Blood Glucose Regulation in Diabetic Patients by Newly designed Smart Controllers

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Abstract:
This paper attempted to propose a SDRE controller with regulation of adapting weighting coefficients for blood glucose concentration control in patients with type 1 diabetes. The weighting coefficients found in the cost function of SDRE controller were adjusted through a neuro-fuzzy network. In other words, the term "smart" in the title refers to neuro-fuzzy networks.
In this paper, a successful practical model was selected and smart and stable techniques were integrated to desirably control glucose levels. To this end, a neuro-fuzzy network was adopted to identify and control the nonlinear system behavior, while comparing LQR and SDRE controllers. At the next stage, a new diabetes controller was designed based on assigning adaptive weights to the SDRE controller. Finally, the newly proposed method was simulated on the diabetes model to demonstrate its great capability in blood glucose concentration control.

Keywords:
Glucose concentration control, SDRE controller, Adaptive Fuzzy Neural Identification

1. Introduction

The human body needs energy for daily activities. The most important source of energy is glucose, which is absorbed daily by nutrition. As the cells are fed, the essential energy will be supplied for physical and mental activity.

The glucose concentrations in the body should be maintained at a certain level. The pancreas secretes insulin and glucagon hormones to regulate blood glucose, because the two factors are complementary. Insulin is released to reduce glucose when plasma glucose concentration is high, while glucagon is released to boost it when the concentrations are too low. Diabetes mellitus is one of the most common endocrine disorders in the human body caused by damage to β cells (Beta) in the pancreas. In this condition, insulin will not secrete sufficiently to regulate blood glucose. In the presence of high glucose, the glucagon stop function will be hindered, pushing the patient's blood glucose to levels greater than normal range, i.e. 70-110 mg/dl equivalent to 4-4 mmol/L. Type 1 diabetes, also known as insulin-dependent diabetes, is caused by destruction of the immune system of β cells. This disease can be associated completely with insulin deficiency.

The followings are important for drug delivery modeling:

1. Limited access time

2. Robustness to uncertainties

The human body is extremely sensitive to variations in glucose concentration. One slight change for a long period can cause brain and heart damage. Therefore, the timing in glucose regulation is vital.

It should be noted that a small change in some parameters can affect the closed-loop performance and even lead to the patient's death. Resistance is one of the remarkable features in practical implementation of the newly designed controller.

The most important goal in treatment of diabetes is to maintain normal blood glucose levels.

Several mathematical models have so far been proposed for diabetes based on insulin and glucose interactions. There are a number of commonly used models for diabetes, falling under the ODE[1] DDE[2] category, including negative feedback model ODE DDE (Tolic and Sturis, 2000) DDE Engelborghs models in 2001 (Gourley and Bennett, 2004) (Mason and Kuang, Li, 2006) models based on diagnostic tests3) Bergman Minimal Model, Palumbo, Panunzi, De Gaetano (2007) [1].

The primary models presented for diabetes could not model the delay from rising blood glucose level until insulin secretion.

1: Ordinary Differential Equation

2: Delay Differential Equation

3: Diagnostic tests

The basic model provided by Palumbo et al. (2010) has been discussed as an applied model in the control of diabetes, such as in [4 and 14].

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Concerning the closed-loop control of diabetes, several techniques have been developed for diabetes mellitus such as linear and nonlinear predictive control methods, nonlinear sliding mode, robust controllers H_∞, classic controllers designed based on linearized equations around stable equilibrium point, nonlinear state feedback, and linear and nonlinear observers design for nonlinear models in References [2-3]. Based on SDRET Adaptive Weighting, this paper intended to propose a solution for optimal control of non-linear delay systems relying on the idea of quasi-linearization. By examining the stability of the newly proposed method based on the new controller, the optimal glucose level in the patient and optimal rate of insulin injection for type 1 diabetics were obtained. Then, the results of the proposed method were compared against the nonlinear control method based on the Palumbo feedback linearization. The most important advantage of the new method lies in its efficiency in controlling a set of delayed non-linear systems in the state variable and generalizability in solving many other problems.

2. State-dependent Riccati controller

This section describes SDRE1 and LQR² algorithms, exploring their similarities and differences. The two control methods serve to find the u* control inputs, which are applied to the system under control (1) to maintain the system, satisfy the preset constraints, minimize the defined cost function (Equation 2) and converge the system state variables toward zero at minimal control effort. [16]

$$\dot{x}(t) = Ax(t) + Bu(t) \tag{1}$$

$$J(x,u,t)=\frac{1}{2}x^T(t_f)Hx(t_f)+ \int_{t_0}^{t_f}\left\{\frac{1}{2}x^T(t)Q\,x(t)+\frac{1}{2}u^T(t)Ru(t)\right\}dt \tag{2}$$

In Q(2), H is the symmetric positive matrix, and R is the positive definite matrix.

In the LQR method, B(x) and A(x) are assumed to be constant and are no longer a function of system state (x). In the SDRE method, however, these two matrices are a function of system state (x). Therefore, the linear LQR method and

1: State-dependent Riccati equation 2: Linear Quadratic Regulators

while SDRE method is nonlinear. In both methods, the general form of control input is calculated from (3):

$$u^*=-R^{-1}B^T(x)Kx \tag{3}$$

In (3), K is the Lagrange coefficients obtained by solving a Riccati equation. This Riccati equation is solved differently in SDRE and LQR. In LQR, the Riccati equation (4) is a first-order differential equation obtained by numerical methods from the final simulation time to initial time (having the final values of K):

$$K=-KA-A^TK-Q+KBR^{-1}B^TK \tag{4}$$

In SDRE, the left side of equation (4) is set to zero (Riccati algebra equation - equation 5), and the algebraic equation obtained by having the initial values of state variables is solved based on initial simulation until final time.

$$0=-KA-A^TK-Q+KBR^{-1}B^TK \tag{5}$$

The main advantages of method $SDRE$, some of which actually valid in method LQR, include:

- This method can be employed in the design of controller, observer and filter
- Offering more freedom to the designer due to lack of system's quasi-linear non-unique representation
- Possibility to easily build compromise between control signal and operation

3. Simulation of adaptive weighting SDRE and comparison against Palumbo

This section simulates the newly proposed controller to control the blood glucose level in patients with type 1 diabetes while determining the appropriate dosage for insulin infusion.

The diabetes model was presented in 2007 [6]. This model is based on experimental data on IV injection according to (6):

$$\frac{dG(t)}{dt} = -K_{xgi}I(t)G(t) + \frac{T_{gh}}{V_g}$$

$$\frac{dI(t)}{dt} = -K_{xi}I(t) + \frac{T_{igmax}}{V_i}f(G(t-\tau_g)) + u(t) \tag{6}$$

$$G(\tau) = G_0(\tau)\,, I(\tau) = I_0(\tau)\,, \tau \in [-\tau_g, 0]$$

where,

$$f(G) = \frac{\left(\frac{G}{G^*}\right)^\gamma}{1+\left(\frac{G}{G^*}\right)^\gamma}$$

$$T_{gh} = K_{xgi}I_bG_bV_g \tag{7}$$

$$T_{igmax} = K_{xi}I_bV_i\frac{1+\left(\frac{G_b}{G^*}\right)^\gamma}{\left(\frac{G_b}{G^*}\right)^\gamma}$$

where $G(t)$ is plasma glucose concentration in millimolol mM, $I(t)$ is plasma insulin concentration in picomol pM, and $u(t)$ is control signal and IV insulin injection rate in picomoles per minute pM/min.

$G_0(\tau), I_0(\tau)$ displays the initial values of plasma glucose and insulin, which are approximately assumed to be $G(0) = G_b$ and $I(0) = I_b$ based on the values of I_b و G_b. The other parameters are given in Table (1).

Patient under study had a body mass index of 50. The parameter Gb=6.14 indicated a higher than normal blood glucose level in the patient, and the insulin resistance index was Kxgi≤10-4. These factors indicate an under-normal insulin secretion rate for a newly diagnosed diabetic patient. Factors such as obesity, inactivity, genetics, etc. have led to a gradual decrease in the insulin secretion rate in the patient. The patient will have symptoms of type 2 diabetes, if not treated.

1: Body Mass Index (BMI)

After being affected by the disease, the patient did not go through any treatment for 1-2 years. Naturally, the patient's pancreatic insulin levels dropped sharply, while insulin resistance remained unchanged, leaving the patient with chronic hyperglycemia.

The glucose reference signal was considered to decrease exponentially from the initial blood glucose level (Gb=10.37 mM to a normal value of 5.12 mM as shown in (8)) (I=48.95)

Table 1: Actual parameters identified for the type 1 diabetic patient

Parameter	Value of parameter	Description
γ	3.205	A constant, positive parameter representing the responsiveness of pancreas to glucose circulation in plasma.
V_g	0.187	Glucose distribution rate
T_{igmax}	0.242	Maximum insulin secretion rate in the second phase
V_i	0.25	Insulin distribution rate in plasma
τ_g	24	Delay in insulin secretion from pancreas in exchange for an increase in blood glucose concentration
K_{xgi}	3.11×10^{-5}	*Reserved glucose rate depending on produced glucose*
T_{gh}	0.003	Hepatic glucose and received glucose index
G^*	9	Glucose concentration steady state value
K_{xi}	1.211×10^{-2}	Plasma insulin concentration decline index

The parameters in nonlinear model of diabetes for patients under study were obtained based on least squares fitting generalized on experimental data on insulin infusion testing as shown in [12].

$$G_{ref}(T)=5.12+(10.37-5.12)e^{-0.02T} \quad (8)$$

$$\dot{\tilde{y}}(t) = G_d - G(t) \quad (9)$$

Hence, it will be an additional quasi-linear representation according to (10).

$$\begin{bmatrix}\dot{G}(t)\\ \dot{I}(t)\\ \dot{\tilde{y}}(t)\end{bmatrix} = \begin{bmatrix}a_{11} & a_{12} & 0\\ a_{21} & a_{22} & 0\\ -1 & 0 & 0\end{bmatrix}\begin{bmatrix}G(t)\\ I(t)\\ \tilde{y}(t)\end{bmatrix} + \begin{bmatrix}0\\ 1\\ 0\end{bmatrix}u(t) \quad (10)$$

where,

$$a_{11} = -K_{xgi}I(t), a_{12} = \frac{T_{gh}}{V_g I(t)}, a_{21} = \frac{T_{igmax}}{V_i G(t)} f\left(G(t-\tau_g)\right), a_{22} = -K_{xi} \quad (11)$$

3.1 SDRE tracking system

In tracking, the relations governing the system will be as follows [17]:

$$\begin{cases}\dot{x}(t) = f(x(t)) + B(x(t))u(x(t),t)\\ x(0) = 0\\ y(t) = Hx(t)\end{cases} \quad (12)$$

These equations are in regulation mode, with the exception that equation y has been added, since the reference signal is tracked by the output as a few variables arise from the state space in the output. The cost function for the tracking problem is according to (13).

$$J = \frac{1}{2}\int_0^T [(y-r)^T(t)Q(y-r) + u^T(t)Ru(t)]dt \quad (13)$$

For the equations to be expressed in terms of $SDRE$, nonlinear function $f(x)$ is reformulated as $f(x) = A(x)x$. As a result, the Hamiltonian matrix will be as follows:

$$H(x,u,\lambda) = \frac{1}{2}(Hx-r)^T Q(Hx-r) + \frac{1}{2}u^T Ru + \lambda^T(A(x)x + Bu) \quad (14)$$

Sufficient conditions for optimal control according to the Hamiltonian matrix can be seen in (15).

$$\begin{cases} \dot{x}^*(t) = \frac{\partial H}{\partial p} = A(x^*)x^* + Bu^* \\ \dot{\lambda} = -\frac{\partial H}{\partial x} = -H^T Q(Hx^* - r) - A^T(x^*)\lambda - \sum_{i=1}^{m} x_i^* \left(\frac{\partial A_{1\to m,i}}{\partial x}(x^*)\right)^T \lambda \\ 0 = \frac{\partial H}{\partial u} = Ru^* + B^T\lambda \end{cases} \quad (15)$$

where $\frac{\partial A_{1\to m,i}}{\partial x}$ is a column derivative operator defined below.

$$\frac{\partial A_{1\to m,i}}{\partial x} = \begin{pmatrix} \partial A_{1i}/\partial x_1 & \cdots & \partial A_{1i}/\partial x_m \\ \vdots & \ddots & \vdots \\ \partial A_{mi}/\partial x_1 & \cdots & \partial A_{mi}/\partial x_m \end{pmatrix} \quad (16)$$

Finally, the control rule is $u^*(t) = -R^{-1}B^T\lambda^*(t)$. However, the question to be be answered now is how to calculate λ^*.

In tracking mode, the response family will be selected in the form of $\lambda = P\big(x^*(t)\big)x^* + s(t)$, where $s(t)$ has been added to the regulation mode. By adding a time-dependent parameter in the overall structure of the response, the tracking problem will be solved easier.

In the same procedure as stated in the regulation mode, (17) will be obtained to calculate P.

$$P(x^*)[A(x^*)x^* - BR^{-1}B^T(P(x^*)x^* + s)] + \dot{s} + D_t P(x^*)x^* = -H^T Q(Hx^* - r) - A^T(x^*)(P(x^*)x^* + s) - \sum_{i=1}^{m} x_i^* \left(\frac{\partial A_{1\to m,i}}{\partial x}(x^*)\right)^T (P(x^*)x^* + s) \quad (17)$$

In this equation, $D_t P(x^*)$ is the time derivative of matrix P defined according to equation $D_t P(x) = \sum_{k=1}^{m} x_k \left(\frac{\partial P(x)}{\partial x_k}\dot{x}_k\right)$.

In regulation mode, the problem is solved by considering small variations in P and A. Upon this assumption, Riccati equation (5) is obtained. In tracking mode, the cost paid for the above assumption involved a trend from optimality to sub-optimality.

In tracking mode, the noteworthy point is that s should also be calculated as follows. Hence, small variations assumed for P and A will be inapplicable. This leads to an increase in calculations of the tracking problem compared to the regulation problem.

$$\dot{s} + A^T(x)s - P(x)BR^{-1}B^T s - H^T Qr + \sum_{i=1}^{m} x_i \left(\frac{\partial A_{1\to m,i}}{\partial x}(x_i)\right)^T (P(x_i)x_i + s) + D_t P(x)x = 0 \quad (18)$$

4. Open-loop results

The behavior of all state variables can be observed in Figure (1), Figure (2) and Figure (3). In these figures, the horizontal axis represents a sampling time of 15 minutes. It can be observed that insulin and glucose concentrations (which should be between 4 and 6) exceed the normal range. Therefore, it is vital to use injectable insulin to reduce glucose. This section provides the results of using the new controller in regulation of glucose concentration through the proposed method.

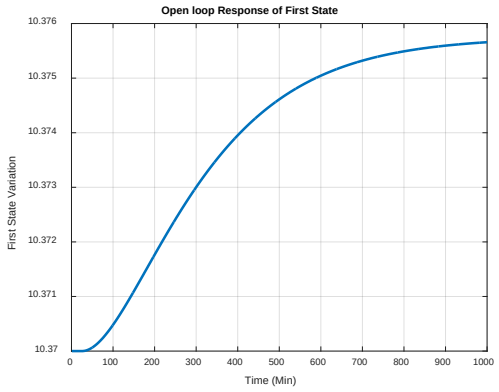

Fig. 1 Variations in the first state variable of diabetic patient (glucose concentration)

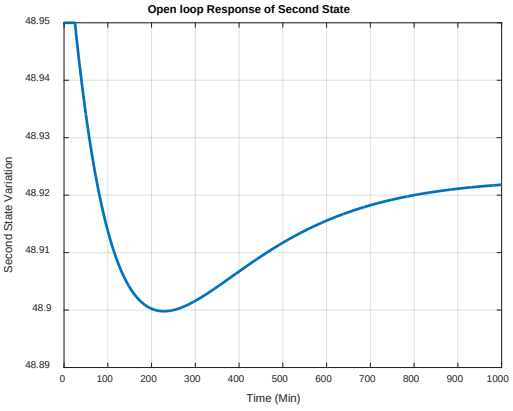

Fig. 2 Variations in the second state variable of diabetic patient (insulin concentration)

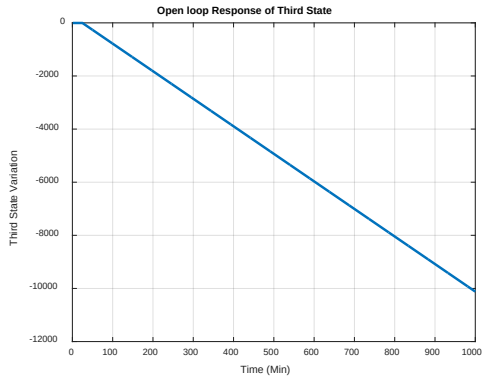

Fig. 3 Variations in the third state variable of diabetic patient (difference between blood glucose concentration and desired concentration)

5. SDRE controller with adaptive weighting

This section explores the results of glucose concentrations control in a diabetic patient using the new approach.

Figure (4) displays the overall closed-loop structure in the presence of adaptive weight regulator.

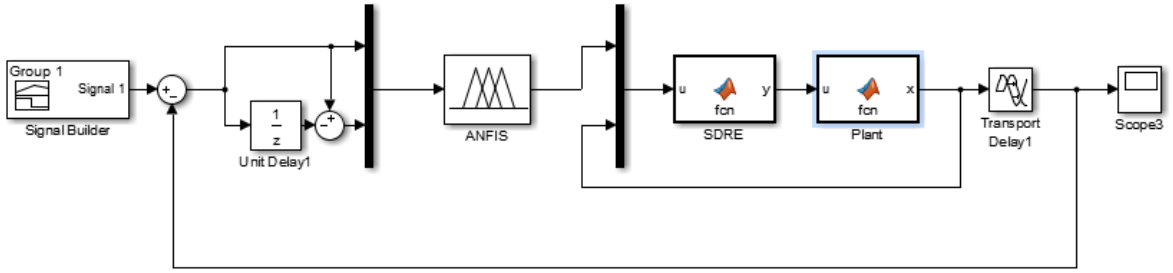

Fig. 4 The overall closed-loop structure of diabetes control in the presence of SDRE controller neuro-fuzzy network for adaptive weighting

In Figure (5), the red curve displays the optimal trend, while the blue curve displays the variations in current glucose in the patient's blood. In this graph, the initial conditions (about 10.3) were selected with a difference from natural conditions. As previously noted in Figure (2), the glucose levels will rise if insulin is not injected. By application of injectable insulin as a control input, however, glucose concentration reached a normal level as seen in the following figure.

This figure also indicates the response from controller LQR previously provided in paper (18), marked red in the graph. Evidently, the lower convergence rate in LQR is lower than that in the newly proposed method.

This can be associated with non-adaptive weighting and linearity of LQR method. Since there is no bias in the output response, the non-adaptability of LQR method plays a greater role in its weaker performance compared proposed method.

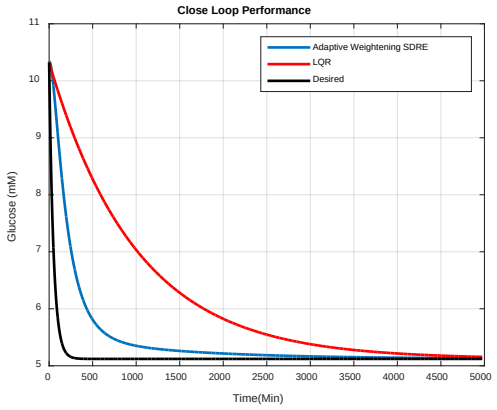

Fig. 5 Closed-loop response of controlled system (glucose variations), comparison of proposed method against LQR

The following figure shows the level of insulin injection functioning as control input.

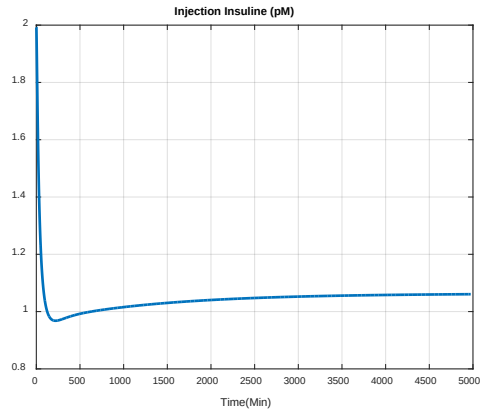

Fig. 6 Level of insulin injected through the proposed controller

In an effort to further explore the various aspects of the new method, it will be compared against the method presented in [19]. The main difference between the two methods lies in adaptive weighting through matrices R and Q involving a neuro-fuzzy network. If the system is in its nominal state, and the tracking path is set to a small range, there will be insignificant difference between the two methods. Glucose will only fall within the 4-6 milloles band slightly faster.

As shown in Figure (7), comparing the method proposed in this paper and that presented in [19], the former travels within the standard the 4-6 milloles band far faster than the latter.

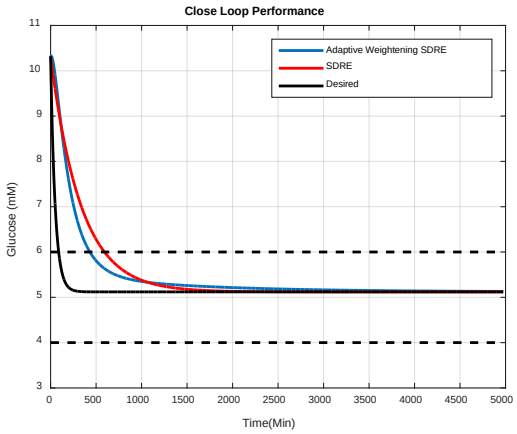

Fig. 7 Closed-loop response of controlled system (glucose variations), comparison of proposed method against SDRE

Nonetheless, the main advantage of the proposed method over that presented in [19] is the time when variations occur in the model parameters. In Figure (8), the result is reported by applying 10% variation in γ. Evidently, there is a significant difference between the method proposed in this paper and that in [19]. That is because in an adaptive weighting, the significance of variables can be regulated to prevent excessive weighting. It should be noted, if there is uncertainty in the system, overweighting of state variables will result in lower response quality and even instability.

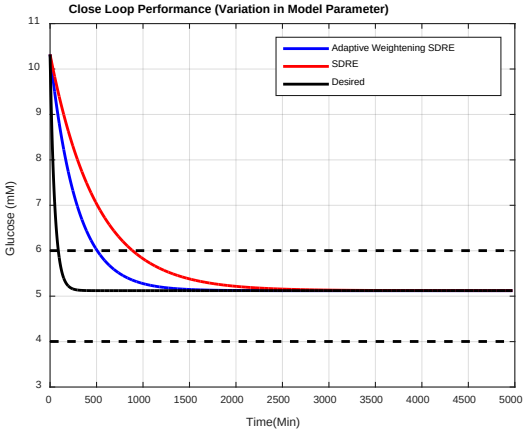

Fig. 8 Closed-loop response of controlled system (glucose variations in the patient), comparison of the proposed method against SDRE if there is 10% variation in $\boldsymbol{\gamma}$

6. Summary and conclusions

One of the most effective methods for controlling diabetes involves an optimal controller to help the patient's glucose achieve normal levels at an optimum insulin secretion rate. In this paper, a new glucose-insulin regulatory system was designed based on Palumbo's delayed nonlinear model for diabetes mellitus. Then, the idea of quasi-linearization in nonlinear delayed systems was adopted along with an optimal closed-loop control method called Adaptive Weighting SDRE to converge the blood glucose with its normal level in type 1 diabetic patients, thus archiving an optimal injection rate. Since control methods for delayed nonlinear systems have not extensively developed other than in Palumbo's feedback linearization as a solution, the newly proposed method can be considered a highly robust strategy. Furthermore, the results were compared against those of Palumbo's method based on feedback linearization.

It is recommended to improve the new method by online model identification, thereby to mitigate closed-loop sensitivity to parametric variations. It is also strongly recommended that a mechanism be developed to satisfy operational constraints, such as predictive controllers. However, the prediction horizon should be sufficiently large.

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