Control Engineering Practice 28 (2014) 26–33

Contents lists available at ScienceDirect

Control Engineering Practice

journal homepage: www.elsevier.com/locate/conengprac

Nonlinear glucose–insulin control considering delays—Part II: Control algorithm

K. Mythreyi, Shankar C. Subramanian *, R. Krishna Kumar

Department of Engineering Design, Indian Institute of Technology Madras, Chennai, TN 600036, India

ARTICLE INFO

Article history:
Received 15 June 2013
Accepted 12 February 2014
Available online 28 March 2014

Keywords:
Blood glucose level
Nonlinear model
Model predictive control
Constraints
Virtual patient

ABSTRACT

The closed loop control of blood glucose levels in a nonlinear glucose–insulin regulatory system is considered in this paper. Based on the subcutaneous glucose sensor readings, a control algorithm is designed and implemented. A mathematical model characterizing the ultradian oscillatory nature of the glucose–insulin regulatory system of diabetic patients is considered and an estimation based model predictive control scheme with physiological and actuator constraints is implemented. An *in silico* preclinical testing is done to corroborate the control algorithm using the UVa/Padova virtual patient software.

1. Introduction

Diabetes is a chronic disease and is increasingly seen in developing countries. The International Diabetes Federation reports that there are 61.3 million people affected by diabetes in India in the year 2011 and this is expected to reach 120 million by the year 2030 (International Diabetes Federation, 2011). According to the World Health Statistics 2012, one out of 10 people has diabetes in the world (Chaib, 2012). It is very important to monitor the blood glucose levels (BGLs) of the diabetic patients regularly. Any deviation in the BGL from the normal range can be compensated by altering the dosage of the insulin. A prolonged excessive glucose levels in the blood may cause renal failure, heart stroke and blindness, and any sudden decrease in the blood concentration may lead to unconsciousness or may even lead to coma. Thus, it is necessary to provide proper medication to the increasing number of diabetic patients in the world.

Treatment for diabetes is of two types: (1) insulin injection and (2) continuous insulin infusion. Infusion pumps are used for continuous insulin infusion. Various infusion pumps that are available in the market are programmable to deliver the required amount of insulin. However, there is a need for an automated infusion pump that can deliver appropriate amounts of insulin to the patient without any manual interference. The three main components of such a closed loop control system are (1) glucose sensor, (2) control algorithm, and (3) infusion pump. The block diagram of the closed loop control system for the glucose–insulin regulatory system is given in Fig. 1.

Amongst the various glucose sensors available in the market, the Medtronic MiniMed® Guardian® REAL-Time Continuous Glucose Monitoring System (CGMS) sensor was used in this research. It can measure the subcutaneous glucose levels once in every 5 min and is found to be suitable for continuous insulin infusion devices. A control algorithm that determines the rate at which insulin needs to be injected to the patient to maintain BGL within the normal range, and an infusion pump that delivers the drug to the patient are developed as a part of the research work presented in this paper.

Various control algorithms such as pole placement technique, PID control based on back propagation neural network (Li & Hu, 2007), Fuzzy-PID control (Li & Hu, 2009), PID control (Marchetti, Barolo, Jovanovic, Zisser, & Seborg, 2008; Semizer, Yüceer, Atasoy, & Berber, 2012), optimal control (Chase et al., 2002), adaptive control, sequential quadratic programming (Semizer et al., 2012), H_∞ control (Chee, Savkin, Fernando, & Nahavandi, 2005), nonlinear control (Palumbo, Pepe, Panunzi, & Gaetano, 2011) and model predictive control (Bruttomesso et al., 2009; Chui et al., 2013; Clarke et al., 2009; Dua, Doyle, & Pistikopoulos, 2006; Hovorka et al., 2004; Lee, Buckingham, Wilson, & Bequette, 2009; Lynch & Bequette, 2002; Markakis, Mitsis, Papavassilopoulos, & Marmarelis, 2008; Parker, Gatzke, & Doye III, 2000; Percival et al., 2011; Steil, Rebrin, Darwin, Hariri, & Saad, 2006) have been implemented based on the mathematical models available in the literature. Model predictive control (MPC) is widely used in the systems with time delay. Doyle, Jovanovic, and Seborg (2007) suggested that the MPC

* Corresponding author. Fax: +91 44 22574732.
E-mail addresses: kondapimythreyi@gmail.com (K. Mythreyi), shankarram@iitm.ac.in (S.C. Subramanian), rkkumar@iitm.ac.in (R. Krishna Kumar).

http://dx.doi.org/10.1016/j.conengprac.2014.02.012
0967-0661

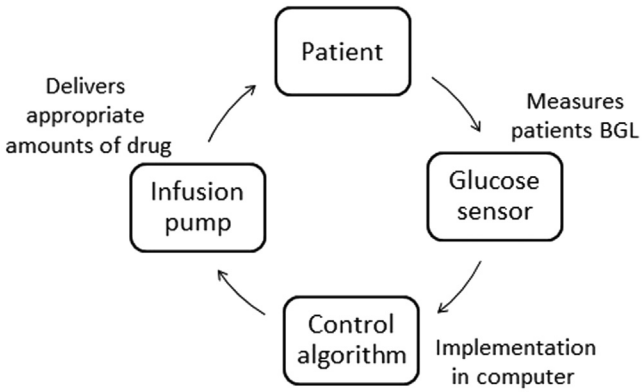

Fig. 1. The block diagram of the continuous insulin infusion system.

algorithm is most suitable for nonlinear system involving delays and constraints. The mathematical models representing glucose–insulin dynamics include delays. The MPC algorithm predicts the BGL outputs at the future instants and thus a decision of the control input is made. The risk of hypoglycemia and the meal absorption dynamics can be predicted ahead of time and the decision is made accordingly.

The focus of this paper is to design and implement an estimation based model predictive control (MPC) scheme with constraints to maintain BGL within the normal range. A mathematical model proposed in Mythreyi (2014) is used for the implementation of the control algorithm. The control algorithm is implemented and corroborated using the UVa Padova T1DM virtual patient software (Kovatchev, Breton, Man, & Cobelli, 2009). An infusion pump is designed and developed to administer the appropriate amount of drug to the patient.

2. Material and methods

The mathematical models representing the glucose–insulin interactions consist of various measurable and non-measurable state variables and the knowledge of these states is necessary to develop a model based control strategy. Therefore, an estimation based control algorithm implementation is performed in this paper. Various estimation based model predictive controls based on mathematical models representing the glucose–insulin interactions have been developed (Gillis et al., 2007; Lynch & Bequette, 2001; Parker, Doyle, & Peppas, 1999). The algorithm developed in Gillis et al. (2007) and Lynch and Bequette (2001) is based on Bergman's model (Bergman, Phillips, & Cobelli, 1891). This is a simple model and represents the dynamic system with a set of three equations characterized by intravenous glucose tolerance test. The algorithm in Parker et al. (1999) is based on Sorenson's (1985) model developed based on the pharmacokinetic–pharmacodynamic approach. However, these models do not represent the oscillatory nature of the glucose–insulin secretions required to represent a realistic patient model. In this paper, an estimation based control algorithm based on the mathematical model representing the ultradian oscillatory nature of glucose and insulin secretions was developed for the first time and the model has been taken from our previous work (Mythreyi 2014).

The mathematical model presented in Mythreyi (2014) represents a realistic patient condition considering ultradian oscillations and is suitable for control algorithm development. An extended Kalman filtering (EKF) technique was used to estimate the state variables at every time step which can further be used in control algorithm implementation. Then a control algorithm can be developed based on these estimates. The model equations and EKF algorithm are provided in this section for the reader's reference.

2.1. Mathematical model

The mathematical model proposed in Mythreyi (2014) is a set of 10 ordinary differential equations (ODEs) with plasma glucose G_p, interstitial glucose G_i, plasma insulin I_p, interstitial insulin I_i, glucose sensor G_s, auxiliary variables G_{p2hat}, G_{p3hat}, I_{phat1}, I_{phat2}, and I_{phat3} as its state variables. The mathematical model is given in the set of equations:

$$\begin{aligned}
\dot{G}_p &= G_{in}(t)+HGP(I_{phat3})f_6(G_i)-U_{ii}(G_p)\\
&\quad -E(G_p)-k_1G_p+k_2G_i-f_7(G_i),\\
\dot{I}_{phat1} &= (3/\tau_1)(I_p-I_{phat1}),\\
\dot{I}_{phat2} &= (3/\tau_1)(I_{phat1}-I_{phat2}),\\
\dot{I}_{phat3} &= (3/\tau_1)(I_{phat2}-I_{phat3}),\\
\dot{G}_i &= k_1G_p-k_2G_i-\beta U_{id}(G_i,I_i),\\
\dot{I}_i &= m_1I_p-m_2I_i-m_4I_i,\\
\dot{I}_p &= \dot{I}^{inj}(t)+\alpha S(G_{p2hat})+(1-\alpha)S(G_{p3hat})\\
&\quad -m_1I_p+m_2I_i-m_3I_p,\\
\dot{G}_{p2hat} &= (1/\tau_2)(G_p-G_{p2hat}),\\
\dot{G}_{p3hat} &= (1/(\tau_2+\tau_3))(G_p-G_{p3hat}),\\
\dot{G}_s &= (\delta/\tau)(G_i-G_s).
\end{aligned} \tag{1}$$

The functions characterizing hepatic glucose production $HGP(I_p)$ (in mg/min), insulin secretion $S(G_p)$ (in mU/min), insulin dependent glucose utilization U_{id} (in mg/min), insulin independent glucose utilization, $f_6(G_i)$ and $f_7(G_p)$ (in mg/min) that represent the effect of hyperglycemia, and insulin secretion $S(G_p)$ (in mU/min) are given by

$$\begin{aligned}
HGP(I_p) &= \frac{160}{1+\exp(0.29(I_p/V_{ip}-7.5))},\\
U_{ii}(G_p) &= 72(1-\exp(-G_p/144V_{gp})),\\
U_{id}(G_i,I_i) &= f_3(G_i)f_4(I_i),\\
f_3(G_i) &= 0.01G_i/V_{gi},\\
f_4(I_i) &= 4+90/(1+\exp(-1.772\ln(I_i(1/V_{ii}+m_4/e))+7.76)),\\
S(G_p) &= 210/(1+\exp(5.21-0.003G_p/V_{gp})),\\
f_6(G_i) &= 1/(1+\exp(5(G_i/(1000V_{gi})-2))),\\
f_7(G_p) &= 20+120/(1+\exp(-2.4(G_p/1000V_{gp}-2))).
\end{aligned} \tag{2}$$

The variables used in these functions are dependent upon various parameters of the patient such as bodyweight BW, volume distributions of plasma glucose V_{gp}, interstitial glucose V_{gi}, plasma insulin V_{ip} and interstitial insulin V_{ii}. The above volume distributions are estimated as 12%, 10%, 4.5% and 10% of BW (Wu, Chui, Hong, & Chang, 2011). The parameters k_1 and k_2 are the transfer rates of glucose exchange between plasma and remote compartments. The parameters m_1 and m_2 are the transfer rates of insulin between plasma and remote compartments. The parameters m_3 and m_4 are the plasma and the interstitial insulin clearance rates. The values of these parameters are given in Table 1.

The exogenous glucose input G_{in} (in mg/min) is represented by a Rayleigh probability density function, where the value of k (in mg/dl) depends upon the amount of food consumed (from Chen & Tsai, 2010, $k=1500$ for 10 g of CHO; 3400 for 30 g of CHO; 4300 for 60 g of CHO; 5100 for 75 g of CHO). The corresponding meal absorption rate equation is given by

$$G_{in}(t) = \frac{kt}{c^2}\exp(-t^2/2c^2). \tag{3}$$

The renal excretion of glucose $E(G_p)$ (in mg/min) depends on the parameters k_{e1} and k_{e2}, the glomerular filtration rate and the renal