COMPUTER METHODS AND PROGRAMS IN BIOMEDICINE 102 (2011) 105–118

journal homepage: www.intl.elsevierhealth.com/journals/cmpb

# Induced $L_2$-norm minimization of glucose–insulin system for Type I diabetic patients

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A R T I C L E  I N F O

*Article history:*
Received 14 December 2009
Received in revised form
29 May 2010
Accepted 28 June 2010

*Keywords:*
Type I diabetes
Robust control
LPV
ICU
Uncertainty

A B S T R A C T

Using induced $L_2$-norm minimization, a robust controller was developed for insulin delivery in Type I diabetic patients. The high-complexity nonlinear diabetic patient Sorensen-model was considered and Linear Parameter Varying methodology was used to develop open-loop model and robust $H_\infty$ controller. Considering the normoglycaemic set point (81.1 mg/dL), a polytopic set was created over the physiologic boundaries of the glucose–insulin interaction of the Sorensen-model. In this way, Linear Parameter Varying model formalism was defined. The robust control was developed considering input and output multiplicative uncertainties with two additional uncertainties from those used in the literature: sensor noise and worst-case design for meal disturbance (60 g carbohydrate). Simulation scenario on large meal absorption illustrates the applicability of the robust LPV control technique, while patient variability is tested with real data taken from the SPRINT clinical protocol on ICU patients.


## 1. Introduction

The normal blood-glucose concentration level in the human body varies in a narrow range (70–110 mg/dL). If the human body is unable to control the normal glucose–insulin interaction diabetes mellitus is diagnosed. The phenomenon can be explained by several causes, most important ones are stress, obesity, malnutrition and lack of exercise. The consequences of diabetes are mostly long-term; among others, diabetes increases the risk of cardiovascular diseases, neuropathy and retinopathy [1].

Consequently, diabetes mellitus is a serious metabolic disease, which should be artificially regulated. This metabolic disorder was lethal until 1921 when Frederick G. Banting and Charles B. Best discovered insulin. Nowadays, the life quality of diabetic patients can be enhanced, although the disease is still lifelong.

The newest statistics of the World Health Organization (WHO) predict an increase of adult diabetes population from 4% (in 2000, meaning 171 million people) to 5.4% (366 million worldwide) by the year 2030 [2]. This warns that diabetes could be the "disease of the future", especially in developing countries (due to stress and unhealthy lifestyle).

Type I (also known as insulin dependent diabetes mellitus or IDDM) is one of the four classified types of this disease (Type II, gestational diabetes and other types, like genetic deflections are the other three categories of diabetes), is characterized by complete pancreatic β-cell insufficiency [1]. As a result, the only treatment of Type I diabetic patients is based on insulin injection (subcutaneous or intravenous), usually administered in an open-loop manner.

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0169-2607/$ – see front matter 
doi:10.1016/j.cmpb.2010.06.019

Due to the alarming facts of diabetes, the scientific community has proposed to improve the treatment of diabetes by investigating the applicability of an external controller. In many biomedical systems, an external controller provides the necessary input, because the human body could not ensure it. The outer control might be partially or fully automated. The self-regulation has several strict requirements, but once it has been designed it permits not only to facilitate the patient's life suffering from the disease, but also to optimize (if necessary) the amount of insulin dosage to be injected.

However, blood-glucose control is a difficult control problem to be solved. One of the main reasons is that the patients are extremely diverse in their dynamics and, in addition, their characteristics are time varying. Due to the inexistence of an outer control loop, replacing the partially or totally deficient blood-glucose-control system of the human body, patients are regulating their glucose level manually. Based on the measured glucose levels (obtained from extracted blood samples), they often decide on their own what is the necessary insulin dosage to be injected. Although, this process is supervised by medical doctors, mishandled situations often appear. Hyper- (deviation over the basal glucose level) and hypoglycaemia (deviation under the basal glucose level) are both dangerous cases, but in the short run the latter is more dangerous, leading for example to coma.

Starting from the 1960s lots of researchers have investigated the problem of the glucose–insulin interaction and control. The closed-loop glucose regulation (as it was several times formulated [3–5]) requires three components:

- glucose sensor;
- insulin pump;
- a control algorithm based on the glucose measurements that is able to determine the necessary insulin dosage.

In the last few decades, many scientists have tried to create mathematical models describing the human blood-glucose system. This chapter provides a short overview of the applied techniques and achieved results, a brief overview can be found in [6] and interested readers are invited to consult other dedicated textbooks, e.g. [7]. The following overview enumerates results of the Intensive Care Unit (ICU) control topic too, as blood-glucose level control is important not only for diabetic patients, but also for intensive care treatment [8].

### 1.1. *Modeling techniques*

Modeling the blood-glucose system and controlling its behavior are two tightly connected questions; hence the problems could not be discussed separately. As a result of numerous researches, two main aspects were proposed: model-less (empirical) and model-based approach [6].

Model-less approaches can be structured as:

- control algorithm based on curve-fitting [9,10] and in ICU [11–13];
- control algorithm based on lookup table [14,15] and in ICU [16–18];
- control algorithm based on rule-based control [19,20] and in ICU [21,22];
- control algorithm based on PID control [23,24] and in ICU [25–27].

A model-based approaches classification can be done as follows:

- linear [28,29];
- nonlinear [30,31];
- comprehensive [3,5,32–34].

### 1.2. *Control of diabetes mellitus*

Regarding the applied control strategies for diabetes mellitus, the palette is very wide [35].

Starting from classical control strategies (PID control [26], cascade control [36]), to soft-computing techniques (fuzzy methods [37], neural networks [38]), adaptive [39], model predictive (MPC) [4,33], or even robust $H_\infty$ control have already been applied [3,4,40–42].

Most of the applied control methods focused on the Bergman minimal model [30] (as a result, the applicability of the designed controllers were limited due to excessive sensitivity of the model parameters). On the other hand, for the most complex glucose–insulin model, the Sorensen-model [34], only linear control methods were applied ($H_\infty$ [3,5], MPC [43]). An acceptable compromise between the model's complexity and the developed control algorithm could be the parametrically varying system description [44], identification [45], optimal control [46,47] and diagnosis [48].

The aim of the present article is to give a possible solution for nonlinear and optimal automated glucose control synthesis. Considering the high-complexity nonlinear Sorensen-model, a nonlinear model-based methodology, the LPV (Linear Parameter Varying) technique is used to develop a robust controller based on $H_\infty$ concepts, using induced $L_2$-norm minimization technique. The robust control was developed by input and output multiplicative uncertainties with two additional uncertainties to those used by [3]. The results are continuously compared with those obtained by [3], where a linear model-based robust control algorithm was used.

Simulation scenario on large meal absorption illustrates the applicability of the robust LPV control technique, while patient variability is tested with real data taken from the SPRINT clinical protocol on ICU patients. The latter case is used to demonstrate the robustness of the obtained controller as the design focused on diabetic patients not ICU ones. However, tight glycaemic control is also very important in ICU, for example hyperglycaemia associated with insulin resistance in ICU is common even for those patients who have not previously had diabetes [8].

### 1.3. *Glycaemic control in intensive care treatment*

The maintenance of the glucose level by the appropriate choice of the insulin inlet in case of a diabetic patient under intensive care is currently an active research field in Biomedical Engineering. [49] showed that tight glucose control can reduce ICU patient mortality by 45% if the glucose level is kept less than 6.1 mmol/L for a cardiac care population. It was shown that automated control algorithms capable of tight