Closed Loop Control of Blood Glucose Level with Neural Network Predictor for Diabetic Patients

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***Abstract*—Despite the recent advancements in glycemic control for diabetic patients, the realization of an automated closed-loop artificial pancreas is still a challenge. The purpose of this research is to develop an integrated control system for *in silico* closed loop administration of insulin for Type 1 diabetic patients based on patients' medical record and real-time control-relevant data. The proposed system consists of a virtual patient model from the online AIDA diabetes simulator, a neural network predictor trained on patients' data for feedback purposes, and a Proportional-Integral Controller and data logging nodes. The virtual patient takes into account the delayed and time-varying insulin and carbohydrate absorption rate associated with the existing subcutaneous insulin delivery and complex glucose metabolism, respectively. The neural network predictor was trained using 23 features including semi-static and dynamic data, with built-in knowledge of all available past blood glucose levels. Then the controller calculates the infusion bolus to be delivered by the insulin pump. Extensive simulations are performed and it is shown that the neural network predictor has less Root-Mean-Square error than the currently used continuous glucose monitors, which takes measurement from the interstitial fluid. Simulation results also demonstrate that our proposed data-driven closed loop system for glycemic control can effectively regulate the blood glucose level of Type 1 diabetic patients without hypoglycemic excursions, and with no preset instruction on meal ingestion.**

***Index Terms*— Diabetes, Blood Glucose Prediction, Insulin Pump, Neural Network, Glycemic Control.**

I. Introduction

Diabetes is a disease that causes hyperglycermia (high blood glucose level) due to patient's difficulty in producing insulin - a hormone for converting glucose to energy which invariably regulate blood glucose level (BGL). The goal of the U.S. National Science Foundation's Smart and Connected Health Program is to develop solutions focused on well-being rather than disease [1]. Consequently, this work proposes a novel computational solution aimed at improving diabetic patient's well-being.

Whereas Type 1 diabetes (T1D) is characterized by absolute lack of insulin, Type 2 (T2D) is characterized by insulin resistance and relative lack of insulin. Lifelong treatment is required by both T1D and T2D patients [2]. The focus of this work is on T1D. T1D can neither be prevented nor cured but it can be treated effectively by external insulin infusion to regulate the BGL [3]. However, a challenge in insulin therapy is how to tailor insulin regimen to individual patient's need and with respect to insulin sensitivity and lifestyle [2].

Kadish developed the first insulin pump in 1964 and Biostator et. al made the first computerized insulin delivery device in the early 1980. However, early insulin pumps were impractical because they were too large, not precise and have other technical limitations [4]. The first commercial pump was made in 1983, but patients have to take finger-prick glucose measurements several times a day in order to adjust insulin doses, which led to the development of Continuous Glucose Monitors (CGMs) [5]. A challenge with CGMs is their inaccuracy, with average absolute error being 12.8mg/dL or higher depending on the type of monitor. This is partly because the time lag before systemic glucose concentration change appears in the interstitial fluid has been estimated to be 4 - 26 minutes [6]. Even with good calibration, there can be 15% to 20% error [7], and latest improvement has been marginal. Another limitation is the required re-calibration due to loss of sensitivity over time. Although the use of insulin pumps and CGMs reduces the patient's burden concerning BGL management, those devices work in open-loop fashion, which still require patient's interpretation and manual compensation for metabolic disturbances. Hence, the closed-loop control of BGL is still an open problem. The rest of the paper is organized as follows: Section II is a review of related work. Section III presents the system architecture. Blood glucose prediction model and performance are described in Section IV. Section V describes the glycemic control design and insulin delivery technique. Simulation results are presented in Section VI. Section VII concludes the paper.

II. Related Work

There have been several efforts aimed at applying control algorithms to blood glucose regulation using physiological models that describes the glucose-insulin dynamics in diabetic patients but those models do not provide accurate representation as they are over-simplified and are replete with assumptions that is unsuitable for real-life application. A fuzzy logic controller with insulin pump in the loop for glucose level regulation of the Bergman model was proposed in [8]. However, it was assumed that patients would not ingest meal for eight hours after the application of the insulin pump, BGL

can be accurately measured, and the insulin absorption pattern was over-simplified. Hence, performance of the controller to real patient may drastically deviate from the simulation result presented. The authors of [9] proposed a model-based control strategy for blood glucose regulation of the Bergman patient model using parametric programming. Assumptions for this strategy include widely spaced meal intake, over-simplified insulin absorption pattern and directly measurable BGL. The simulation of a Proportional Derivative (PD) and Proportional Integral Derivative (PID) control of Hovorka patient model was presented in [10]. Insulin absorption pattern was included in the model, and five meals of varying boluses were considered. However, it took more than 12 hours for the BGL to reach target value. A PID control strategy with insulin feedback to regulate blood glucose level was presented in [11], where supplemental carbohydrates were needed to correct hypoglycemia due to pharmacokinetic (PK) delay relating to subcutaneous delivery of insulin. An empirical algorithm for overnight blood glucose regulation based on hourly blood glucose measurement was proposed by [12], where the patients' meal intake during the day were tightly controlled in order to minimize venous BGL excursion based on the insulin therapy. The authors of [13] studied the feasibility of the Medtronic MiniMed external physiological insulin delivery system in youth with type 1 diabetes. They concluded that overnight closed-loop control performance was better than day time due to no meal disturbance and proposed an additional premeal priming bolus of insulin to improve postprandial glycemic excursions caused by peak plasma insulin action occurring 1 to 2 hours after insulin delivery. The mean relative absolute deviation of the sensor from the venous blood glucose was 13.2 +/- 10.9%, and there is concern relating to the risk of hypoglycemia.

It is also pertinent to note that machine learning techniques have been applied to predict hypoglycemic (low blood glucose level) excursions in [3] and [14]. The authors of [15] and [16] used the AIDA simulator data to train a Support Vector Machine (SVM) and Recurrent Neural Network (RNN) models respectively for BGL prediction to help patients take countermeasures against impending hyper- or hypo-periods.

An artificial pancreas is a closed - loop system consisting of synthetic components working as a substitute for endocrine pancreas [17]. But major technical problems in the development of a fully integrated closed - loop system include sensor drift, inaccuracy of the interstitial fluid glucose measurement taken by the CGM, the time lag and pattern of carbohydrate absorption, and peak insulin action occurring at about 1 to 2 hours after infusion with variability among patients [17], [18], [19]. The BGL for non-diabetic adults are less than 140mg/dL two hours after meal but does not go below 70mg/dL [20]. A practical approach to mitigate the reported technical challenges in order to achieve appropriate glycemic control is the subject of this research.

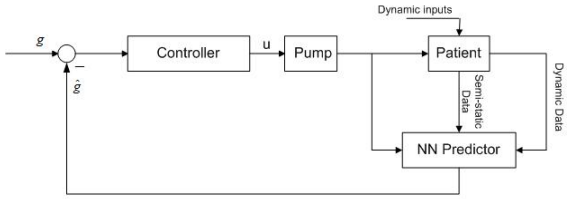


Figure 1: Data-Analytic-Enabled Blood Glucose Control Model

III. System Architecture

In this work, an integrated closed-loop system for automatic insulin administration has been proposed. It consists of a virtual patient [21], a time-shifted neural network (NN) predictor, data logging nodes, and a PI controller to compute appropriate insulin boluses by the insulin pump. The system is described in Figure 1.

The target BGL is denoted by g, whereas $\hat{g}$ denotes the BGL observation from the NN predictor, and u is the insulin infusion command. The NN predictor takes patients' semi-static data, as well as dynamic data and command signal from the insulin pump to compute BGL that will be reached at a future time for feedback purpose. This framework takes into account the delayed, continuous and time-varying action of the insulin associated with the subcutaneous insulin delivery route and provides a means to not only obtain better observation than the existing glucose monitors but also future measurements.

IV. Blood Glucose Prediction

The free online AIDA diabetes simulator [22] was used to generate data which was prepared with built-in past BGL information. Data set-up, neural network training and performance evaluation are described in the subsections below.

A. Data Set-up

The training data has 23 features that can be categorized as semi-static and dynamic for a prediction window of 9 hours. The semi-static data are the weight, renal threshold of glucose, creatinine clearance rate, hepatic insulin sensitivity, peripheral insulin sensitivity, initial plasma insulin level, and initial blood glucose level, which are denoted as wt, rtg, ccr, sh, sp, pb, and $g0$ respectively. The dynamic data are the sampling time, sampled blood glucose levels before the end of prediction window, up to three carbohydrate intake along with ingestion time within the prediction horizon, and the four infusion boluses by the insulin pump, which are denoted as t_s, $g1$, $g2$, $g3$, $g4$, $g5$, $m1$, $m1t$, $m2$, $m2t$, $m3$, $m3t$, $u1$, $u2$, $u3$, and $u4$. There were 2,100 sample data generated, which represents 300 blood glucose profile for 9 hours simulation. Knowledge of BGL history was built into the data as part of the features to enhance prediction performance. Each dynamic input vector precedes the current time step. A sampling rate of 90 minutes was selected to compensate for the delayed and time-varying subcutaneously-injected insulin action, which peaks between 1 and 2 hours. A shorter rate could lead to hypoglycemia

as insulin is administered before the last infusion could take effect. A larger rate was not selected so that glucose absorption and increase due to meal ingestion, which could be multiple, can be counter-acted in good time. Four regular-type insulin infusion were applied at the sampling rate, and up to three random-size meal can be ingested.

B. Predictor Model and Training

The complex nature of glucose metabolism and insulin delivery, as well as data-intensive management of diabetes makes machine learning models attractive for describing hidden processes. Feedforward neural network model described in (1) and (2) was employed but with knowledge of past predictor outputs built into the input data as described in the previous subsection.

$$\hat{g}_n^{(l+1)}(k) = f(x_n^{(l+1)})(k) \tag{1}$$

$$x_n^{(l+1)}(k) = w_n^{(l+1)}(k)\hat{\mathbf{g}}^l(k) + b_n^{(l+1)}(k) \tag{2}$$

where l denotes layer, n denotes unit or neuron, and k is the time step. $\hat{\mathbf{g}}^l$ is the output vector from layer l, $\mathbf{x}^l$ is the input vector into layer l, w_n^l are the weights from layer $l-1$ to unit n of layer l, and b^l are the biases from layer $l-1$ to to unit n of layer l.

A two-layer neural network model was trained with 8 hidden neurons using the Neural Network (NN) toolbox in MATLAB. Considering the heuristic that the number of sample data should be 10 times larger than the weight dimension and experimenting with different number of hidden neurons, it was observed that 8 hidden neurons was optimal for our application. Also, the built-in past BGL knowledge in our data set-up provides unique performance improvement for our application. Levenberg-Marquerdt algorithm [23], [24], [25] was used for training, which is considered a faster algorithm than the standard back-propagation algorithm, and data splitting into 70% training, 15% validation, and 15% testing was performed by 'dividerand' function.

C. Performance Evaluation

The predictor performance was measured using the Root Mean Square Error (RMSE), and the output versus target regression coefficient (R). The goal is to obtain an RMSE that is closer to zero relative to the magnitude of the predicted values and a correlation coefficient that is closer to 1. As shown in Figure 2, the training, validation and testing Mean Square Error (MSE) were 20, 29, 35 respectively. Hence, the RMSEs were 4.5, 5.4, and 5.9 mg/dL respectively, whereas, the currently used continuous glucose monitor deviates by 15% to 20% from the actual blood glucose values [7]. Also, due to the similar characteristics of the validation and test error curves, there is no significant overfitting. The regression plots in Figure 3 showed good fits between the predicted outputs and the targets with high R values.

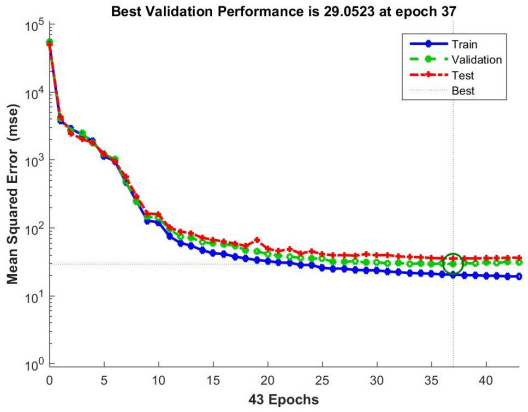


Figure 2: Neural Network Predictor Performance

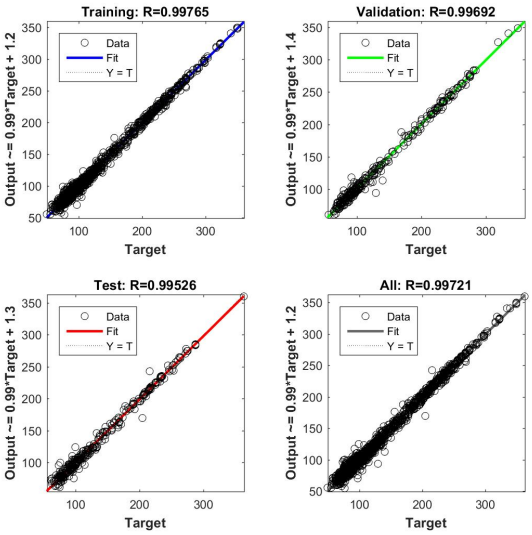


Figure 3: Neural Network Predictor Output Versus Target Regression

D. Justification for Using the AIDA simulator

The reasons for adopting the AIDA online simulator [22] utilized in generating patient's data are: 1) Real patients' data are difficult to obtain due to privacy and ethical issues. 2) Experiments on human subject is costly and time-consuming. 3) Large data set can be generated by the simulator. 4) Greater flexibility can be achieved as specific scenarios can be simulated. Furthermore, the British Diabetic Association (BDA) conducted an independent assessment based on feedback from internal assessors as well as health-care professionals. Following a fairly accurate rating by health-care professionals, the BDA decided to catalogue the simulator in the BDA's health-care professional brochure [26]. More details about the simulator model and limitations such as non capture of stress, exercise, alcohol, etc. are reported in [27] and [28].

V. Glycemic Control Design and Insulin Delivery

A PI controller was designed to compute the control command for the appropriate insulin dose at predefined discrete times. This controller is suiting to our application as it does not require the mathematical description of the complex physiological processes relating to BGL in the body to compute the control command. The insulin infusion command is a function of the difference between the target glucose level and the observation as described in (3).

$$u(k) = \begin{cases} K_p e(k) & \text{if } k = 0 \\ K_p[e(\hat{k}) + \dfrac{\Delta t}{\tau_I}(e(0) + \sum_{i=1}^{k} \ e(\hat{i}))] & \text{if } k = 1 \end{cases} \tag{3}$$

$$e(k) = g - \hat{g}(k) \tag{4}$$

$$e(\hat{k}) = g - \hat{g}(k + \tau) \tag{5}$$

The Proportional gain (K_p) and the integral gain ($\frac{K_p}{\tau_I}$) are the tunable parameters. Δt is the sample time, k is the current time step, and τ is the positive time shift. BGL observation was time-shifted by 30 minutes to capture the long-term effect of the time-varying insulin action due to subcutaneous insulin delivery for a more effective control action. Hence, $e(k)$ is the error between the BGL target and predictor output at the current time step, whereas $e(\hat{k})$ is the error between the BGL target and predictor output at a specified future time. The initial BGL observation was not time-shifted as there was prior infusion, and invariably no active insulin action. The proportional gain adjusts the insulin delivery with respect to the error signal, while the integral gain adjusts insulin delivery with respect to the sum of all past errors. The derivative term was not used as the rate of change of BGL over time fluctuates with meal disturbance and insulin infusion.

The goal of the controller is to maintain the BGL within 70mg/dL and 140mg/dL two hours after meal ingestion as typical for non-diabetic patients in [20]. The design was done using MATLAB toolbox. By tuning the control parameters, optimal performance was obtained with K_p= -0.078 and τ_I= -0.00015. The predictor, controller, and sensor nodes were integrated as shown in Figure 4. The system was implemented *in silico* using MATLAB Simulink with predictor outputs having RMSE of 5.9mg/dL relative to the virtual patient. Existing subcutaneous insulin delivery mode as well as random meal intake pattern was considered in this work. Therefore, the existing insulin pumps can be easily utilized and patients have the freedom to embrace any meal pattern of their choice. The integrated system was able to dynamically and automatically set insulin infusion without hypoglycemic excursions.

VI. Simulation Results

In order to prove the effectiveness and robustness of our system, the controller performance for five patients with diverse medical details and meal ingestion patterns were simulated as follows. The variables were selected in a way to present

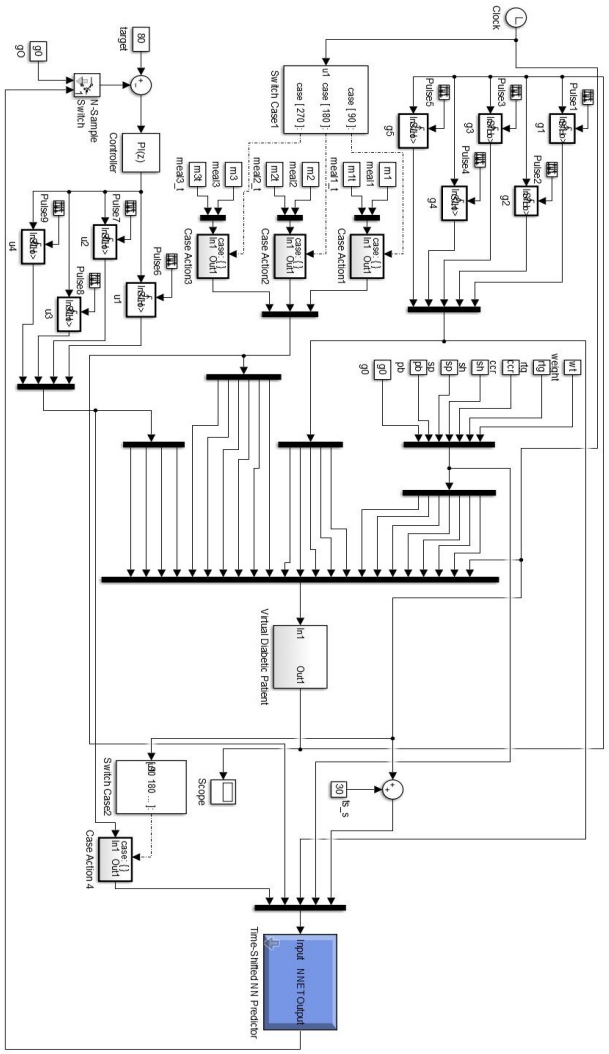


Figure 4: Integrated System Model

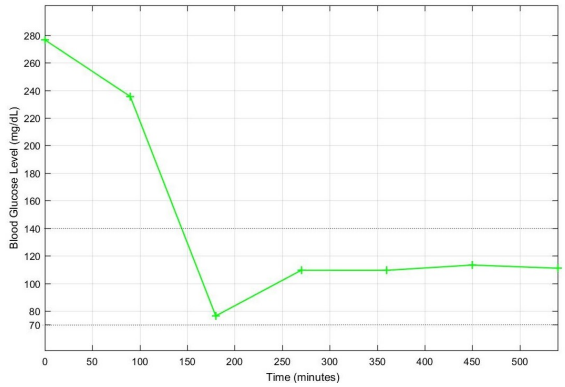
diverse situation that the system may encounter in practice as shown in Table I.

Case 1 represents a patient with relatively large weight and large carbohydrate ingestion pattern, whereas Case 2 is a patient with medium weight and medium carbohydrate ingestion pattern. A patient with small weight and small carbohydrate ingestion was described by Case 3 while Case 4 depicts a patient with large weight and medium carbohydrate ingestion. Finally, Case 5 characterize a patient with small weight but large carbohydrate ingestion. Other essential patient vitals are provided in Table I.

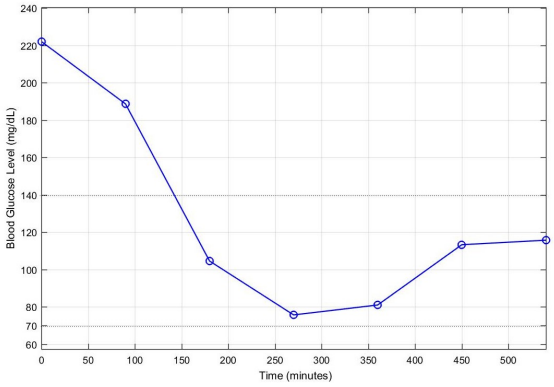
Figure 5 showed that the control system was able to keep the blood glucose level between 70mg/dL and 140mg/dL two hours after meal ingestion, which is consistent with the standard of American Diabetic Association [20] for non-diabetic patients. Based on the generated data from [22], our control system achieved the goal of normo-glycemia till the end of the simulation without hyper-or-hypoglycemic excursions in all cases that may be encountered in practice as shown in sub

Table I: Patients' Semi-static Data and Meal Ingestion Pattern

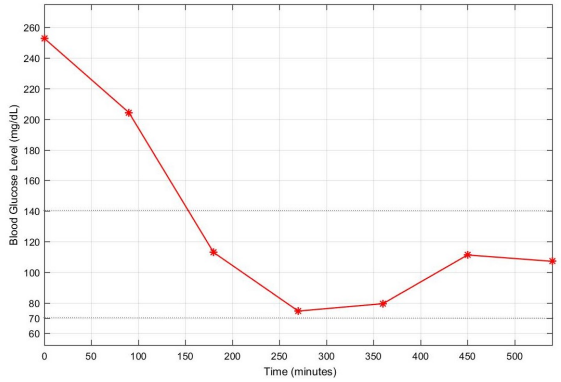
	wt(lb)	rtg(mg/dL)	ccr(mL/min)	sh	sp	m1(g)	m1t(min)	m2(g)	m2t(min)	m3(g)	m3t(min)
Case 1	191	176	120	0.8	0.8	39	30	57	120	63	245
Case 2	152	160	90	0.5	0.7	35	32	43	120	55	255
Case 3	128	121	82	0.3	0.8	28	50	23	135	39	240
Case 4	240	192	120	0.5	0.5	36	37	29	155	43	252
Case 5	101	150	100	0.7	0.8	41	40	53	142	67	265



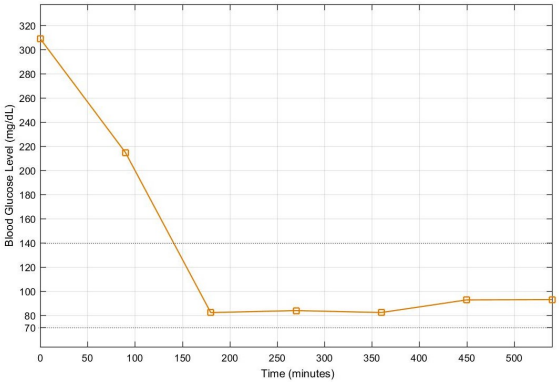
(a) Case I



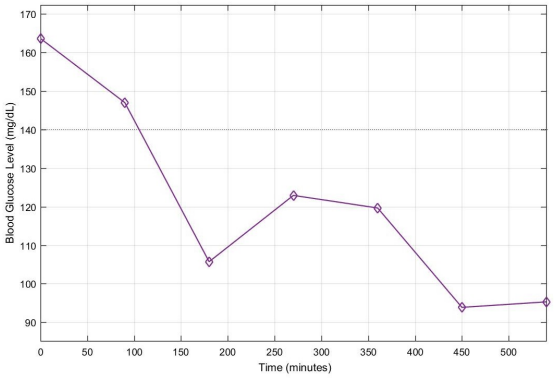
(b) Case II



(c) Case III



(d) Case IV



(e) Case V

Figure 5: Control Sytem Performance for Five Diverse Virtual Patients.

figures (a) to (e), despite varying patients' medical data and random meal intake pattern. This pre-clinical simulation set up yields results in a fraction of time required for clinical trials and can help to guide clinical experiments.

VII. Conclusion

Pharmacokinetic (PK) models of diabetic patients utilizes a theoretical number of compartments to describe elimination and absorption kinetics which may not provide enough accuracy for effective control studies. An integrated approach has been presented in this work by employing machine learning techniques. Specifically, a neural network predictor has been trained to describe the complex glucose-insulin relationships for Type 1 Diabetic patients. The predictor performance was shown to be better than that of implanted sensors which are affected by the body's immune response and delayed diffusion of the glucose from the blood to the subcutaneous tissue. Outputs from the predictor was fed back to the controller to compute insulin boluses for the virtual patient. The simulation results showed that the designed control system can effectively administer insulin automatically irrespective of the patient's meal intake pattern, and the proposed simulation framework is a time and cost effective tool for guiding clinical studies towards the development of artificial pancreas. The presented approach can be extended to Type 2 diabetes and it is expected that even better results can be obtained by utilizing more data samples. Further research will require real-patient data and consideration of other factors that may influence blood glucose level such as stress, exercise, etc., as well as *in vivo* testing of the control strategy.

VIII. Acknowledgment

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