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Model-Based Predictive Control of Blood-Sugar Level in Intensive Care

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***Abstract*— Predictive control of blood glucose in critical ill patients has been investigated. Standard control algorithms for blood glucose only adjust the insulin infusion rate for lowering the blood sugar level. Hypoglycaemic situations are critical is this case since no automatic control action can be lunched. To avoid hypoglycaemia, controller performance is usually chosen low what results in large settling times. In the proposed predictive control scheme, glucose and insulin infusions are administrated. This allows to track a specified blood glucose profile exactly. The employed controller is model-based and tested in computer simulations.**

I. Introduction

Automatic closed-loop control of blood sugar (BS) in critical ill patients is investigated. A clinical study by Van den Berghe et. al [1] has shown, that an intensive insulin therapy reduces the mortality rate in intensive care units (ICU) significantly. At the moment, in sedated patients in ICU, medical staff manually controls the blood glucose levels on behalf of the patient and determines an appropriate insulin dose. Insulin is usually given by intravenous bolus or infusion in response to elevated BS readings. In an intensive insulin therapy, BS levels of about 5 mmol/l instead of the usual 10 mmol/l in ICU are realised by a more tightened BS check and intervention of the medical staff. However, hypoglycaemic situations are more likely to occur at an intensified insulin therapy [1]. Additionally, the workload of the medical staff is definitively higher for an intensive insulin therapy.

An automatic closed-loop system may help to mitigate these problems. In a closed-loop feedback system, a blood glucose sensor measures blood glucose or a surrogate of it continuously. Recent research has been directed to the use of minimally invasive and non-invasive methods to measure BS levels. First closed-loop systems with a subcutaneous electro-enzymatic sensor have been developed and experimentally tested in ICU [2]–[4].

All known blood glucose control algorithms regulate only the insulin delivery to the patient via an insulin pump. The control action, insulin infusion, can only lower the blood glucose concentration. However, aggressive control is not possible, since the controller cannot react on an undershoot of the blood sugar below the reference. No automatic control action for raising the blood sugar is available. Thus, hypoglycaemia would be unavoidable. Closed-loop systems with insulin infusion rate as a single control variable are therefore tuned to possess a low bandwidth. Settling times are consequently rather large.

The application of an intravenous glucose infusion represents a simple method for raising blood sugar levels in ICU. This article investigates a control system in which insulin and glucose infusions are administrated for controlling the blood sugar level. Faster settling times of the closed-loop system and a reduced risk of hypoglycaemic situations are expected. The control approach has been validated in simulations using a nonlinear model of the glucose-insulin system. In Section II the nonlinear model is described. The design of the used predictive controller is based on a linear discrete-time transfer function model. Section III outlines the controller design. Simulation results are shown in Section IV.

II. Nonlinear Model

The developed controller has been tested in simulations first. A modified minimal model of the insulin-glucose metabolism proposed by Furler et al. [5] has been chosen. The model proposed originally consists of an one-compartment model for the glucose subsystem and a four-compartment model for the subsystem of insulin. Two of the four insulin compartments describe the antibody dynamics and are not considered in this work. This assumption is justified because the presently available highly purified insulin preparations are a lot less immunogenic than those used when Furler et al. [5] developed their model. The original model was extended by a term for endogenous insulin secretion [6]. The equations describing the model are

$$\begin{aligned}
\frac{\mathrm{d}\,x_1(t)}{\mathrm{d}\,t} &= (-P_1 - x_2(t))\,x_1(t) + P_1 G_0 + \frac{u_1(t)}{V_G} \\
\frac{\mathrm{d}\,x_2(t)}{\mathrm{d}\,t} &= -P_2 x_2(t) + P_3\,(x_3(t) - I_0) \\
\frac{\mathrm{d}\,x_3(t)}{\mathrm{d}\,t} &= \frac{u_2(t) + I_s(t)}{V_I} - n x_3(t) \\
I_S(t) &= I_{S1} \cdot x_1(t) - I_{S2}
\end{aligned} \tag{1}$$

In the mathematical description the nomenclature given in Table I is adopted. Parameter values for a person with impaired insulin secretion and insulin resistance are listed in Table II.

The output, blood glucose concentration $y = x_1$, can be influenced by the insulin infusion rate u_2 and/or by the glucose infusion rate u_1.

III. Predictive Controller Design

For controller design, the model (1) has been linearised at basal state and time-discretised with sampling-time

TABLE I

NOMENCLATURE OF THE MODEL.

State	Explanation	Unit
x_1	plasma glucose concentration	mmol/l
x_2	insulin concentration (remote compart.)	1/min
x_3	free plasma insulin concentration	mU/l
Parameter	**Explanation**	**Unit**
G_0	basal plasma glucose	mmol/l
I_0	basal plasma insulin	mU/l
I_S	endogenous insulin secretion	mU/min
u_1	rate of exogenously infused glucose	mmol/min
u_2	rate of insulin infusion	mU/min
V_G	glucose distribution space	l
V_I	insulin distribution volume	l
P_1	glucose effectiveness factor	1/min
P_2	delay in insulin action	1/min
n	fractional disappearance rate of insulin	1/min

TABLE II

MODEL PARAMETERS FOR 70 KG BODY WEIGHT.

Parameter	Value	Unit
G_0	4.5	mmol/l
I_0	15	mU/l
V_G	12	l
V_I	12	l
n	0.09	1/min
P_1	2.8	$1/(10^2\,\mathrm{min})$
P_2	2.5	$1/(10^2\,\mathrm{min})$
P_3	13	$\mathrm{l}/(10^6\,\mathrm{min}^2\cdot\mathrm{mU})$
I_{S1}	1.6	$(\mathrm{mU}\cdot\mathrm{L})/(\mathrm{mmol}\cdot\mathrm{min})$
I_{S2}	6.0	mU/min

$t_s = 5\,\mathrm{min}$. Fig. 1 depicts the linear model whereas the paths from the control signals to the blood glucose are described by linear pulse transfer functions. Note that both control signals are limited for technical reasons ($0 \le u_1 \le 9.25\,\mathrm{mmol/min},\ 0 \le u_2 \le 30\,\mathrm{U/h}$). The model without the constraints can be written as

$$y(k) = \frac{q^{-1}\mathsf{B}_1(q^{-1})}{\mathsf{A}(q^{-1})}u_1(k) + \frac{q^{-1}\mathsf{B}_2(q^{-1})}{\mathsf{A}(q^{-1})}u_2(k) + \frac{\mathsf{C}(q^{-1})}{(1-q^{-1})\mathsf{A}(q^{-1})}v(k) \tag{2}$$

where $\mathsf{A}, \mathsf{B}_1, \mathsf{B}_2$ and C are polynomials in the delay operator q^{-1}. The term q^{-1} describes an one step input-output delay. Measurement noise and disturbances are described by the last transfer function term of Eq. (2) with the white noise input $v(k)$. The polynomial C can be treated as design parameter which influences the sensitivity of the model-based predictive controller with respect to noise. Including the term $(1-q^{-1})$ into the noise/disturbance path of the model allows the description of piecewise constant disturbances and leads to integral control of the predictive controller.

The applied discrete-time predictive control scheme is depicted in Fig. 3. At time instant kt_s the N-step-ahead blood glucose concentration $\hat{y}(k+N|k)$ is estimated.

The model-based prediction is a function of the current and future control signals $\hat{u}_1(i|k), \hat{u}_2(i|k), \quad k \le i \le N-1$ and relies furthermore on the current measurement $y(k)$ and past observations of the output and control

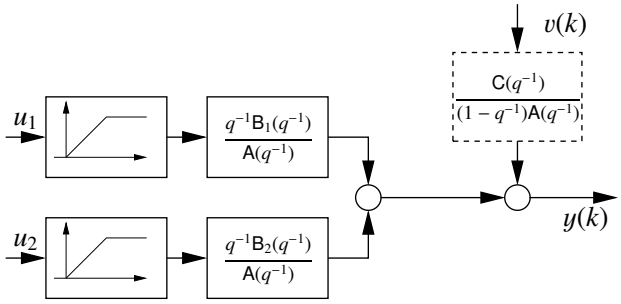

Fig. 1. Transfer function model used for controller design with the control signals u_1 (glucose infusion rate) and u_2 (insulin infusion rate) as well as the white noise input v. Output is the plasma glucose concentration y.

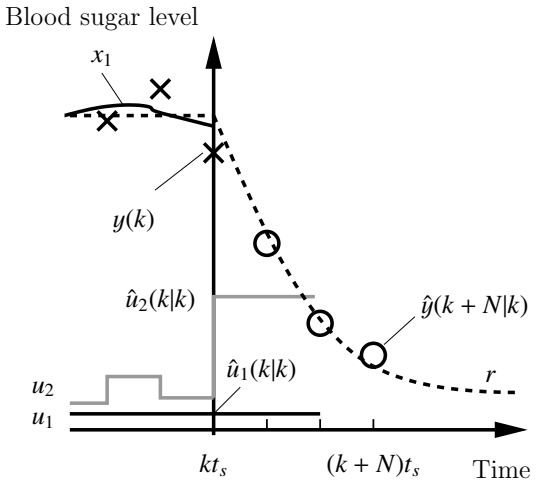

Fig. 2. Predictive control scheme.

signals. For simplifying the predictive controller it is assumed that

$$\hat{u}_1(k|k) = \hat{u}_1(k+i|k), \quad i = 1 \ldots N-1 \tag{3}$$
$$\hat{u}_2(k|k) = \hat{u}_2(k+i|k), \quad i = 1 \ldots N-1 \tag{4}$$

The control signals $\hat{u}_1(k|k)$ and $\hat{u}_2(k|k)$ are determined by an optimiser and applied to the infusion pumps. The optimiser aims at minimising a cost function J taking the control signal constraints into account. The chosen cost function is defined as

$$J = \frac{1}{2}(r(k+N|k) - \hat{y}(k+N|k))^2 + \frac{1}{2}\gamma_1\hat{u}_1(k|k)^2 + \frac{1}{2}\gamma_2\hat{u}_2(k|k)^2 \tag{5}$$

where r is an online adapted reference trajectory which leads the blood glucose concentration towards a normoglycaemic level in a fast and smooth fashion. The cost function describes the control effort and gives a measure how far the N-step-ahead prediction of the BS level is away from the reference trajectory. Weighting of the control effort is achieved by the positive constants γ_1 and γ_2. Note, that the inclusion of the control effort in J is necessary in order to avoid an administration of glucose and insulin at the same time by the controller.

The N-step-ahead minimum variance prediction can be calculated as follows [7]:

$$\hat{y}(k+N|k) = y_{\text{future}} + y_{\text{past}} \tag{6}$$

$$\begin{aligned} y_{\text{future}} = {} & \mathsf{E}_1(q^{-1})\hat{u}_1(k+N-1|k) \\ & + \mathsf{E}_2(q^{-1})\hat{u}_2(k+N-1|k) \end{aligned} \tag{7}$$

$$\begin{aligned} y_{\text{past}} = {} & \frac{\overline{\mathsf{F}}(\mathsf{q}^{-1})}{\mathsf{C}(q^{-1})}y(k) \\ & + \frac{q^{-1}(\mathsf{F}_1\mathsf{C}-\overline{\mathsf{F}}\mathsf{B}_1)}{\mathsf{A}(q^{-1})\mathsf{C}(q^{-1})}u_1(k) \\ & + \frac{q^{-1}(\mathsf{F}_2\mathsf{C}-\overline{\mathsf{F}}\mathsf{B}_2)}{\mathsf{A}(q^{-1})\mathsf{C}(q^{-1})}u_2(k). \end{aligned} \tag{8}$$

The term y_{future} depends on future control signals whereas y_{past} depends on the current and past BS measurements and past control actions. The polynomials $\mathsf{E}_1, \mathsf{E}_2, \mathsf{F}_1, \mathsf{F}_2$ and $\overline{\mathsf{F}}$ are determined by the set of Diophantine equations

$$\begin{aligned} \mathsf{B}_1(q^{-1}) &= \mathsf{A}(q^{-1})\mathsf{E}_1(q^{-1}) + q^{-N}\mathsf{F}_2(q^{-1}) \\ \mathsf{B}_2(q^{-1}) &= \mathsf{A}(q^{-1})\mathsf{E}_2(q^{-1}) + q^{-N}\mathsf{F}_2(q^{-1}) \\ \mathsf{C}(q^{-1}) &= \mathsf{D}(q^{-1})\overline{\mathsf{E}}(q^{-1}) + q^{-N}\overline{\mathsf{F}}(q^{-1}). \end{aligned}$$

Note that using (3) and (4) renders the prediction term y_{future} (7) to

$$y_{\text{future}} = \mathsf{E}_1(1)\hat{u}_1(k|k) + \mathsf{E}_2(1)\hat{u}_2(k|k). \tag{9}$$

The N-step-ahead prediction is therefore a linear function of the interesting control signals. This leads to an analytical solution of the optimisation problem in the case of no constraints. Quadratic programming can be used to solve the optimisation problem if constraints are active. The polynomial C must have its roots inside the unit circle to make the predictor stable. From (8) it is clear that the polynomial C defines the poles of a low-pass filter applied to the noisy measurements. By choosing "slower" poles, the controller becomes less sensitive to measurement noise.

IV. Results and Discussion

The predictive controller has been verified in simulation with the nonlinear model (1). The aim was to bring the BS level from an initial value of $10\,\text{mmol/l}$ to a desired value of $5\,\text{mmol/l}$ in about 50 min without any hypoglycaemic situation (undershoot). A 3-step-ahead prediction was used in the cost function with $\gamma_1 = 5 \cdot 10^{-5}$ and $\gamma_2 = 2 \cdot 10^{-6}$. The chosen polynomial $\mathsf{C} = (z-0.8)(z-0.7)(z-0.6)$ guarantees good robustness of the closed-loop system with respect to measurement noise. In simulation a white measurement noise with a standard deviation of 0.11 mmol/l was injected.

Simulation results are shown in Fig. 3. On the top axis of Fig. 3 the blood sugar level (solid line) and its reference (dashed line) are shown together with the measurements (crosses) and the 3-step-ahead prediction (circles). The second axis shows the glucose infusion rate u_1 (solid line) and a pre-programmed additional glucose infusion (dashed line) mimicking an intravenous nutrition profile. The nutrition infusion is unknown for the predictive controller and starts at 200 minutes. Insulin infusion rate u_2 of the predictive controller is shown on the bottom axis.

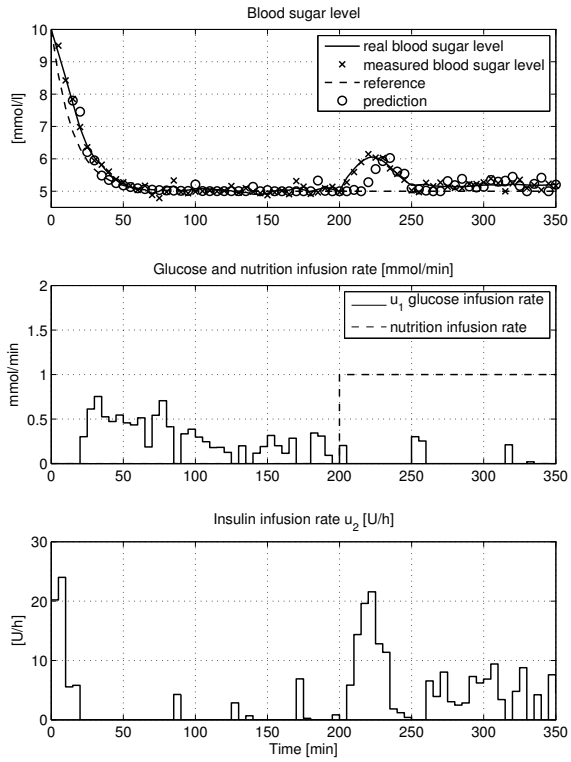

Fig. 3. Simulations results: After 200 minutes an additional glucose infusion is given mimicking an intravenous feeding.

The predictive controller performs sufficiently well. The BS level follows the reference trajectory closely and no hypoglycaemic situation occurs. Initially, insulin is only given. In order to avoid an undershoot the controller administrates subsequently glucose. The disturbance from 200 minutes on causes only a short error in the prediction. After ca. 25 minutes the disturbance is observed so that the prediction fits again to the real BS level. The slightly elevated BS returns to the desired value.

V. Conclusion

The simulation results with the newly developed predictive controller are very promising. An undershoot of blood sugar can be avoided even for fast settling times. Future work will focus on the experimental identification and validation of the model used for controller design and clinical validation of the predictive controller.

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