Biomedical Signal Processing and Control 13 (2014) 237–246

Contents lists available at ScienceDirect

Biomedical Signal Processing and Control

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

A switching hybrid control method for automatic blood glucose regulation in diabetic Göttingen minipigs

Katrin Lunze*, Marian Walter, Steffen Leonhardt

Department of Electrical Engineering, RWTH Aachen University, Aachen 52074, Germany

ARTICLE INFO

Article history:
Received 29 November 2013
Received in revised form 8 April 2014
Accepted 13 May 2014
Available online 11 June 2014

Keywords:
Blood glucose control
Switching control method
Impulsive control process
Diabetic Göttingen minipigs

ABSTRACT

A new hybrid control method for blood glucose concentration is developed which switches between two operation modes. The effects of meal-induced disturbances on blood glucose concentrations are expected to be more serious than the time-varying behaviour of glucose metabolism during nocturnal phases. Thus, the control method determines insulin impulses (boli) as a manipulated variable during the day and calculates continuous insulin infusion (basal rates) at night. To test the controller-based insulin therapy *in vivo*, animal trials with diabetic Göttingen minipigs are used as a proxy for human studies. The controller parameters are selected by *in silico* studies based on mathematical minipig models, and the resulting individualised controllers are experimentally verified. For this, two control performance requirements must be taken into account: blood glucose concentrations below the critical threshold of 50 mg/dl have to be avoided, and blood glucose peaks caused by ingestion of minipig diet have to be quickly counteracted. Results from these animal experiments show that the closed-loop system satisfies both control requirements and improves insulin therapy compared with a standard therapeutic protocol.

1. Introduction

1.1. Glucose metabolism

In healthy subjects, the blood glucose concentration is stabilised by the pancreas in the physiological normal range of 80–120 mg/dl. In the case of type 1 diabetes patients, the natural mechanism for blood glucose control is damaged. This means that, in particular, the β-cells in the pancreas which normally produce and release the glucose-reducing hormone insulin are destroyed. Therefore, in the absence of any form of insulin therapy, the fasting blood glucose concentration in type 1 diabetes patients increases to an unphysiologically high level compared to nondiabetic steady-state glucose concentration.

Until now, the diabetic patients are challenged by having to manually adjust the required insulin doses in a discrete-time process, whilst also estimating potential metabolic disturbances, e.g. carbohydrate ingestion or physical activity. To reduce blood glucose variability and related health risks, the control process needs to be transformed into a continuous-time system, which has been termed an 'artificial pancreas' (Fig. 1). In this case, the blood glucose concentration is measured continuously by means of an implanted sensor and insulin is infused continuously via a pump. A control algorithm between the sensor and actuator calculates the insulin dose required by the patient, thereby implementing a true closed-loop system.

1.2. State-of-the-art blood glucose control

In recent decades, the growth rate in the incidence of diabetes has stimulated efforts to refine insulin therapy and improve blood glucose regulation, thereby preventing secondary complications of diabetes. To this end, many ideas concerning therapy devices and control algorithms have been published, as reviewed e.g. in [1,2]. Different simulation platforms, including a mathematical diabetic patient model, were developed and are used to test control algorithms [3–6]. Recently, some research groups have focused on clinical closed-loop studies [7–11]. However, the risk of insulin overdose remains; this can lead to hypoglycaemia (low blood glucose concentration) with a potential life-threatening situation for the patient, due to the following uncertainties related to both the signal and process:

* Corresponding author.
E-mail address: lunze@hia.rwth-aachen.de (K. Lunze).

http://dx.doi.org/10.1016/j.bspc.2014.05.004
1746-8094/

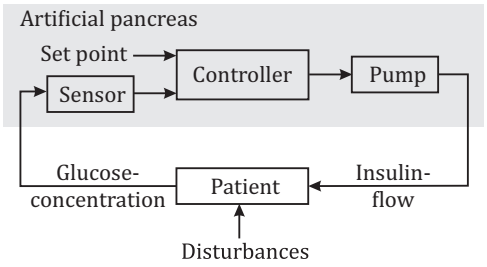

Fig. 1. The artificial pancreas as control system in diabetic patients.

- The continuous glucose measurement systems (CGMS) which are commercially available provide a low-pass filtered glucose signal due to the subcutaneous measurement; this may not be reliable enough for control application [12,13].
- Commercially available insulin pumps deliver insulin subcutaneously resulting in a time delay between insulin application and arrival in blood.
- The metabolic response to insulin is time-variant; this results in uncertainties regarding the effect of insulin on the blood glucose concentration.

To develop a reliable therapy system which can be applied to diabetic humans in everyday situations, diabetic animals represent a proxy of type 1 diabetes patients for the initial control tests. Here, animal trials can be regarded as an intermediate step between *in silico* and *in vivo* control evaluations to test therapy systems under realistic conditions [14,15].

1.3. Paper structure

The present project focuses on the development of an artificial pancreas for diabetic Göttingen minipigs; the metabolism of these pigs is comparable to that in humans [16]. To present the new control method and the corresponding strategy for control design, this paper

1 briefly introduces the animal trials and two mathematical models of porcine glucose metabolism (Section 2, see also [17]),
2 explains the control challenges and limitations, and introduces a hybrid switching control algorithm for blood glucose stabilisation in the animals (Sections 3–5), and
3 experimentally evaluates the control performance (Section 6).

2. Animal models

2.1. Animal trials

In $n = 8$ Göttingen minipigs an acute diabetes mellitus was chemically induced, see [18]. Subsequently, the impulse response behaviour of the porcine diabetic glucose metabolism to external glucose and insulin stimuli was analysed by means of blood glucose measurements. For manual and controller-based insulin application an insulin pump for human therapy (Accu-Chek® Combo Spirit, Roche Diagnostics, Rotkreuz, Switzerland) was applied, and for continuous glucose monitoring in the subcutaneous space a CGMS (G4™ Platinum, Dexcom™, San Diego, CA, USA) was used. Via two central venous lines, blood samples were drawn manually for reference measurement of blood glucose with a blood gas analyser (ABL 810 Flex, Radiometer Medical ApS, Herlev, Denmark). Due to different aims of the trials and to the individually varying clinical conditions of the animals, the controller tests were performed in minipig (MP) 7 and MP 8 only. For detailed information see [18,17].

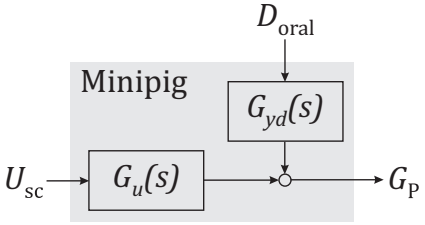

Fig. 2. Linear approximate minipig model.

The entire study protocol was approved by the Animal Care and Use Committee of the State Agency for Nature, Environment and Consumer Protection, North Rhine-Westphalia, Germany.

2.2. Mathematical glucose metabolic models

2.2.1. Nonlinear model

To approximate the glucose metabolism of diabetic minipigs by a mathematical model, the nonlinear complex human model of Sorensen [5] was used as a basis. This is the only model that includes subsystems for glucose as well as for both of the counteracting hormones, insulin and glucagon. The Sorensen model was extended and the model parameters were adapted to diabetic Göttingen minipigs as a new species. For more information on the resulting 16th-order model, see [17].

2.2.2. Linear model

For controller design and initial selection of the controller parameters, the nonlinear complex model was reduced to a 5th-order linear model which consists of a disturbance transfer function $G_{yd}(s)$ and a command transfer function $G_u(s)$ (Fig. 2). The model parameters were determined by minimising the difference between calculated blood glucose trajectories of the nonlinear model and its linear approximate resulting from impulse-shaped input signals of oral glucose uptake $D_{oral}(t)$ or subcutaneous insulin dosage $U_{sc}(t)$. Here, the function `fminsearch` of the MATLAB/Optimization toolbox was applied, and the impulse responses of the nonlinear model served as reference signals. The model simplification was performed twice for MP 7 due to the different physiological conditions and once for MP 8. The resulting disturbance and command signal transfer functions are described in the following sections with the corresponding parameters shown in Table 1.

Disturbance transfer function. The effect of orally uptaken glucose on the blood glucose concentration is approximated by an IT_1-element

$$G_{yd}(s) = \frac{K_d}{s \cdot (T_d \cdot s + 1)}. \quad (1)$$

Here, T_d can be interpreted as the glucose transient time through the gastro-intestinal tract and K_d as the glucose bioavailability. To determine the parameters K_d and T_d, the glucose trajectory of the nonlinear minipig model resulting from a disturbance impulse of

$$D_{oral}(t) = 1\,\text{g}\ \ \text{Glucose} \cdot \delta(t) \quad (2)$$

was used as a reference signal. $\delta(t)$ is the dirac function.

Table 1
Parameters for the linear minipig model.

	MP 7_1	MP 7_2	MP 8
K_d	2.5×10^{-3}	2.3×10^{-3}	1.9×10^{-3}
T_d	24.81	58.88	27.45
K_u	−3.47	−2.77	−2.57
T_u	61.79	62.18	31.00