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Automated Control of Blood Glucose in the OR and Surgical ICU

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***Abstract* — A device which integrates existing intravenous continuous glucose monitors and infusion pumps into a central hub for automated intravenous intensive insulin therapy, targeting non-diabetic critically-ill patients is presented. Additionally, a fuzzy logic based controller that is capable of automatically making closed-loop decisions to achieve tight glycemic control between a euglycemic range of 90 to 120 mg/dl is presented. Initial bench top testing shows a significant improvement in glycemic control with fuzzy logic control when compared to manual infusion protocols currently used in hospitals; future animal testing will be performed to verify these results *in vivo*.**

I. Introduction

STRESS-induced hyperglycemia is a common condition affecting patients in the operating room (OR) and surgical intensive care unit (SICU). Stress-induced hyperglycemia affects both diabetic and non-diabetic patients. In one study, 54.6% of cardiac surgery patients alone had at least one hyperglycemic incident during their operation [1]. In bariatric surgery patients, hyperglycemia developed an hour into an operation and lasted at least 9 hours [2]. Hyperglycemia is a serious concern because it increase rates of infection, organ failure, and morbidity; it is also an independent risk factor for adverse complications, including death [3].

Currently, tight glycemic control is obtained through manual implementations of intensive insulin therapy (IIT). IIT has been proven to reduce in-hospital mortality by 34% [4], but is very labor intensive. Each reading takes 4.7 minutes which necessitates 1 to 2 hours of a caregiver's day is dedicated to glucose measurements [5]. Additionally, there is also a low adherence to manual IIT protocols due to the fear of hypoglycemia, ultimately leading to reduced efficacy when using intensive insulin therapy.

II. Method of Approach

A closed-loop blood glucose control system would greatly reduce both the adverse effects of hyperglycemia and the labor required for tight glycemic control. Before developing the solution, several constraints were identified. First, the slow reaction time of subcutaneous infusions of insulin required the use of intravenous infusions. To ensure patient safety, the system must have an automated glucose infusion in the event of an emergency. Because the system is automated, the traditional 50% glucose bolus is no longer practical; thus an infusion of 20% glucose is more appropriate. Concentrations lower than 20% would risk the development of hypertension. Secondly, the control system should account for a wide range of patients and varying conditions. Third, the device should be compatible with existing continuous glucose monitors (CGM) and drug (insulin) infusion pumps. The physical dimensions of the device should be sized appropriately to fit seamlessly within either OR or SICU settings. Finally, the device needs to be easy to use; training time required to be proficient in use of the device should be on the order of hours.

In terms of control theory, because of the complexity of glucose insulin dynamic models, model predicative control and proportional–integral–derivative (PID) control were quickly eliminated. In contrast, the success of existing manual IIT protocols suggested that a controller derived from these existing protocols would be effective. Each hospital uses a slightly different infusion protocol; the controller presented is based on the protocol used at the Johns Hopkins Bayview Medical Center.

The Hopkins Protocol outlines a sequence of actions to take when administering insulin to a SICU patient. The protocol determines infusion rates based on *current blood glucose levels*, *change in blood glucose*, and *current insulin infusion rate*. The values account for kinetics and reaction time for intravenous infusions, and therefore minimal modification was needed to meet the set constraints. One shortcoming universal to all manual IIT protocols is the strict definitions of boundaries between euglycemia, hypoglycemia, and hyperglycemia. In reality, these three states are not so discretely divided. As a result, when blood glucose levels fall close to these boundaries, the recommended actions may be too extreme. This can lead to oscillations in blood glucose levels instead of achieving a target steady state.

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One solution is to apply fuzzy logic to the afore-mentioned rule-based system. Fuzzy logic uses membership functions to determine current state by weighing all the states and combining them. For example, at the lower euglycemic range, fuzzy logic will define the patient to be *mostly euglycemic* and *partially hypoglycemic*. This approach allows for much finer control of the insulin infusion rates and subsequently the patient's blood glucose levels. This allows the oscillations to be minimized, and the new system should have a shorter settling time than that of the unmodified Hopkins Protocol.

III. Results

A. System Design

Our device regulates blood glucose levels intravenously in a closed-loop system; it is targeted for the OR and SICU and can maintain a euglycemic range (between 90 and 120 mg/dl). The device is able to make closed-loop decisions using a fuzzy logic controller while adapting to varying insulin sensitivities. The controller uses eleven intuitive rules to output a change in insulin infusion rate, which allows for a controller that is adaptive to varying patient conditions.

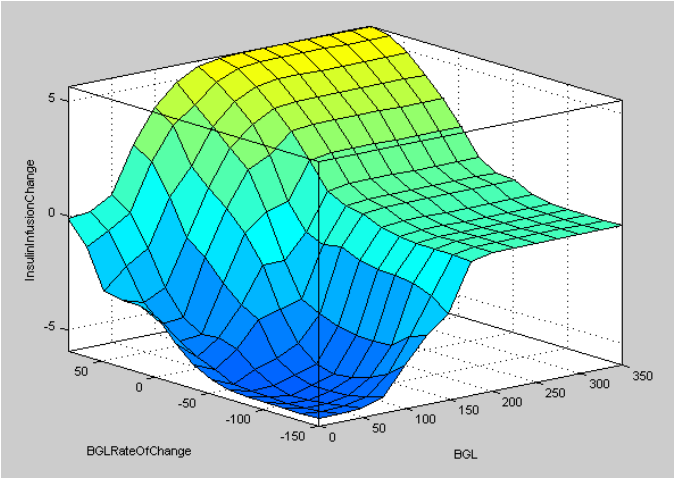

Fig. 1. Surface plot mapping three inputs to the output via eleven intuitive rules.

The fuzzy logic controller contains three inputs and one output. The inputs are (I1) the current blood glucose concentration, (I2) the rate of change of the blood glucose concentration, and (I3) the current insulin infusion rate. The output is the desired change in insulin infusion rate. Each input and output is expressed as fuzzy membership functions consisting of Gaussian and sigmoidal functions. The three inputs each possess three membership functions while the output has five. These membership functions describe imprecise concepts such as "low blood glucose" or "high blood glucose." Eleven intuitive rules map the inputs to outputs, allowing adaptation to different patient conditions. The rules are as follows:

1. If (I1 is Low) and (I2 is Negative) then (O is Negative)
2. If (I1 is Low) and (I2 is Zero) then (O is Negative)
3. If (I1 is Low) and (I2 is Positive) then (O is Zero)
4. If (I1 is Good) and (I2 is Negative) then (O is Negative)
5. If (I1 is Good) and (I2 is Zero) then (O is Zero)
6. If (I1 is Good) and (I2 is Positive) then (O is Positive)
7. If (I1 is High) and (I2 is Negative) then (O is Zero)
8. If (I1 is High) and (I2 is Zero) and (I3 is Low) then (O is Positive low)
9. If (I1 is High) and (I2 is Zero) and (I3 is Medium) then (O is Positive Low)
10. If (I1 is High) and (I2 is Zero) and (I3 is High) then (O is Positive High)
11. If (I1 is High) and (I2 is Positive) then (O is Positive)

With three inputs and three membership functions for each input, it would seem that there should be twenty-seven rules based on the possible combinations of membership functions. However, the rules were developed on an as-needed basis in order to take full advantage of the intuitive nature of fuzzy logic and reduce complexity. For example, the current insulin infusion rate was empirically determined to be necessary only at high glucose levels in order to prevent significant overshooting into the hypoglycemic range. This is seen in rules 8, 9, and 10.

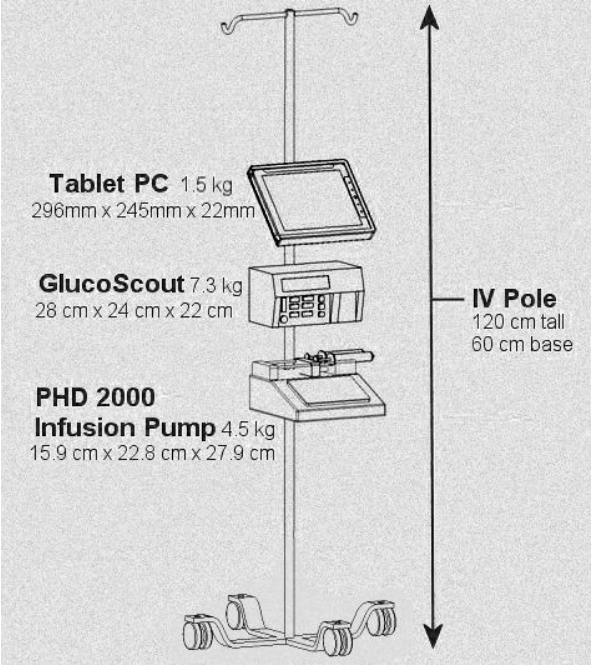

Fig. 2. Proposed setup for intensive insulin therapy system. The controller is embedded into the Tablet PC.

The blood glucose control system and graphical user interface has been embedded into a 12-inch National Instruments touch panel PC (model TPC 2012) running on Microsoft Windows XP Embedded. The device is IV pole mountable using a custom-machined C-clamp as this was determined to be the most appropriate form factor for the OR and SICU setting. The device also supports serial, USB, and Ethernet connections for compatibility with a large range of infusion pumps and continuous glucose monitors.

Both the fuzzy logic controller and the Hopkins Protocol have been implemented into the software using LabView and are accessible through the user interface. The software is also able to take manual inputs of blood glucose levels if a continuous glucose monitor is unavailable.

B. System Performance

Both versions of the controller were tested *in silico* using the Hovorka glucoregulation model [6]. This model consists of five submodels that simulate endogenous insulin secretion, insulin kinetics, glucose kinetics, insulin action, and enteral glucose absorption. In order to simulate the blood glucose levels of a critically-ill patient, the model incorporates eight ordinary differential equations and thirty-two patient dependent parameters. Parameters from six critically-ill patients were empirically determined by Hovorka; from this information, we generated a trace for untreated glucose levels, glucose controlled by the Hopkins Protocol, and glucose as controlled by the fuzzy logic controller.

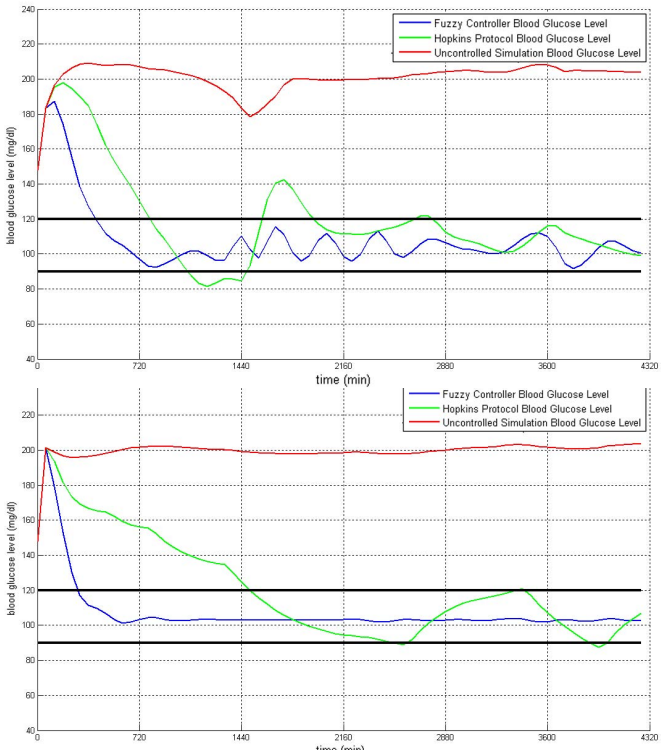

Fig. 3. Simulated studies of two patients, each performed for 72 hours. Red–Uncontrolled. Green–Hopkins protocol. Blue–Fuzzy Logic controller.

The results show that both controllers effectively bring a hyperglycemic patient into the euglycemic range. Despite changing insulin sensitivities and different patient parameters, the target range was always achieved. From these traces we were also able to measure cumulative error, hours spent in hyperglycemia, hours in euglycemia, and hours in hypoglycemia. Table 1 summarizes these results. In all categories, the fuzzy logic controller was able to meet or outperform the digital implementation of the Hopkins Protocol. Though the oscillations were not eliminated by the fuzzy logic controller, they showed a marked decrease in amplitude. The quick response of the fuzzy logic controller tended to lead the patient into slight hypoglycemia during initial stabilization, but never lasted for unsafe periods of time.

Additional simulations with this glucoregulation model continue to show that fuzzy logic consistently outperforms the unmodified Hopkins Protocol. The simulation has been rerun, with randomized parameter values to simulate a wide variety of patients. The modified fuzzy logic controller continued to outperform the Hopkins Protocol, and demonstrated a reduced initial overshoot of blood glucose levels. In terms of total error, all 201 trials outperformed the Hopkins protocol. In 196 of the trials, the fuzzy logic system spent less time in hyperglycemia than the Hopkins Protocol. In only one trial was the Hopkins protocol able to maintain euglycemia for a longer period of time. Finally, 156 of the fuzzy logic trials spent less time in hypoglycemia than their Hopkins Protocol counterparts. The results of these simulations support the that for a wide range of patient conditions, the fuzzy logic controller is superior at maintaining tight glycemic control.

HOPKINS PROTOCOL VS. FUZZY LOGIC PERFORMANCE

Category	Number of Trials where Fuzzy Logic Performed Better*	Percentage of Fuzzy Logic Trials that Performed Better
Mean Error	201	100.00%
Time Spent in Hyperglycemia	196	97.51%
Time Spent in Euglycemia	200	99.50%
Time Spent in Hypoglycemia	156	77.61%

**Out of a total of 201 trials*

IV. CONCLUSION

While the benefits of intensive-insulin therapy have been proven, the feasibility of implementing it in the OR or SICU remains uncertain. By developing an automated control system, we can close the loop between patient, CGM, and pump and make this therapy accessible and practical. The two systems that have been explored have been a digital implementation of the Hopkins Protocol, and a fuzzy logic version. Bench top testing has proven that the Hopkins Protocol can establish euglycemic control over a

patient's blood glucose levels; however, the fuzzy logic control provides greater regulation and dampened oscillations. An area of concern is the initial drop in blood glucose levels with fuzzy logic when stabilizing the patient. Slight modifications of the intuitive rules and member functions were able to lessen the effect, and additional changes should be able to eliminate the problem in the future. Further testing in rats to provide *in vivo* data will begin following protocol approval.

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