Proposed Clinical Application for Tuning Fuzzy Logic Controller of Artificial Pancreas utilizing a Personalization Factor

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Abstract

Background: Physicians tailor insulin dosing based on blood glucose goals, response to insulin, compliance, lifestyle, eating habits, daily schedule, fear of and ability to detect hypoglycemia.

Method: We introduce a method that allows a physician to tune an APS for a particular patient. It utilizes the physician’s judgment and weighting of various factors. The Personalization Factor (PF) is a scaling of the dose produced by the Fuzzy Logic Controller (FLC) and is used to customize the dosing. The PF has discrete values of 1 through 5. The proposed method was developed using a database of results from 30 UVa/Padova Simulator \textit{in silico} subjects (10 adults, 10 adolescents, and 10 children). Various meal sizes and timing were used to provide the physician information on which to base an initial dosing regimen and PF. Future decisions on dosing aggressiveness using the PF would be based on the patient’s data at follow-up.

Results: Three examples of a wide variation in diabetes situations are given to illustrate the physicians thought process when initially configuring the APS for a specific patient.

Conclusions: FL controllers are developed by encoding human expertise into the design of the controller. The FLC methodology allows for the real-time scaling of doses without compromising the integrity of the dosing rules matrix. The use of the PF to individualize the APS is enabled by the FL development methodology.

Introduction

Type 1 diabetes mellitus is an autoimmune disease causing insulin deficiency. At the present time the only treatment is the administration of insulin either by multiple shots per day or by an infusion pump. The DCCT studies showed that improved control of the blood glucose lessens the frequency of complications of diabetes\textsuperscript{1}. Efforts to create an artificial pancreas (AP) have intensified with the commercial availability of continuous glucose sensors\textsuperscript{2}.

FL was developed at UC Berkeley in 1965 as a generalization of bi-value, true/false mathematical logic.\textsuperscript{7} Mathematically, FL can be viewed as a black box that maps an input space onto an output space as shown in Figure 1 (Mathworks REF).
Real world, ‘crisp’ parameters are read into the fuzzy domain black box, processed there, and then the solution re-transformed (defuzzified) back into real world parameters. A notional diagram of that process is shown in Figure 2.

The diagram above illustrates how fuzzy logic works. For simplicity purposes, this diagram shows only 2 of the input parameters - blood glucose and change in blood glucose, and has excluded acceleration.
The blood glucose input range is partitioned into five regions, representing the ranges that are meaningful to the clinician. Blood glucose regions are represented by overlapping triangles. The overlapping regions allow the blood glucose input value to be transformed into a fuzzy variable, which intuitively is a blend of at most two regions. A blood glucose value of 195 is therefore represented as a blend of High and Very High, with ‘strength’ of 50 percent each as indicated by the red and green boxes. The process is the same for blood glucose rate, and acceleration. The example input rate of 1.0 mg/dL/min is transformed into a fuzzy variable of Z and P with strengths of 0.25 and 0.75 respectively.

The two-dimensional inference engine, or decision matrix, processes the blood glucose and rate fuzzy input variables into an output fuzzy variable, by means of if-then rules predefined by the clinician. For example, if BG is VH and Rate is Z, then Dose is 0.7. The Mamdani defuzzification (REF) procedure sets the strength of the output variable to be the minimum of the inputs. Hence the 0.7 output dose variable has strength 0.25 as represented by the blue strength of the Rate variable. The larger red value is suppressed. For a given blood glucose value and rate input value, more than one if-then dosing rule may execute, producing an output fuzzy variable that is also a blend of dosing values, as represented by truncated overlapping triangles, or trapezoids. The output dose is then calculated as the center of mass of the overlapping trapezoids.

The FL process described here, when viewed as a black box, is a bounded, uniformly continuous function (ref). From a safety standpoint this is important because it means that throughout the entire range of input values, a small change in BG, rate or acceleration input value always results in a small change in the dose. Furthermore, the output dose can never exceed values defined by the output membership function. Algorithmically, the FL controller may be designed as the composition of linear table-lookup functions.

When developing a FL controller, the complexity or internal structure of the process to be controlled, the human glucoregulatory system in this case, is not directly used. Instead the expertise of the clinician manages the system in terms of how external attributes such as blood glucose and insulin are used in the dose decision process. FL controllers are often said to embody the expertise of practitioners. That expertise is codified in the partitioning of the input and output regions, and the if-then dosing rules in the decision matrix.

This controller does not take into account insulin on board (IOB) when calculating the dose. That feature could be incorporated as an additional membership function, or as a post processor function as described in a paper to be presented at the 2010 ADA conference (Eyal ref).

The notional FL controller shown in Figure 2 may be extended to include blood glucose acceleration as a third input. To show the mapping of BG, Rate and Accel using a 2-dimensional matrix, the acceleration inputs are repeated for each of the five rates. A mapping of the points A,B,…H on the sample BG trajectory into the input-partitioned Inference Engine is shown in Figure 3. As demonstrated in Figure 2, each discrete input value is transformed into at most 2 fuzzy variables. Hence, since all possible combinations of BG, Rate and Acceleration are represented in the dosing matrix, a given input vector (BG, Rate, Accel) may invoke up to eight dosing rules.
Figure 3.
Correlation of points on a blood glucose trajectory with sets of rules in the FL dosing matrix

The below dosing matrix was developed in 2003 by R. Mauseth, in collaboration with other northwest endocrinologists. The matrix was developed independently from any glycemic simulator. The dosing matrix prescribes for all continuous blood glucose input sequences, a bounded, uniformly continuous sequence of insulin doses.

Figure 4.
5-minute dosing matrix

This initial controller was tested in a small clinical trial using 4 human subjects and produced good results for fasting and small meals. However, for large meals the majority of the subjects had late postprandial hypoglycemia. See Figure 5.

Figure 5
Results of 4 subject clinical trial using initial FL controller
We recognize that one of the shortcomings of the initial FL controller was that its dosing matrix did not take into account insulin on board (IOB), the cumulative effects of past insulin doses. The original controller also provided minimal personalization, or tuning, for a particular patient. Further improvement of the controller has been done to add additional capabilities to prevent hypoglycemia following a large meal.

**Improved Fuzzy Logic Controller**

Collaboration with researchers at UCSB and Sansum Diabetes Research Institute (SDRI) resulted in important improvements to the FL controller, the first being the addition of the Personalization Factor (PF).

The FLC AP v2 top-level design is shown in Figure 6. It provides for individually tailored dosing through the use of a Personalization Factor (PF). The PF is a scaling factor that is applied to the dose produced by the FL dosing matrix. Each subject’s PF is proportional to his/her total daily dose (TDD), as shown below:

\[
PF(i) = \frac{TDD(i)}{TDD^*}
\]

where \(i\) denotes the subject index and \(TDD^*\) is a defined standard TDD. In this study, five values for \(TDD^*\) were compared, e.g., 30, 37.5, 45, 52.5, and 60 (U/day). For convenience, \(PF_j(i)\) \((j = 1, \ldots, 5)\) is the PF for subject \(i\) under \(j\)th \(TDD^*\). Clearly, the first group, \(PF_1()\), is the most aggressive and the fifth group, \(PF_5()\), is the least aggressive.

**Figure 6**

The system level diagram for the FL AP controller

As of the publication of this article, the FL AP controller now employs an insulin governor that further prevents post meal hypoglycemia. (Ref: ADA 2010 oral presentation)

**Physician Utilization of Controller**

FLC has the potential for physician input to a dosing matrix. It also allows easy physician input, i.e. physical scaling (tuning) of the dosing. This paper is meant to illustrate the potential use of a personalization factor with this controller.

**Results and Discussion**
The proposed method was derived using 30 in silico subjects (10 adults, 10 adolescents, and 10 children) from FDA-accepted UVa/Padova metabolic simulator. Several situations were studied, a standard day, fasting, and evaluation of the effects of various meal sizes using the 5 PF levels. The standard day consists of 3 meals, 45-gram carbohydrate breakfast, 70-gram carbohydrate lunch and 80-gram carbohydrate dinner for all three age groups. The fasting was for 24 hours and the various meal sizes were 40, 80, 120, 160 and 200-gram carbohydrate meals.

The in silico testing was chosen to attempt to mimic situations that a clinician might encounter in dealing with a patient’s medical management. The physician then weighs the pros of improved glycemic control versus the cons of the possibility of adverse events. For future studies the 300 in silico subjects for the UVa/Padova simulator may assist in the defining of the various risk/benefit analyses. The in silico testing is only meant to give a physician a starting point for different patients. It also allows the physician to illustrate to the patient various aspects of their own care as a teaching and decision making tool. Each patient will then make his or her own modifications as instructed and restricted by the physician.

Physicians treating patients with diabetes tailor the insulin dosing to the patient. Goals are different for each patient and each patient has different responses to therapy and levels of compliance as well as a unique lifestyle and eating habits. Each patient’s daily schedule is different and may not be consistent from one day to the next. The fear of hypoglycemia and inability to detect and treat hypoglycemia limits the physician’s aggressiveness of treatment. The personalization factor allows the physician to customize the aggressiveness of a controller to best fit a patient’s needs. A set Pf for a patient would be used most days but the ability to change the Pf could be easily utilized on special occasions, much like changing a temporary basal rate on an insulin pump.

In silico testing could give a starting point, but will need to be adjusted for every patient. Several weeks after initiating the controller the physician would meet with the patient and review their records of activity, food intake and downloads from their pump/sensor. Using their own data, and referring to the in silico data, problems could be solved. Periods of different insulin sensitivity from exercise, illness or menses may be accommodated with temporary changes in the PF.

This paper is not meant to show specific patient outcomes but is more of a description approach to individualizing a controller for a patient. Several examples of how a physician might go through the decision-making process on imaginary patients are given below. Basically the sequence is to lower the average BG until LBGI becomes higher than desired for that specific patient, which may very from patient to patient.

The basic process for the physician is as follows:
1. Using the standard day chart, establish desired control for the patient
2. Select the appropriate PF using the standard day bar chart
3. Evaluate the risk of hypoglycemia due to missed meals and for sleeping in using the fasting day chart.
4. Evaluate the consequences of varied meals using the varied meal sizes charts

Example 1 is a 35 year-old male, who is hypoglycemia aware, desires tight control, tolerates hypoglycemic episodes well and has a very routine schedule of a desk job with
daily exercise at noon. His weekends also follow a similar routine. He never eats more
than 80 grams of carbohydrate at a meal.
With this patient, the physician would review Figure 3 and evaluate the degree of glycemic control desired versus the risk of hypoglycemia. They evaluate their goals looking at a PF of 1, which results in an average blood glucose of 120mg/dL (A), which equates to an A1c of 6.2. They would then consider the Low Blood Glucose Index (LBGI) of 3.0 (B) and determine that the risk was too high. They instead select a PF of 2, with an average glucose of 130mg/dL (C) equating to an A1c of 6.4 and a LBGI of 1.5 (D) for the standard day.

The physician would then use Figure 4 for evaluating the risk of hypoglycemia due to missing meals for this PF (E). The physician would then consult Figures 5 and 6 and discuss the potential consequences of varied meal sizes at PF 2. Using Figure 5 they examine the effects of controlling meal sizes (F) and hypoglycemia risk Figure 6 (G) noting the risk of hypoglycemia is higher with the 80 gram meal.

If the patient was having something irregular such as Thanksgiving dinner with a different meal size, or was doing a triathlon, he might adjust the PF temporarily for only that event.

Example 2 is a 6 year-old female, hypoglycemia unaware, who attends school 5 days per week with no school nurse. She has had 1 hypoglycemic seizure and her parents are very
fearful of future episodes. The patient's eating schedule is very erratic. She has basketball and dance classes on the same day, 3 days per week, but the times of day vary.

Using this information the physician would review Figure 7 and discuss with her parents, the degree of control desired. They consider a PF of 4 based on this chart, giving them an average blood glucose of 155mg/dL (A), which equates to an A1c of 7.1 and an LBGI that is 0.9, which is very acceptable. A PF of 3 (B) would lower the average Blood glucose of 145 equating to an A1c of 6.9 but the LBGI would increase to 2.5, which is almost 3 times that of a PF of 4, which is unacceptable.

Then they would consult Figure 8 and determine the hypoglycemic risk of allowing the child to sleep in when using PF4 (C). They would also review Figures 9 and 10 to evaluate the consequences of large meals on blood glucose (D) and risk of hypoglycemia (E). The benefits of a more controlled carbohydrate intake could also be demonstrated.

Example 3 is a 14 year-old male, with an A1c of 12%, who is unwilling to follow any meal plan. He tests sporadically but is willing to test frequently enough to calibrate a continuous glucose monitor. The patient has absolute fear of hypoglycemia in front of his peers. He wakes up for school at 6am on weekdays and sleeps until noon on weekends.
Using this information, the physician would consult figures 11, 12, 13, and 14 to select the appropriate PF to improve this young man’s control while avoiding hypoglycemia. Figure 11, shows that a PF 5 (A), giving an average glucose of 165mg/dL (A1c of 7.4), was very acceptable. The LBGI would be almost zero (B), which would avoid almost all hypoglycemia. Evaluation of risks of hypoglycemia with varied meal sizes would be determined using Figures 13 and 14. The patient is then shown the benefit of decreasing carbohydrate intake versus the risk of hypoglycemia with extremely large meals (C, F (120g to 200g)).

The patient sees that if he can keep his carbohydrate intake less than 120 grams per meal, a lower PF (e.g. PF4/120 meal) (E) or even a PF3 if meals are 80 grams or less, could be used without the increased risk of hypoglycemia versus a higher PF (PF5/200g meal) with larger meals (D). Even using the higher PF of 5, the change in average glucose would equate to a 4.6-point drop in A1c and lower his risks of complications by 93%

Having the patient participate in the AP controller tuning decision-making would hopefully increase their ownership, improve their understanding of their choices and lessen their fears of hypoglycemia.

**Conclusions**
The use of a FLC AP system with the use of a personalization factor allows a great deal of flexibility and input from the physician. The use of the *in silico* simulation results aids
in patient instruction and initial decision-making. We hope this method will decrease fears of hypoglycemia, improve quality of life, improve overall diabetes control and lessen the burden of diabetes on the individual.

References

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**List of Abbreviations:**
AP = Artificial Pancreas
APS = Artificial Pancreas System
DCCT = Diabetes Control and Complications Trial
FL = Fuzzy Logic
FLC = Fuzzy Logic Controller
JDRF = Juvenile Diabetes Research Foundation
BG = Blood Glucose
PID = Proportional Integral Derivative control
MPC = Model Predictive Control
PF = Personalization Factor
TDD = Total Daily Dose
UVa = University of Virginia

*in silico* = simulated diabetic subjects in the UVa/Padova simulator
FDA = US Food and Drug Administration
LBGI = Low Blood Glucose Index
HBGI = High Blood Glucose Index
A1c = Hemoglobin A1c. Glycosylated (or glycated) hemoglobin.

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