model, a step response of model (2) was considered and it was found that it could be well fitted by a first-order model

$$G_2(s) = \frac{Glut4_{pm}(s)}{i_p(s)} = \frac{K_2}{(\tau_3 s + 1)} \tag{3}$$

The responses of the full order model (2) and the first order model (3) are shown in Fig.4. As can be seen the low-order model can describe the insulin dynamics well. Once the

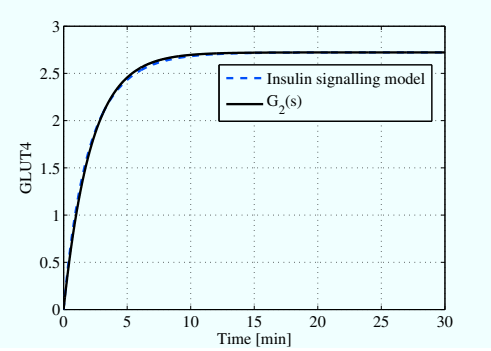

Fig. 4. Comparison between the dynamics of the GLUT4 translocation from the linear insulin signalling model G_2(s) and the nonlinear insulin signalling model (2).

models $G_1(s)$ and $G_2(s)$ have been obtained, the insulin feedback gain and the outer glucose feedback controller were designed and tuned for the average patient of the UVA simulator [11]. In this case, a proportional-derivative controller was chosen. An integral part was not included in order to avoid excessive insulin infusion. The PD-controller, named controller in Fig. 1, is

$$u_c(t) = K_p \left[e(t) + t_d \frac{de(t)}{dt} \right] \tag{4}$$

where, K_p is the proportional gain and t_d is the derivative time. The tuning values for the PD are K_p=-3.2 and t_d=60 min and the insulin feedback gain is K_{IFB}=2.4. The model parameters for $G_1(s)$ are K_1=1,τ_1=55 min and τ_2=55 min, for $G_2(s)$ are K_2=1 and τ_3=2.15 min. Also for comparison, a pure glucose feedback controller (GFB) using a PD-controller with the same tuning parameters was considered too. Finally, performance was evaluated for a T1DM patient population keeping the tuning parameters obtained previously fixed.

III. *In silico* TRIALS

Preclinical testing trial is an important step to evaluate the performance and robustness of closed-loop glucose control schemes. The UVa/Padova T1DM simulator [11] was accepted by the U.S. Food and Drug Administration as an alternative to animal trials of Type 1 diabetes control strategies. It provides realistic results and covers a wide range of the variability observed within the diabetic population. The educational version of the simulator was selected for testing the proposed glucose controllers in order to also evaluate the inter-patient performance of the control schemes. The nominal controllers (IFB, GFB) were all tested on a one week scenario. The trials were started at the initial condition of each adult patient given by the simulator with the controller in closed-loop mode. Then, each controller in turn was applied to all individuals of the adult population, keeping the tuning parameters fixed at their nominal values, i.e., no retuning in between patients. The adult population had the same multiple meals routine provided by the simulator during a one week scenario. The scenario included five meals with a total of 205 g CHO per day; breakfast at 7:00 with 45 g CHO, lunch at 12:00 with 70 g CHO, snack at 16:00 with 5 g CHO, dinner at 19:00 with 70 g CHO and snack at 23:00 with 5 g CHO. The performance assessment is performed using the percentage within ranges metrics and Control Variability Grid Analysis (CVGA) [12]. The grid associates to each patient a point in a plane during the scenario. The two coordinates correspond to the minimum and maximum glucose measure in the analysed time interval. The CVGA obtained for the adult population of patients will have a cloud of points onto the grid. The result is summarized by counting the percentage of points in the nine regions (where A is the best and E is the worst levels of glycaemic control quality). Figures 5-6 shows the CVGA for controllers with and without multilevel information. With the IFB controller, a tight and robust control is achieved with all patients being located inside the A and B regions. Using the classic GFB approach, 40% of the population were inside the D region and 20% inside the C region, which is considered as bad control. In Fig. 6 it can be observed how controller using multilevel information achieve a robust performance for inter-patient variability. Note that the IFB controller has a good performance using the nominal tuning for the average patient (see the star mark "★" in CVGA's figures). However, when the GFB controller is applied to the entire population, a significant degradation in the control performance for the classic GFB (60% outside of zones A and B) compared with the IFB controller was obtained. As can be seen in Fig. 5, IFB keeps the performance for the whole population closer to the nominal patient, achieving a smaller cloud of points. The controllers were also compared using the percentage within ranges metrics. This metric gives the percentage of testing period during which the patient's BG is within the acceptable (70-180 mg/dL), hypoglycaemic ($<$ 70 mg/dL) and hyperglycaemic ($>$ 180 mg/dL) ranges. The results in Table I show that IFB has an excellent performance avoiding the hypoglycaemic episodes. It is well known that hypoglycaemic episodes are the major limiting factor in the glycaemic management, and they also produce serious consequences in the health of diabetic patients [13]. Patients using the controller without multilevel information have 20.1% of the time in hypoglycaemic zone (below 70 mg/dl) and 12.2% above 180 mg/dl. The IFB controller keeps the glucose above 70 mg/dl at all times, thereby avoiding the risk of hypoglycaemia. This is a remarkable improvement resulting from the use of intracellular information in glucose control. It can be seen that the major difference between the controllers is in the zone below 70 mg/dL glucose. This is be-

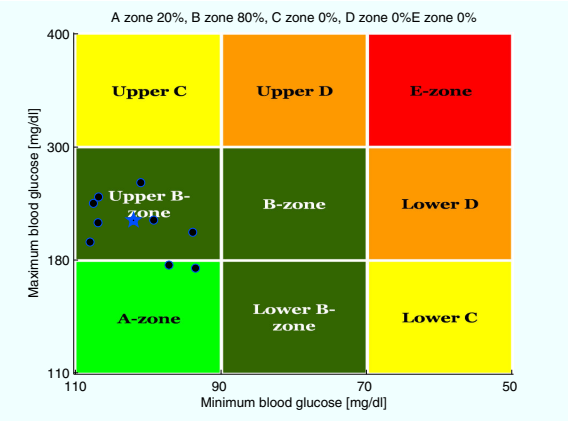

Fig. 5. CVGA for insulin feedback controller. The grid is divided into nine square zones associate with different degrees of clinical risk ranging from A (excellent control) to E (poor control). Each circle represents the coordinates associated with a single patient (x is the minimum glucose value and y is the maximum glucose value). The star mark "★" represents the average patient used for nominal tuning.

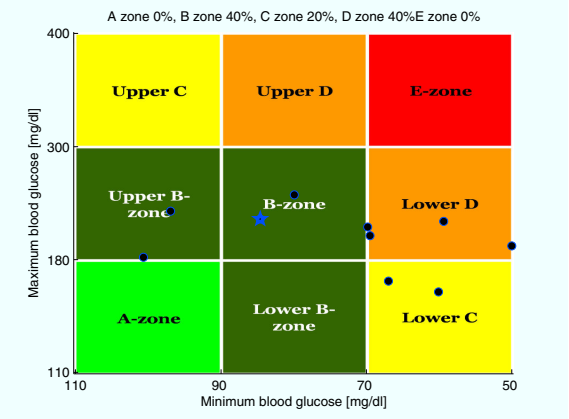

Fig. 6. CVGA for glucose feedback control. The grid is divided into nine square zones associate with different degrees of clinical risk ranging from A (excellent control) to E (poor control). Each circle represents the coordinates associated with a single patient (x is the minimum glucose value and y is the maximum glucose value). The star mark "★" represents the average patient used for nominal tuning.

cause the additional information available limits overdosing insulin thereby avoiding hypoglycaemic events. The results show that the incorporation of multilevel information for designing glucose control algorithms improves the glucose control considerably.

IV. Conclusion

In this paper, a novel approach to developing closed-loop glucose controllers using multilevel models has been presented. The principle idea is to utilize the knowledge of intracellular processes affecting glucose dynamics to achieve improved blood glucose control. The proposed multilevel model describes the interactions between the high-level glucose dynamics and the low-level intracellular signal transduction. The latter is important also for describing the daily variations in insulin sensitivity seen in diabetic patients. An insulin feedback controller was proposed based on the multilevel model. By applying the IFB controller to well established *in silico* adult populations of T1DM diabetic patients, two highly significant improvements from using intracellular information were obtained. First, a significantly reduced risk of hyperglycaemic and, in particular, hypoglycaemic episodes. Second, a significant increase in the robustness of the control, evidenced by a small interpatient variability for fixed controller parameters in comparison to standard pure glucose feedback controllers. As shown in this paper, incorporation of intracellular information opens up new possibilities for glucose controller design, mainly because variables that play a key role in the glucose homeostasis can be incorporated.

TABLE I

Controllers' performance assessment (value±SD).

Controller	IFB	GFB
% 70-180	89.6±8.7	67.7±10.3
% below 70	0.0±0.0	20.1±9.8
% above 180	10.4±5.2	12.2±6.9

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