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Efficient Method for Insulin Control Pumping in Type 1 Diabetes

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Abstract: The main objective of this study is to inject insulin for type 1 diabetes patient by pumping the insulin. The blood glucose level has to be monitored with the help of glucose tolerance test. For efficient method to control type 1 diabetes, we will use embedded linear parameter varying methodology controller. In this study, there are three steps, researchers need to focus. First is the sensor values read from the sensors has to be monitored, second is the lab information (patient's basic level of tests). Third the feedback after the compensation of the first and second steps. Depending on the patients test details the insulin has to be injected. For example, if the person sensor value is greater than the reference limit then he has to be provided with insulin for a longer period. So, the comparison of lab details with the patients current sensor values play a vital role in determining the insulin level for a patient. Finally, the feedback has to be obtained with the help of those comparisons and it has to be sent once again as a loop to the controller for later comparison and also for database information. Here, the controller is the key element for updating all the information about the patient and it will control all the parameters of the board. Here, researcherss are using EEPROM to save all the data on location basis. It is capable of holding 256 bytes at a time and each location can store one byte information at a time.

Key words: Blood glucose, insulin, glucose tolerance test, pre-diabetes, controller section, pumping method

INTRODUCTION

Diabetes is the most common disease in India. The Indian population, nearly 60% of them are suffering with this disease. Insulin is an enzyme, secreated by the pancreas. The pancreas releases insulin into the blood. If the body does not make insulin or if the insulin does not work the way it should, glucose stays in the blood instead and blood glucose level gets too high, carrying pre-diabetes or diabetes. Diabetes mellitus is a group of metabolic diseases characterized by high blood sugar levels that result from defects in insulin secretion or action or both. Elevated levels of blood glucose lead to spillage of glucose into the urine. Normally, blood glucose levels are tightly controlled by insulin. When the blood glucose elevates, insulin is released from the pancreas to normalize the glucose level. Diabetes is a chronic medical condition, meaning that although it can be controlled, it lasts a lifetime. Over time, diabetes can lead to blindness, kidney failure and nerve damage. These types of damage are the result of damage to small vessels, referred to as micro vascular disease. Diabetes is also an important factor in accelerating the hardening and narrowing of the arteries leading to strokes, disease and other large blood vessel diseases. This is referred to as macro vascular disease. In this research, the condition we are going to consider is type 1 (juvenile) which is usually diagnosed in children, teenagers and young adults. Here, the beta cells of the pancreas no longer make insulin because the body's immune system has destroyed them. Treatment for type 1 diabetes includes taking insulin and possibly another injectable medicine, making wise food choices, being physically active, taking aspirin daily for some and controlling blood pressure and cholesterol.

From a biological perspective

Regulation in a healthy system: In order for us to model any biological system, researchers need to first understand exactly what is happening within a human body. Researchers need to ask what causes this effect and why. The key organs that control blood glucose are the pancreas and the liver. The key hormones are insulin and glucagon. In the pancreas, there are clusters of endocrine cells scattered throughout the tissue. The α-cells produce glucagon and the β-cells produce insulin. The pancreas secretes these antagonistic hormones into

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the extracellular fluid which then enters the circulatory system and regulates the concentration of glucose in the blood. For biologists, this is known as a simple endocrine pathway.

From a mathematical perspective

Regulation in a healthy system: Researchers worked with the Cobelli and Mari (1983) Model because it is of intermediate complexity and as such this model is sophisticated enough to improve its utility in diagnosis yet simple enough to pass validation tests. This model incorporates many of the important mechanisms but it is fit to a particular patient. The model is implemented in MATLAB, Version 7.0.1 and is designed with a windows interface that allows the user to easily simulate a 24 h daily life of a normal, type 2 or 1 diabetic subject. A Simulink Version is also available. Three meals a day are considered. Both open and closed-loop controls are available for simulating a type 1 diabetic subject (Del Favero *et al*., 2011). A simulation model of the glucose-insulin system in normal life conditions can be very useful in diabetes research, e.g., testing insulin infusion algorithms and decision support systems and assessing glucose sensor performance and patient and student training (Man *et al*., 2007). In 2008 to 2009, it was completed a first multi-national study aimed to compare nocturnal glycaemic control achieved with traditional therapy (open-loop) with a closed-loop therapy relaying on a Model Predictive Controller. Twenty T1DM patients were recruited. Insulin was infused with an OmniPod Rpump (Insulet Corporation, Bedford, MA), installed on the admission day. Changes in the injected insulin where performed when prescribed by the open loop therapy or once every 15 min during the closed loop experiment (Del Favero *et al*., 2011).

Minimal models must be parsimonious and describe the key components of system functionality. Thus, a sound modeling methodology must be used to select a valid model, i.e., a well founded and useful model which fulfills the purpose for which it was formulated (Cobelli and Ruggeri, 1983). In addition because it is not possible to estimate the values of all system parameters from *in vivo* dynamic data, many of the unit processes must be lumped together. Therefore, desirable features of a minimal model include: physiologically based; parameters that can be estimated with reasonable precision from a single dynamic response of the system; parameters that vary within physiologically plausible ranges and ability to describe the dynamics of the system with the smallest number of identifiable parameters (Vicini *et al*., 1997).

A clinical model of glucose-insulin interaction in insulin-dependent diabetes mellitus has been developed for patient and medical staff education. While the AIDA Software can simulate a wide variety of insulin dosage and diet (nutrition) adjustments, it should be stressed that the purpose of AIDA is to create a learning environment for communicating and training intuitive thinking when dealing with such adjustments. In this respect, AIDA appears most of use for recreating clinical situations in diabetes care rather than trying to predict best outcome (Lehmann and Deutsch, 1992). The 30 years ago, the possibility for external closed-loop control of Blood Glucose (BG) levels in people with diabetes has been established with an instrument commercially known as the Biostator which used intravenous (i.v.) BG sampling and i.v. insulin and glucose delivery (Vicini *et al*., 1999).

However, the closed-loop control is cumbersome and unsuited for outpatient use. Thus, increasing academic, industrial and political effort has been focused on the development of minimally-invasive closed loop using subcutaneous (s.c.) systems using Continuous Glucose Monitoring (CGM) and s.c. insulin delivery. Several s.c.-s.c. systems, generally using CGM coupled with insulin infusion pump and a control algorithm have been tested (Cobelli and Mari, 1983; Salzsieder *et al*., 1985; Sorensen, 1985; Andreassen *et al*., 1994). A recent United States Senate hearing emphasized the artificial pancreas initiative. In September 2006, the Juvenile Diabetes Research Foundation (JDRF) initiated the Artificial Pancreas Project and funded six centers worldwide to carry closed-loop glucose control research. These centers include the universities of Cambridge (England), Colorado, Santa Barbara, Stanford, Virginia and Yale. So, far, preliminary results have been reported from three closed-loop control studies conducted at Medtronic, Cambridge and Yale using equipment provided by Medtronic MiniMed Inc. (Hovorka *et al*., 2004). A nonlinear model predictive controller has been developed to maintain normoglycemia in subjects with type 1 diabetes during fasting conditions such as during overnight fast. Glucose-insulin feedback loop: the two subsystems are then modeled separately: for the insulin secretion model, glucose is the (known) input and insulin the output while for the model of insulin action on glucose production and utilization, insulin is the (known) input and glucose the output (Basu *et al*., 2003, 2006).

Hepatic extraction: When inferred from plasma insulin concentrations, insulin secretion cannot be isolated from hepatic, insulin extraction since plasma data reflect the fraction of pancreatic secretion which appears in

plasma, denoted as post hepatic insulin secretion and approximately equal to 50% of pancreatic secretion. Plasma C-peptide concentration thus reflects C-peptide plasma rate of appearance which apart from the rapid liver dynamics is a good measure of C-peptide pancreatic secretion which in turn coincides with insulin pancreatic secretion.

Whole body kinetics: To be identified on plasma C-peptide measurements, the secretion model must be integrated into a model of whole body C-peptide kinetics. The widely used model compartment 1, accessible to measure, represents plasma and rapidly equilibrating tissues, compartment 2 represents tissues in slow exchange with plasma. Model equations are conveniently expressed in terms of C-peptide concentration earlier basal in the two compartments, denoted as CP_1 and CP_2 (pmol/L).

Advancements in subcutaneous continuous glucose monitoring and subcutaneous insulin delivery are stimulating the development of a minimally invasive artificial pancreas that facilitates optimal glycemic regulation in diabetes. The key component of such a system is the blood glucose controller for which different design strategies have been investigated in the literature. It has been shown that CVGA has multiple uses: comparison of different patients over a given time period, of the same patient over different time periods, of different control laws and of different tuning of the same controller on the same population (Taylor *et al*., 1996; Man *et al*., 2006; Pillonetto *et al*., 2001).

Hypotheses

Steps for implementation:

- Step 1: person entry through Infra Red sensor
- Step 2: lab test based on sensors and displays in liquid crystal display
- Step 3: lab test report details saved in electrically erasable programmable read only memory
- Step 4: monitoring glucose, temperature, pressure sensor values and also displays in LCD
- Step 5: write the corresponding values in respective addresses in EEPROM
- Step 6: compare the test report with current values with the help of stored information's
- Step 7: provide suitable level of insulin to the patient and send a feedback to the controller
- Step 8: repeat the process of reading the sensor values and control through controller section

MATERIALS AND METHODS

Embedded model system: Embedded model system is shown in Fig. 1. Glucose level sensor, pressure sensor, temperature sensor are the sensors used in this study. The sensors will be of analog format so, researchers will use analog to digital converter to convert analog to digital values. Whenever, the patient enters the lab they need to be monitored and provided with exact solution with the help of database.

Whenever, the patient glucose level goes beyond the normal level, automatically insulin will be injected with the help of controller section. In this study, researchers will first look for the entry of the person. If the person enters the hospital then the lab test has to be conducted for them. Researchers will conduct only one test based on glucose level. This we need to call as lab report. Next we will check the glucose, temperature, pressure of the person and maintain a database with all the details based on time. Next from the details, we will compare the test result with the original values. In this there are three conditions to be compared and monitored. The first one is normal level of glucose and the next is below level of glucose and the final one is higher level of glucose. From this comparison, researchers will come to know how much of insulin we need to inject to the person and this will be send as a feedback to the controller again for maintaining the glucose level in the blood the data's shown in Table 1. The process will be repeated for a certain period of time to maintain a database because whenever we need we will check the database with the help of time calculations and it will be easy for maintaining a patient detail in a database manner.

The entry of the person is based on sensors and whenever the person enters then lab test has to be conducted for the patient and the details will be stored in EEPROM and as well as display's in LCD. Then, with the help of sensors researchers will measure the information's and should displays in LCD. At the same time the measured values will be saved in EEPROM for comparison and as well as for getting the details of the patient at any time. Compare the stored information's of the sensors and lab test value with the help of EEPROM. With the comparison, researchers will provide suitable level of insulin to the patient. Repeat the process with the help of controller.

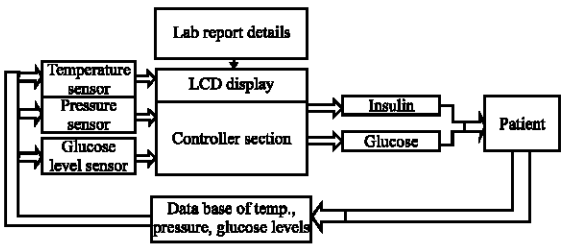

Fig. 1: Embedded model system

Table 1: Blood glucose levels

BGL 70-89 mg dL^{-1}	BGL 90-119 mg dL^{-1}	BGL 120-179 mg dL^{-1}	BGL≥180 mg dL^{-1}	Altering in infusion rate
-	-	BGL↑ by >40 mg/dL/h	BGL↑	↑Infusion by 2Δ
-	BGL↑ by >20 mg/dL/h	BGL↑ by 1-40 mg/dL/h	BGL↓ by 1-40 mg/dL/h	↑Infusion by Δ
BGL↑	BGL↑ by 1-20 mg/dL/h	BGL↓ by 1-40 mg/dL/h	BGL↓ by 41-80 mg/dL/h	No infusion change
BGL↓ by 1-20 mg/dL/h	BGL↓ by 21-40 mg/dL/h	BGL↓ by 41-80 mg/dL/h	BGL↓ by 81-120 mg/dL/h	↓Infusion by Δ
BGL↓ by >20 mg/dL/h	BGL↓ by >40 mg/dL/h	BGL↓ by >80 mg/dL/h	BGL↓ by >120 mg/dL/h	↓Infusion by 2Δ

Algorithm: Plasma glucose (upper) and insulin (lower) concentrations measured during IVGTT (right), OGTT (middle) and MTT (left, panel):

$$\begin{cases} \dot{G}(t) = -a_1 G(t) - a_2 I(t) - J(t) \\ \dot{I}(t) = a_3 G(t) - a_4 I(t) \end{cases} \quad (1)$$

The chosen minimal model, assumes that glucose kinetics can be described with one compartment (the early portion of glucose data is not considered) and that remote (with respect to plasma) insulin controls both net hepatic glucose balance and peripheral glucose disposal:

$$\begin{cases} \dot{Q}(t) = NHGB(Q(t), I'(t)) - R_d\left(Q(t), I'(t)\right) + D \times \delta(t) & Q(0) = Q_b \\ \dot{I}(t) = -k_3 \times I'(t) + k_2 \times \left[I(t) - I_b\right] & I'(0) = 0 \\ G(t) = \dfrac{Q(t)}{v} \end{cases} \quad (2)$$

NHGB is the net hepatic glucose balance which depends upon plasma glucose and remote insulin I':

$$NHGB\left(Q(t), I'(t)\right) = NHGB_0 - \left[k_5 + k_6 \times I'(t) \times Q(t)\right] \quad (3)$$

and R_d the rate of glucose disappearance form the peripheral tissues also function of plasma glucose and remote insulin, I':

$$R_d\left(Q(t), I'(t)\right) = R_{d0} - \left[k_1 + k_4 \times I'(t)\right] \times Q(t) \quad (4)$$

This non-linear model requires a reparameterization in order to become a priori uniquely identifiable:

$$\begin{cases} \dot{Q}(t) = -\left[p_1 + X(t)\right] \times Q(t) + p_1 \times Q_b + D \times \delta(t) & Q(0) = Q_b \\ \dot{I}(t) = -p_2 \times X(t) + p_3 \times \left[I(t) - I_b\right] & X(0) = 0 \\ G(t) = \dfrac{Q(t)}{v} \end{cases} \quad (5)$$

Where:

$X(t) = (k_4 + k_6) \times I'(t)$

$p_1 = k_1 + k_5$

$p_2 = k_3$

$p_3 = k_2 \times (k_4 + k_6)$

$p_4 = NHGB_0 - R_{d0} = p_1 \times Q_b$

X = Insulin action

p_1 = The fractional (i.e., per unit distribution volume) glucose effectiveness measuring glucose ability per se to promote glucose disposal and inhibit glucose production

p_2 = The rate constant of the remote insulin compartment from which insulin action is emanated

p_3 = A scale factor governing the amplitude of insulin action

The model allows the estimation of insulin sensitivity as:

$$S_I^{IVGIT} = \frac{p_s}{p_2} \times V \quad (dL/kg/min \text{ per } \mu U/mL) \qquad (6)$$

RESULTS AND DISCUSSION

The model also allows us to predict the effect of the various control signals on glucose production as well as the insulin independent and dependent components of glucose utilization in addition; hepatic insulin extraction can also be predicted. The model consists of a glucose and insulin subsystem. The glucose system is described by a two-compartment model, the first representing glucose mass in plasma and rapidly equilibrating tissues and the second the slowly equilibrating tissues.

Glucose utilization has both an insulin-independent component occurring in plasma and an insulin-dependent component in the second compartment. The insulin-independent utilization is constant and represents glucose uptake by CNS and erythrocytes while the insulin-dependent utilization is controlled non-linearly by glucose in the tissue compartment and insulin in the interstitial fluid. Endogenous glucose production control by glucose and insulin implements recent knowledge, in particular it assumes that fast suppression occurs through a portal insulin signal while slower inhibition by a delayed insulin signal, possibly a surrogate of interstitial fluid/free fatty acids signaling. A new model of glucose transit through the gastro-intestinal tract is used to describe glucose ingestion and absorption. This feature is important because previous simulation models either allowed only intravenous glucose administration.

PIC simulator IDE is used as a simulator for this study. Modules used in this simulation are LCD, microcontroller view and EEPROM for seeing the desired sensor values and outputs.

In this the LCD is mainly used to display the contents and microcontroller view is used for setting the sensor values manually because it is only a simulation view and EEPROM is used to display the sensor values on each address and as well as output's on each slot.

The insulin system is described by a two-compartment model. Degradation is assumed to occur linearly in the periphery while liver degradation is assumed to be time-varying in agreement with current knowledge. Insulin secretion is assumed to be dependent on both plasma glucose concentration and its rate of change As with all models, there are some limitations.

The most important is that count regulatory hormones such as glucagon, epinephrine and growth hormone have not been considered. This will be considered in future model developments. This will be also important for extending the model to type 1 diabetes. Another limitation concerns the glossocentric nature of the model, i.e., the role of other fuel substrates like free fatty acids and their interaction with glucose and insulin is not considered. Finally, when modeling daily life, it would be important to include diurnal variation of parameters A new in silico model of the glucose-insulin regulatory system has been presented. Focusing on quantitating physiological events after a meal is of obvious importance because this route is used in everyday life. The postprandial state has also been intensively investigated in recent years, thus one can take advantage of all new quantitative knowledge that has become available. The model is made by a number of parsimonious sub models describing the various unit processes that have been identified using a forcing function strategy. This falls into 3 basic components of the insulin regimen:

- A correction dose based on the difference between actual BG level and a target BG level, divided by a correction factor of insulin sensitivity (in BG counts per unit of insulin or more correctly mg/dL/unit)
- A meal bolus or a single large dose of insulin to cover a meal about to be eaten based on a count of carbohydrate grams of the food multiplied by the Insulin to carb ratio (I/c) in units per gram
- Basal insulin or slow release (background) insulin that a person needs all the time. New insulin analogs such as Lantus and Levimur last for 12-24 h and give a low slow dose of background insulin

An equation often taught to diabetic children to calculate their insulin requirement before a meal is:

$$\text{Pre-meal insulin injection (in units)} = \text{Correction dose} + \text{Meal bolus}$$

Where:

$$\text{The correction dose} = \frac{\text{Actual BG level} - \text{Target BG level}}{\text{Insulin sensitivity factor in BG counts per unit}}$$

And:

$$\text{The meal bolus} = \frac{\text{Grams of carbs in food about to be eaten}}{\text{Insulin to carb ratio for that meal}}$$

Here, are the key variables in the algorithm and their definitions:

- Target value: the desired intermediate value (often 110 mg dL^{-1}) used to calculate a precise correction bolus (as opposed to the upper and lower values of a target range)
- Insulin sensitivity factor: the ratio of the expected impact of insulin on the blood sugar given in mg/dL per unit of insulin. Example, one persons sensitivity might be a drop in 60 mg dL^{-1} of blood sugar per unit of insulin given
- Insulin to carb ratio: the ratio of grams of glucose covered by one unit of insulin usually given as grams per unit. The ratio is specific to one meal for that one diabetic person (breakfast = 15 g u^{-1}, lunch = 19 g u^{-1}, etc.)
- Basal rate: the rate of continuous insulin delivery for basal needs equivalent to the total daily basal insulin such as from Lantus or Levimur

Enter the insulin pump compared to the long acting insulins, the continuous infusion of fast-acting insulin for basal needs offers these benefits:

- Accurate low rate delivery making CSII possible
- Elimination of the peaks and valleys of those insulin profiles
- The dynamic ability to dial back the basal insulin to react to an impending low blood sugar or to avoid hypoglycemia due to exercise or spontaneous activities
- Control and memory of the basal profile, to actually fit the basal profile to the specific needs of individuals

The same features that make for a good fit of basal insulin also benefit the pump user for all insulin needs:

- Accurate small boluses as needed for more precise carb counting
- Precise correction doses, allowing partial units (0.05-0.1 units) and lower BG targets instead of the upper level of a target range
- Achieving tighter blood glucose control which ultimately realizes a lower HbA1c

Therefore, the algorithm for interfacing with the insulin pump is the same as with intensive insulin therapy but utilizes a basal rate of fact-acting insulin. The key parameters as shown in the "data store" boxes in the diagram above are all needed to control the insulin pump and can be "learned" by the insulin pump with the use of adaptive variables.

CONCLUSION

They proposed a physiologically based model of the glucose-insulin system. The modeling strategy is novel and has taken advantage of a unique meal data set both in normal and type 1 diabetes in which not only plasma concentrations but also relevant glucose and insulin fluxes during a meal were available. The model should prove valuable as simulator in several situations dealing with the pathophysiology of diabetes. The availability of a simulation model of the glucose-insulin control system during meals and normal daily life is highly desirable for studying the pathophysiology of diabetes and in particular for the design and evaluation of glucose sensors, insulin infusion algorithms and decision support systems for treating diabetes, in particular type 1 (insulin dependent). In fact, it may be possible, appropriate, convenient or desirable to perform such evaluation experiments on the diabetic subject because some experiments cannot be done at all or are too difficult, too dangerous or not ethical. In the "insulin shock" experiments, researchers simulated hypoglycemia by injecting an overabundance of insulin into the blood. However, the experiments only simulated a temporary hypoglycemia in an otherwise normal system for a healthy or diabetic individua,l i.e., normal concentration levels, rates and parameters for their particular system. Contrary to "insulin shock", hyperinsulinism is a chronic disorder which resultsin an overproduction of insulin which drives down the plasma glucose concentrations (chronic hypoglycemia).

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