Closed Loop Insulin Delivery System

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Abstract— This paper presents the design of a closed loop insulin delivery system for type 1 diabetic patients. The system consists of three basic components: on-line blood glucose transducer, embedded fuzzy controller, and piezoelectric insulin pump. The on-line blood glucose transducer samples the measurements at 15 minutes per sample. This transducer is subcutaneously inserted into the human body. It collects a blood sample from the dermis layer of the skin and sends the measured data to the embedded controller. The actuator is a piezoelectric insulin pump which is composed of a linear ultrasonic piezoelectric motor with a nanopositioning servo controller and insulin reservoir. The reservoir is a syringe with micro-needles head to avoid the pain and to increase the micro-fluid reliability. The embedded fuzzy controller stores and analyzes the on-line measurements. It takes the decision and calculates the required dosage of insulin to keep the blood glucose level in the safe range. Predictive fuzzy rules are developed based on the measurement of glucose in the blood and its average over the last five samples. The controller drives two independent insulin pumps. One pump is used for long acting insulin type as daily basal function and the other pump is used for rapid acting insulin to regulate continuously the glucose concentration in the blood.

I. INTRODUCTION

Diabetes is a metabolic disorder resulting from the permanent lack of insulin production from the pancreas (type 1 diabetes) or the chronic degradation of the functionality of endogenous insulin (type 2 diabetes), which results in raising the glucose concentration in blood because without insulin, the cellular system cannot properly convert carbohydrates such as sugars, starches, or other foods into energy usable by the body [1]. These factors eventually result in several complications, such as cardiovascular disease, chronic renal failure, retinal damage, nerve damage, and microvascular damage [1]. From a report of the World Health Organization (WHO), currently, around 180 million people suffer from diabetes all over the world, and it is thought that over 350 million people will suffer from diabetes by the year 2030. Besides, the number of people died from diabetes was approximately 1.1 million in 2005, and half of this number is aged less than 70 years old. It is also thought that 136 billion dollars are spent annually in the United States for 12 million diabetes patients [2].

In the human body, only insulin and glucagon play a role of regulating blood glucose levels within a very narrow range by bearing it from blood to the most cells, such as muscles and adipose tissues, turning it to energy [3]. Typically, either excess or shortage of glucose in blood is known as a metabolic disorder. The condition where the blood glucose is much lower than expected is called hypoglycemia causing drowsiness, mental malfunctioning, irritability, and loss of consciousness [3]. To the contrary, the condition where the blood glucose levels are much higher is called hyperglycemia, and long-term hyperglycemic conditions eventually result in diabetes [3].

Based on mathematical equations representing the insulin-glucose mechanism, therapies are systematically established. Broadly, controlling the blood glucose levels is achieved by means of three strategies, namely, open-loop, closed-loop, and partially closed-loop schemes. In general, the fully and partially closed-loop schemes involves several medical devices but the open-loop scheme does not. While in the closed-loop scheme, a system is aimed to completely encompass the diabetic, open- and partially closed-loop require the physician’s contribution to complete the loops. Therefore, typically any decisions of the insulin injections are made by a physician in open- and partially closed loop schemes [4].

The open-open system for the insulin-dependent diabetes therapy does not employ any glucose sensors. However, occasionally calling the “open-loop” system is not appropriate and more precisely, the system should be called the “programmed” insulin infusion system because of its incomplete openness. That is, the control loop can be closed by the physician and the diabetic when interacting on the system [5]. The idea is that from an analysis of the insulin curve in the non-diabetic, it was turned out that the curve approximately traces a combination of a double exponential curve and a basal insulin infusion. According to this mathematical model, an intravenous insulin delivery system was designed such that it followed the real pancreas functionality of the non-diabetic [5]. Typically, the closed-loop system for type 1 diabetes therapy utilizes the glucose sensor and schematically consists of three phases: blood glucose measurements, insulin demand calculation, and insulin injection. The closed-loop system repeats this sequence. So far, along with the glucose sensor, the closed-loop system also employs an insulin pump which continuously infuses insulin via a subcutaneous root [6]. In a partially closed-loop scheme of the insulin-dependent diabetes therapy, measurements are conducted three to seven times per day, and insulin injections are also performed three to four times under the supervision of a physician. These decisions, for example, the number and type of insulin injections, insulin dosage [6], are made according to model based or algorithmic-based decision support systems, such as DIAS, AIDA, and T-IDDM [6].

Manuscript received August 25, 2010. This work was supported in part by KSU – KETT- KACST, KSA under Grant (08-NAN388-2).

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The rest of the paper is organized as follows. In Section 2, we briefly summarize the basic information about type 1 and 2 diabetes. Section 3 presents the mathematical model of the insulin-glucose dynamics and the subcutaneous insulin absorption. In Section 4, the proposed closed loop insulin delivery system is described and the design of insulin pump is presented. Finally, we conclude this paper in Section 5.

II. TYPE 1 AND 2 DIABETES

Diabetes first emerged around 2000 B.C. while insulin and its functionality were discovered in 1921. Since the discovery of insulin, insulin-dependent diabetes therapies mostly concern how to delay the emergence of the complications in use of insulin supplement [7]. Diabetes is characterized in a condition that blood keeps high glucose levels unchanged into energy resulting in several complications. Although insulin is largely concerned with this reaction, diabetes fully or partially lacks this functionality [4]. Diabetes eventually causes cardiovascular disease, chronic renal failure, retinal damage, nerve damage, and micro vascular damage. Diabetes is typically classified into two types: type 1 and type 2 diabetes [4]. In type 1 diabetes, from the malfunction of the pancreas resulting from the destruction of the β cells, a supply of endogenous insulin completely stops. This requires other sources of insulin supplementation.

On the other hand, in type 2 diabetes, the insulin functionality gradually weakens, but does not completely stops. Since the diabetic more or less has the endogenous insulin supply, diabetes therapies mostly focus on exercises or regimens consuming or suppressing excessive glucose in blood. However, both type 1 diabetes and type 2 diabetes are considered chronic and currently incurable. Now, advanced technology in microcontrollers and sensors enable autonomous insulin dependent diabetes therapies systematically adjusting the insulin supply. More precisely, according to feedback from one or more blood glucose sensors, a rate of insulin supply of an insulin pump is determined, which works like an “artificial pancreas.” The advantages of an “artificial pancreas” are safe, automatic, and noninvasive. This paper aims to contribute in this direction towards an artificial pancreas.

III. DYNAMICAL MODEL

The complete model of diabetic patient consists of two parts:
- Insulin – glucose level
- Subcutaneous insulin absorption

A. Insulin – glucose level

Bergman model is widely used in the blood glucose-level control [8-9]. It offers a good benchmark for testing the relationship between insulin and glucose. The model can be depicted as follows:

\[
\dot{G}(t) = -(p_1 + X(t))G(t) + p_2G_0 + D(t)
\]
\[
\dot{X}(t) = -p_2X(t) + p_3[I(t) - I_0]
\]

Where \(G(t)\) is the concentration of glucose, \(I(t)\) is the concentration of insulin, \(X(t)\) is the dynamic insulin response, \(G_0\) is the basal level of glucose, and \(D(t)\) is the rate of exogenous glucose infusion; The Bergman model ignores the effects of glucagon. \(D(t)\) shows the meal glucose disturbance and can be modeled by decaying exponential function of the following form [10]:

\[
D(t) = A \exp(-Bt), \quad B > 0
\]

Where \(t\) is the time in min and \(D(t)\) is in (mg/dl/min). \(p_1, p_2, p_3, G_0,\) and \(I_0\) are the corresponding parameters.

B. Subcutaneous insulin absorption

An important component of the complete model is the description of how insulin is absorbed and enters plasma after a sc injection. Subcutaneous infusion is far superior to the intravenous delivery because it can be much easier and can be safely managed by patients themselves. This model is affected by many factors including the associated state of insulin, concentration, injected volume, injection site/depth and tissue blood flow. A single model describing in detail the various processes of subcutaneous absorption for all the commercially available insulin preparations is not available, but several models of sc insulin absorption have been proposed [11-12]. Insulin infusion via subcutaneous route can be modeled by the following equations:

\[
x_1(t) = -k_{21}x_1(t) + u(t)
\]
\[
x_2(t) = k_{21}x_1(t) - (k_d + k_e)x_2(t)
\]
\[
I(t) = \frac{k_e}{V_d} x_2(t) - k_d I(t)
\]

Where

- \(X_1\): Subcutaneous insulin mass where the injection takes place,
- \(X_2\): Subcutaneous insulin mass proximal to plasma,
- \(I\): Plasma insulin concentration,
- \(k_{d}\) & \(k_e\): Rates constants the degradation constants in the subcutaneous tissue and plasma respectively (min\(^{-1}\)),
- \(u(t)\): Rate of insulin administration (U min\(^{-1}\))
- \(k_{21}\) & \(k_d\): Rate constants describing insulin transport within the subcutaneous space and from the sc depot to plasma, respectively (min\(^{-1}\)),
- \(V_d\): Plasma distribution volume (ml kg\(^{-1}\)).

The above complete model of the set of equations (2) and (3) is a nonlinear dynamic model and its parameters have significant uncertainty from one patient to another and also it depends its activities. Consequently, linear control design is expected to give a limited performance to the diabetic system. In the literature, the fuzzy controller has proved its potential to control efficiently nonlinear systems with parametric uncertainty. Therefore, this type of controller design is adopted in the next section.

IV. CLOSER LOOP INSULIN DELIVERY SYSTEM

The proposed closed loop insulin delivery system is shown in figure 1.

Each rule has two antecedents: the current measurement and its rate of change from the historical data. The controller output actuates the insulin pump that delivers the required quantity to maintain the blood glucose level in a safe range. The different blood glucose levels are shown in figure 2.

In the above figure, three different regions are defined:
- Region (I), the normal level of blood glucose (BG) is in the range from 70mg/dl to 120mg/dl for health persons. In this case, the pancreas provides a basal rate of insulin ≈22mU/dl [18].
- Region (II), the abnormal level of BG if its value is greater than 120 mg/dl which is called hyperglycemia. In this case, the pancreas delivers more insulin to decrease the glucose concentration in the blood.
- Region (III), the abnormal level of BG if its value is less than 70 mg/dl which is called hypoglycemia. In this case; the pancreas delivers more glucagon to increase the glucose concentration in the blood.

The embedded fuzzy controller fuzzifies the current measurement and the average of last 5 samples. Therefore, the inputs to the decision making are defined as follows:
- BG: Current measurement of blood glucose concentration
- BGA: Average blood glucose concentration for the last 5 samples

The fuzzy rules are developed to provide the insulin I as follows (rapid action insulin type):
- IF BG is Eug THEN I is Bas
- IF BG is Hpo THEN I is Low
- IF BG is Hpr and BGA is Hpr THEN I is Big

A. Blood glucose transducer

This block presents on-line measurements using blood glucose transducer which samples the measurements of blood glucose at fixed sampling rate. This transducer is subcutaneously inserted into the human body. This includes collecting a blood sample from the dermis layer of the skin at depth of 0.1 mm. This layer of skin is rich in nerves and blood vessels. The transducer transmits directly the measured data to the embedded controller. The transfer function of this device can be approximated as first order system [1].

\[ G(s) = \frac{K_1}{1 + \tau_1 s} \]  \hspace{1cm} (4)

Where \( K_1 \) is the steady state gain
\( \tau_1 \) is the time constant

B. Fuzzy controller

The controller block receives the on line measurements at sampling rate of 1 sample/15 min. The controller stores the data and analyzes its history. The controller generates its output using If-Then fuzzy rules [13-17].

The different blood glucose levels are shown in figure 2.
IF BG is Hpr and BGA is Eug THEN I is Med
IF BG is Hpr and BGA is Hpo THEN I is Bas

Where:
Eug is the normal membership function
Hpo is shortest membership function of BG concentration
Hpr is the excess membership function of BG concentration
Bas is the basal membership function of insulin.
Low, Med, and Big other insulin membership functions as shown in figure 3.

The universe of discourse for BG and BGA is 300 mg/dl.
The universe of discourse for insulin is selected to 100 mU/dl.
Similar fuzzy rules can be developed for the long action insulin type based on the on-line historical measurements. It is proposed to use embedded controller as ASIC (FPGA chip) to implement a wearable device. This type of controller consumes less energy and can perform the required analysis to control the insulin pump.

C. Insulin pump

The insulin pump consists of three parts: linear actuator (ultrasonic piezoelectric motor), insulin reservoir (syringe), and micro-needles to be inserted in the skin of the patient body. The linear actuator as piezoelectric motor is the candidate one to actuate the pump for the following reasons:
- Compact size and miniaturization more than stepper and dc motors
- High power for actuation
- Precise position control
- Low operating voltage

The insulin pump delivers about 1 ml/day where for most patients 3 ml of insulin lasts three days [19]. Where 1 ml is equivalent to 100 units of insulin ($\approx 1 \text{ cm}^3$). The insulin dosage will be divided into two types:
a) Main dosage to be given at 15 minutes before the main three meals (8 am, 2 pm, and 8 pm). Each dosage is 0.1 ml of insulin (e.g. Actrapid or Lispro). This insulin type has the average action after subcutaneous injection: start of action within 30 min, maximum action between 1-3 hours, and duration of action until 8 hours. Supplementary dosage to be given regularly each 15 minutes (sampling time). The controller determines this value according to the feedback measurements. Its maximum value is 0.01ml/dosage.

b) Basal treatment using very long acting insulin (e.g. Lantus or NPH). This insulin type is very important for providing a background basal level. The dosage is $\approx 0.22$ ml/day at evening. This type after subcutaneous injection is acting for 24 hours.

Two similar insulin pumps can be used. The former is used for the long acting insulin (basal function) and later is used for the rapid acting insulin. Each pump consists of:
- Micro-needles
- Syringe

- Piezoelectric linear motor
- Nanopositioning servo controller

The proposed design of insulin pump is shown in the following figure.

The insulin is filled in a standard syringe of 3 ml capacity with 10 mm diameter. Therefore, the travelling range of the piezoelectric motor has to be selected as 30 mm. The type of linear motor has to be accurate in its positioning; so a closed loop control is required to compensate the injection back pressure. In this case, the embedded controller in the insulin delivery system calculates the required new position/dosage and sends this value as set point to the local closed loop nanopositioning servo control. The nanopositioning control loop acts to deliver the required dosage for each insulin type. The use of micro-needles increases the system reliability and decreases the feeling of pain. The candidate motor is the SQUIGGLE motor developed by new scale technologies [19].

The linear SQUIGGLE motor uses the hula hoop vibrations. In the SQUIGGLE motor, four PZT plates are bonded to flat surfaces on the outside of the metal tube at 90 degree spacing. The poling directions are aligned such that a common drive voltage on opposite pairs of plates produces opposing strain. The hula hoop vibration mode is created by generating PZT strain in orthogonal plate pairs at the resonant frequency with 90 degree phase shift. This motor offers several advantages over DC motors and stepper motors which are used in classical biomedical pumps. These advantages are:
- Small size and less power consumption
- Not affected by electromagnetic fields
- No gear reduction is required for speed control
- High generating force due to the use of piezoelectric material
- Highly precise in positioning control
The motor with local nanopositioning feedback control can be considered as piezoelectric servo motor. The following figure presents the proposed embedded control for the closed loop insulin delivery system which is so called “Artificial Pancreas”.

![Artificial Pancreas Diagram](image)

Fig. 6. Artificial pancreas

The recent micro/nano technology permits to develop the hardware components to implement the artificial pancreas and it is expected within the coming years to explore the commercial products for this application.

V. CONCLUSION AND FUTURE WORK

This paper presents a closed loop insulin delivery system for diabetic patients. The patient dynamic model is composed of two main parts: insulin subcutaneous injection and insulin-glucose concentration in the blood. The complete model is nonlinear with parametric uncertainty. Therefore, a classical linear control theory provides a limited performance for this class of problems. Fuzzy control is the candidate to be used where it has proved its performance in the literature to control nonlinear systems and parametric uncertainty.

The proposed closed loop system consists of on-line glucose transducer, embedded controller (FPGA), and insulin pump. The insulin pump uses ultrasonic piezoelectric linear actuator instead of the commercially used DC motors or stepper motors. This gives more advantages where no friction, no noise, compact size, less power consumption, highly precise positioning control and high force to drive the insulin syringe. Two similar pumps are used; one for basal function and the other for continuous treatment at sampling rate 15 min. The syringe is equipped by micro-needles head for subcutaneous injection to decrease the feeling of pain and to increase the reliability of injection process. In the future, the proposed system will be more investigated via simulation work and the insulin pump will be implemented. The investigation of fuzzy rules for better treatment and the sensitivity to the design parameters will be investigated.

ACKNOWLEDGMENT

The authors would like to thank King Saud University (KETT) and KACST, Kingdom of Saudi Arabia for the financial support provided for the research project (08-NAN388-2).

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