Application Of Fuzzy Logic Controller For Intensive Insulin Therapy In Type 1 Diabetic Mellitus Patient

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Abstract: - The work we describe here is aimed at assisting out-patients affected by insulin dependent diabetes mellitus with an advisory/control algorithm. This advisory/control algorithm incorporates expert knowledge about the treatment of this disease by using Mamdani type fuzzy logic controllers to regulate the blood glucose level (BGL). We proposed two-level architecture for control system. The goal of the Low Level Module is to suggest the next insulin dosage of both short and intermediate acting insulin (Regular and NPH) formulation that are programmed in a three-shots daily basis before meals, depending on the blood glucose measurement. The High Level Module adjusts the maximum amounts of insulin provided to the patient in a time-scale of days. This module aims to work as a supervisor of the low level module. Simulations are illustrated, using a flow-limited model for diabetes mellitus based on the work of Puckett.

Key-Words: - Diabetes mellitus, Fuzzy logic controller, Intensive insulin therapy

1 Introduction
Several organs, hormones and enzyme systems are involved in the regulation of the blood glucose levels in human body. Insulin, a hormone secreted by pancreatic beta cells, is the most important hormone in the regulation of blood glucose levels. It influences the rates of glucose utilization by the tissues and regulates the storage of the fuel, therefore helps to keep blood glucose concentrations within a narrow range of about 90-130 mg/dl. Diabetes mellitus is an endocrine metabolic disorder in which the body does not produce or properly use insulin. The results of the Diabetes Control and Complications Trial (DCCT) [1] showed that an intensive insulin therapy can reduce the incidence of these illnesses in the long term. Consequently, an intensive therapy is encouraged for type 1 diabetic mellitus (TIDM) patients prescribed either by a continuous subcutaneous insulin infusion (CSII) pump, or a multiple daily injections regimen (MDIR). In this contribution, the latter one is studied, which is the most common scenario in chronic patients, due to the high cost and availability of portable CSII pumps. With this consideration, if an intensive therapy is followed by the patient, the prescribed insulin treatment must be carefully selected by the physician. It is then appealing to have an advisory/control system for the patient in order to update each daily dose of insulin [2], [3], [4], [5], [6], [7]. In the control theory field, the fuzzy logic has emerged as a powerful tool to incorporate expert knowledge about the systems into the controllers design [8], [9], in particular, the ability of synthesizing expert knowledge in the fuzzy logic framework has raised a lot of attention in the biomedical engineering field. The control strategy presented in this work formalizes expert knowledge in the fuzzy logic framework. Section 2 gives an overview of the mathematical modeling of the insulin-glucose dynamics in a TIDM patient. Section 3 introduces the synthesis of the knowledge-based (Mamdani-type) fuzzy controllers. Finally, Section 4 introduced the simulation results. Section 5 presents concluding remarks and future work.

2 Diabetic patient modeling
The model to be presented here is a flow-limited model for diabetes mellitus based on the work of Puckett [12]. This model is constructed of two sub-models. The glucose sub-model contains tissues including heart, brain, liver, kidney and muscle where the glucose is used for energy. The insulin sub-model includes subcutaneous tissue as a source for insulin. It is assumed that the pancreas is completely lacking insulin production and changes in blood glucose and insulin concentrations for each tissue are fast and the balances are in a quasi-steady state (i.e. \( dG / dt \approx 0 \)) shortly after a disturbance (i.e. the carbohydrate intake).

2.1 Insulin sub-model
Insulin travels through several regions of the body as
it moves from the injection depot to the target cells. Diabetic educators usually teach patients to inject insulin into the subcutaneous tissue in such a way as to put it in the interstitial fluid and not a blood vessel. The insulin must then diffuse through the interstitial environment to nearby capillaries. After crossing the capillary wall, it is carried to the main circulation. The circulating hormone crosses the capillary wall in various tissues and diffuses through the interstitial milieu to the cell walls. Insulin’s binding with receptors in the cell membrane then cause intracellular signals which activate appropriate changes in the cell’s metabolism. After initiating the signal, the hormone dissociates from the receptor, or the complex is internalized. The internalized insulin is released unaltered or degraded. The following three pool model describes the absorption from an injection of short acting insulin (regular) at t=0:

\[
\frac{d[I_p]}{dt} = -k_p[I_p] \quad [I_p](t = 0) = [I_p]_0 \quad (3)
\]

\[
V_s \frac{d[I_s]}{dt} = k_p[I_p] - k_s[I_s] \quad [I_s](t = 0) = [I_s]_0 \quad (4)
\]

\[
V_B \frac{d[I_B]}{dt} = k_s[I_s] - k_B[I_B] + k_B[I_B]_0 \quad [I_B](t = 0) = [I_B]_0 \quad (5)
\]

\[\tau_p = k_p^{-1}, \tau_s = V_s / k_s, \tau_B = V_B / k_B\]

Where, \([I_p]\) is total amount of insulin in pocket, \(k_p\) is rate constant for the transport of insulin from the pocket into the surrounding interstitial fluid, \([I_s]_0\) is injected insulin, \([I_s]\) is insulin concentration in interstitial fluid, \([I_B]\) is concentration of insulin in the capillary blood, \(k_s\) is rate constant for the transport from the interstitial region to the capillary blood, \(V_s\) is effective volume of the interstitial fluid, \(V_B\) is effective volume of circulating blood, \(k_B\) is rate constant for removal of insulin in the liver and kidney, \(\tau_p, \tau_s, \tau_B\) are time constants. The insulin sub-model parameters are tabulated in Table 1.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\tau_p) (min)</td>
<td>63</td>
</tr>
<tr>
<td>(\tau_s) (min)</td>
<td>63</td>
</tr>
<tr>
<td>(\tau_B) (min)</td>
<td>16</td>
</tr>
<tr>
<td>([I_B]_0) ((\mu U))</td>
<td>17.5</td>
</tr>
<tr>
<td>([I_B]_0) ((\mu U))</td>
<td>0</td>
</tr>
</tbody>
</table>

### 2.2 Glucose sub-model

Setting \(dG/dt = 0\) in all tissues we get:

\[
V_B \frac{d[G_B]}{dt} = -TGU - GE + GA + LGP
\]

In summary, we present the different sub-models making up the glucose portion of the overall model here:

**Total Glucose Uptake (TGU)**

\[
TGU = k[I_A][G_B] + CNU
\]

\[
\frac{d[I_A]}{dt} = \frac{1}{T_M} ([I_B]_0 - [I_A])
\]

Where, \(k\) is a constant value, \([I_A]\) is effective insulin concentration, \([G_B]\) is circulating blood glucose concentration, \(CNU\) is glucose and insulin independent uptake which is approximately a constant, \([I_B]_0\) is circulating blood insulin concentration delayed by the pure time delay \(T_{D,TGU}\).

**Glucose Excretion (GE)**

\[
GE = 1.25 \frac{dt}{\min} \left( ([G_B] - 176 \frac{mg}{dl}) U ([G_B] - 176 \frac{mg}{dl}) \right)
\]

where, \(U([G_B] - 176mg/dl)\) is step function indicating the threshold at approximately 176 mg/dl.

**Glucose Absorption from the small intestine (GA)**

\[
\frac{d[G]}{dt} = - \frac{1}{T_A} \cdot GA + \frac{F}{T_A T_{GE}} [G_G] \quad GA(t < t_M) = 0
\]

\[
\frac{d[G_G]}{dt} = - \frac{1}{T_{GE}} [G_G] + [CHO_G] \quad [G_G](t < t_M) = 0
\]

\[
[CHO_G] = \frac{1}{4 \min} \cdot CHO_M (t - t_M) u(t - t_M) -
\frac{1}{4 \min} \cdot CHO_M (t - t_M - 1) u(t - t_M - 1) -
\frac{1}{4 \min} \cdot CHO_M (t - t_M - 4) u(t - t_M - 4) +
\frac{1}{4 \min} \cdot CHO_M (t - t_M - 5) u(t - t_M - 5)
\]

Where, \([CHO_G]\) is total amount of hydrolyzed meal carbohydrate that have entered the stomach, \(CHO_M\) is carbohydrate content of the meal (in mg/kg), \(t_M\) is time of meal (in minutes), \([G_G]\) is total amount of glucose in the stomach, \(F\) is fraction of meal carbohydrates that actually absorb into the blood.

**Rate of Liver Glucose Production (LGP)**

\[
LGP = a_1 \left( 1 - \frac{[GI]_D - a_3}{[GI]_D - a_3 + a_4} \right)
\]

\[
\frac{d[GI]_D}{dt} =
\begin{cases}
  k_A ([G_L]_D [I_B]_D - [GI]_D) & \text{if } \frac{d[GI]_D [I_B]_D}{dt} \geq 0 \\
  k_A ([G_L]_D [I_B]_D - [GI]_D) & \text{if } \frac{d[GI]_D [I_B]_D}{dt} < 0
\end{cases}
\]

\([GI]_D(t = 0) = [G_B]_0 [I_B]_0\)
\[ [G_L] = [G_B] + \frac{GA}{QL} \]  

(15)

Where, \([G_L]_0\) is average glucose concentration entering the liver delayed by the pure time delay \(T_{DLGP}\), \([I_o]_0\) is circulating blood insulin concentration delayed by the pure time delay \(T_{DLGP}\), \([GL]_0\) is delayed in a first order manner with a time constant \(1/k_A\) or \(1/k_D\), \(Q_l\) is a constant value. The glucose sub-model parameters are tabulated in Table 2.

Table 2. Constant parameters of glucose Sub-model

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>(V_B) (dl/kg)</td>
<td>1.0754</td>
</tr>
<tr>
<td>(T_{DLGU}) (min)</td>
<td>30</td>
</tr>
<tr>
<td>(T_{IA}) (min)</td>
<td>21.3</td>
</tr>
<tr>
<td>(k) (1/min)</td>
<td>0.000382</td>
</tr>
<tr>
<td>(CNU) (mg/kg-min)</td>
<td>1.67</td>
</tr>
<tr>
<td>(T_{GE}) (min)</td>
<td>156.59</td>
</tr>
<tr>
<td>(T_{A}) (min)</td>
<td>34.66</td>
</tr>
<tr>
<td>(F)</td>
<td>1</td>
</tr>
<tr>
<td>(Q_l) (ml/min)</td>
<td>810</td>
</tr>
<tr>
<td>(a_1) (mg/kg-min)</td>
<td>1.13</td>
</tr>
<tr>
<td>(a_2)</td>
<td>0.43</td>
</tr>
<tr>
<td>(a_3) (mg – (\mu)U / dl – ml)</td>
<td>7259</td>
</tr>
<tr>
<td>(a_4) (mg – (\mu)U / dl – ml)</td>
<td>765</td>
</tr>
<tr>
<td>(T_{DLGP}) (min)</td>
<td>30</td>
</tr>
<tr>
<td>(k_{A} (1/min))</td>
<td>0.3671</td>
</tr>
<tr>
<td>(k_{D} (1/min))</td>
<td>0.0036</td>
</tr>
</tbody>
</table>

3 Problem statement and control method

Three meals are considered per day: breakfast, lunch and dinner; where the lunch is the major one of the day. Roughly, there is a time interval of 6 h between each meal. In the proposed injection plan, the insulin doses are programmed previous to each meal, where the NPH provides the basal insulin, and the transient effects after each meal (post-prandial peaks) are regulated by the regular. Because of slow basal insulin absorption, the morning and lunch doses for NPH are skipped, and only regular is injected. The control objective is then stated in Table 3.

Table 3. Control objective

<table>
<thead>
<tr>
<th>Plasma Glucose</th>
<th>Normal</th>
<th>Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before eating</td>
<td>Less than 110</td>
<td>90 to 130</td>
</tr>
<tr>
<td>Two hours After eating</td>
<td>Less than 110</td>
<td>Less than 180</td>
</tr>
<tr>
<td>Bedtime</td>
<td>Less than 120</td>
<td>110 to 150</td>
</tr>
</tbody>
</table>

The advisory/control scheme presented in this work is based on a two-level architecture, see Fig. 3.

3.1 Low Level Module

The low level module is structured with a Mamdani type fuzzy architecture and computes the regular (\(I_r\)) and NPH (\(I_{nph}\)) insulin doses given to the patient before each meal. The input variables to this module are:

- Time of the day (t): the information of time is used to determine whether a NPH insulin dose is injected next or not.
- Glucose measurement (G): the information of the BGL is used for the euglycemic analysis.
- Previous regular dose (\(I_{rd}\)): the regular dose calculated in the previous meal is used to analyze the glycemic control.
- Previous NPH insulin dose (\(I_{nphd}\)): due to the absorption process of the NPH, its dose in the morning is considered to evaluate also the glycemic control.

The two outputs regular (\(I_r\)) and NPH doses (\(I_{nph}\)) are normalized to the interval \([0,1]\), and the actual injection preparation (\(I^a_r; I^a_{nph}\)) is calculated when the amplitudes are scaled according to the values

Table 4. Inputs characteristics for low level module

<table>
<thead>
<tr>
<th>Input</th>
<th>Interval</th>
<th>Membership Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>t</td>
<td>[0,24] h</td>
<td>Morning (SMF)</td>
</tr>
<tr>
<td>G</td>
<td>[40,400] mg/dl</td>
<td>Low (SMF)</td>
</tr>
<tr>
<td>(I_{rd})</td>
<td>[0,1]</td>
<td>Small (SMF)</td>
</tr>
<tr>
<td>(I_{nphd})</td>
<td>[0,1]</td>
<td>Small (SMF)</td>
</tr>
</tbody>
</table>

Table 5. Outputs characteristics for low level module

<table>
<thead>
<tr>
<th>output</th>
<th>Interval</th>
<th>Membership Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>(I_r)</td>
<td>[0,1]</td>
<td>None (TMF)</td>
</tr>
<tr>
<td>(I_{nph})</td>
<td>[0,1]</td>
<td>None (TMF)</td>
</tr>
</tbody>
</table>
\[ I_{r}^{\text{max}} = I_{r}^{\text{max}} \times I_{r}, \]
\[ I_{nph}^{\text{max}} = I_{nph}^{\text{max}} \times I_{nph} \]

The input and output characteristics are shown in Table 4 and 5 respectively, including the interval of variation for each variable and the fuzzy sets associated with the type of membership function used (fuzzification method). By the definition of the input fuzzy set, a total of 108 IF-THEN rules were defined. These rules were of AND (minimum) type antecedent. The output (defuzzification method) is calculated by the centroid method. The major trends in the rules description are:
- The morning and lunch doses of NPH insulin are skipped.
- The regular doses increases as the BGL increases.
- If the previous dose of insulin is small and the BGL is above normal, then increase the doses.

A sample of the proposed rules for the low level module is detailed next:

**IF** Time=Morning and Glucose=Low and \( I_{r}^{\Delta} = \text{Large} \) and \( I_{nph}^{\Delta} = \text{Large} \) **THEN** \( I_{r} = \text{Small} \) and \( I_{nph} = \text{Medium} \).

### 3.2 High Level Module

The high level module is synthesized using physician knowledge [10], [11] by applying a Mamdani type fuzzy logic structure and regulates the amounts of insulin given to the patient by evaluating the glycemic control in a time-scale of days. According to control objective listed in Table 3, the systemic glucose deviation from the target glucose level (TGL) can be measured as:

\[ J = \frac{1}{n} \sum_{k=1}^{n} \theta(k) \]  

where \( n \) is the number of measurements used for evaluation, and \( \theta(k) \) (pointwise deviation from TGL) is defined as:

**a)** For BGL measured before eating:

\[ \theta(k) = \begin{cases} 
G(k)-130 \text{ mg/dl} & G(k)-130 \text{ mg/dl} \\
G(k)-90 \text{ mg/dl} & G(k)-90 \text{ mg/dl} \\
0 & 90 \leq G(k) \leq 160 \text{ mg/dl} \\
110 \leq G(k) \leq 150 \text{ mg/dl} & \text{otherwise}
\end{cases} \]

**b)** For BGL measured 2 hours after eating:

\[ \theta(k) = \begin{cases} 
G(k)-180 \text{ mg/dl} & G(k)-180 \text{ mg/dl} \\
G(k)-110 \text{ mg/dl} & G(k)-110 \text{ mg/dl} \\
0 & 110 \leq G(k) \leq 150 \text{ mg/dl}
\end{cases} \]

**c)** For BGL measured at bedtime:

\[ \theta(k) = \begin{cases} 
G(k)-150 \text{ mg/dl} & G(k)-150 \text{ mg/dl} \\
G(k)-160 \text{ mg/dl} & G(k)-160 \text{ mg/dl} \\
0 & \text{otherwise}
\end{cases} \]

Where \( \Gamma \) is a constant that includes an additional weight for low glucose concentrations (hypoglycemic scenarios). Consequently, the high level module must adjust the insulin dosing in three global scenarios:
- Increase it, if an hyperglycemic condition is detected.
- Decrease it, in the case of an hypoglycemic condition.
- Maintain it, for a normal condition.

These dosing adjustments are performed in a time-scale of days, where they could be specified per day or week according to the physician's advise. The adjustment is done the next morning by modifying the scaling factors \( I_{r}^{\text{max}} \) and \( I_{nph}^{\text{max}} \) using an integral type of updating rule:

\[ I_{r}^{\text{max}}(i) = I_{r}^{\text{max}}(i-1) + \Delta I_{r}, \]
\[ I_{nph}^{\text{max}}(i) = I_{nph}^{\text{max}}(i-1) + \Delta I_{nph} \]

where \( \Delta I_{r} \) and \( \Delta I_{nph} \) are the adjustments given by the high level module. The index \( i-1 \) refers to the old scaling factor, and \( i \) to the new adjusted one. The input information used by the high level module includes details of the glycemic control during the previous days, and the previous insulin adjustments, this is:

### Table 6. Inputs characteristics for high level module

<table>
<thead>
<tr>
<th>Input</th>
<th>Interval</th>
<th>Membership Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>( J )</td>
<td>[-20,20] mg/dl</td>
<td>Negative (SMF)</td>
</tr>
<tr>
<td>( J_{r} )</td>
<td>[-20,20] mg/dl</td>
<td>Negative (SMF)</td>
</tr>
<tr>
<td>( \Delta J_{r} )</td>
<td>[-2,2] U</td>
<td>Negative (SMF)</td>
</tr>
<tr>
<td>( \Delta J_{nph} )</td>
<td>[-4,4] U</td>
<td>Negative (SMF)</td>
</tr>
</tbody>
</table>

### Table 7. Outputs characteristics for high level module

<table>
<thead>
<tr>
<th>Output</th>
<th>Interval</th>
<th>Membership Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \Delta I_{r} )</td>
<td>[-2,2] U</td>
<td>Very Negative (SMF)</td>
</tr>
<tr>
<td>( \Delta I_{nph} )</td>
<td>[-4,4] U</td>
<td>Very Negative (SMF)</td>
</tr>
</tbody>
</table>
- The glucose deviation ($J$) in (17).
- Memory of the previous deviation ($J_p$).
- The previous adjustments $\Delta I_r$ and $\Delta I_{nph}$.

The input and output characteristics are shown in Table 6 and 7 respectively, including the interval of variation for each variable and the fuzzy sets associated with the type of membership function used (fuzzification method). By the definition of the input fuzzy set, a total of 81 IF-THEN rules were defined. These rules were of AND (minimum) type antecedent. The output (defuzzification method) is calculated by the centroid method. The premise of these rules can be summarized in three points:
- If there is a tendency for the glucose deviation to increase above the TGL, then increase the scaling factors.
- If there is a tendency to decrease below the TGL, then reduce the scaling factors.
- If the glucose deviation is in the TGL, then try to decrease the scaling factor without leaving the TGL.

A sample of the proposed rules for the low level module is detailed next:

\[
\begin{align*}
\text{IF} & \quad J_r = \text{Negative and } J_p = \text{Negative and } \Delta I_r = \text{Zero and } \\
& \quad \Delta I_{nph} = \text{Zero} \quad \text{THEN} \quad \Delta I_r = \text{Negative and } \Delta I_{nph} = \text{Negative}.
\end{align*}
\]

4 Simulations

The numerical simulation was implemented in MATLAB/Simulink using the Fuzzy Logic Toolbox. A total of 25 days ($T = 36000$ min) were simulated with three meals per day: breakfast: 8 h, lunch: 14 h, and dinner: 20 h. Three boluses of insulin are programmed per day by a subcutaneous injection, where a combination of Regular and NPH insulin is programmed. The high level module supervises intensively the low level module every day to adjust the scaling factors. During the simulation period (25 days), a total of 100 doses are computed. The hypoglycemic weight $\Gamma$ in (18) and (20) was selected to 5 [5] during the computation of glucose deviation $J$.

At the first case of our simulation, the patient starts with small scaling factors for both types of insulin, producing small insulin doses and high glucose levels. The algorithm adjusts the insulin dosages in order to reach the TGL. For this scenario, a $\pm 15\%$ error (typical error in commercial devices) in each of the glucose measurements is assumed. At the second case of our simulation, in order to analyze the effect of heavy variations in the meal intakes, the patient varies his carbohydrate intake during meals by 25% from the nominal ones, using a uniform distribution.

Fig.2 and Fig.3 present simulations for the case 1 and 2 respectively: meal carbohydrates intakes, blood glucose concentration, glucose deviation function, and insulin doses. It is observed that there is no instability in the system although the measurement error can be as high as 15%, and meal intakes can have up to 25% variation. Hypoglycemia was detected when the BGL decreased below 60 mg/dl during simulations, and no hypoglycemic conditions are detected. For both two cases studied, the advisory/control algorithm is able of regulate the plasma glucose around the TGL despite initially low scaling factors and measurement errors (case 1) and variable carbohydrates intake (case 2).

5 Conclusion

In this study, a fuzzy logic controller has been proposed to maintain the normoglycaemic for diabetic patient of type I. The treatment strategy is based on a four-daily doses of regular and NPH insulin and which is applied through a subcutaneous route. In order to incorporate knowledge about patient treatment, the controllers are designed using a Mamdani-type fuzzy scheme. Simulation results with a physiological model of the TIDM patient show the effectiveness of structure for blood glucose regulation. Hence the results presented are encouraging for clinical studies, however in that case, some other physiological factors not addressed in the TIDM mathematical model could affect the actual performance, and further tuning could be necessary according with the results achieved in each patient. As shown in this paper, the fuzzy logic framework has the potential to synthesize expert knowledge to treat diseases. Therefore, the approach and methodology introduced could be a valuable tool for educational purposes. Moreover, in future work, the inclusion of an exercise regime in the overall model of the TIDM patient in order to have a more realistic simulation will be considered.

References:


