A Cerebellar-based Approach to the Modeling of The Healthy Human Insulin Response to Food Disturbances

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EXTENDED ABSTRACT

Diabetes is a metabolic disorder where the body is no longer able to properly regulate the use and storage of glucose in the blood. The current medical treatment of diabetes primarily involves insulin medication coupled with strict dietary control. Insulin regulation is achieved by means of discrete insulin injections or premeditated insulin infusions via mechanical pumps. Discrete insulin injections are therapeutically suboptimal as insulin control is essentially open-looped. Insulin infusion through a programmable pump, on the other hand, offers the potential for closed-loop regulation of the diabetic blood glucose level due to the controllable insulin infusion rate.

The fundamental objective of a therapeutically optimal closed-loop glucose regulatory system is to artificially recreate and replicate the healthy insulin profiles in a diabetic patient in response to metabolic disturbances such as food intakes and exercises. However, current closed-loop glucose regulatory systems generally employ static mathematical models of the human glucose metabolic process to autonomously derive the amount of insulin required by a diabetic patient. These metabolic models often require re-tuning to address the metabolic biodiversity in a diabetic population as well as the intra and inter-day metabolic variability of each individual patient.

In this paper, the functional principles of the human cerebellum are harnessed to dynamically model the biological autonomic regulation of insulin in a healthy subject. This approach is motivated by the cerebellums pivotal role in facilitating many of the sub-conscious but precise cognitive and human behavioral manifestations. Specifically, a cerebellar-inspired computational model named PSECMAC is employed to functionally model the circulating plasma insulin concentration in response to serum glucose fluctuations after food ingestions in a healthy subject. The modeling capability of PSECMAC has been evaluated with the glucose metabolic data of a healthy person and a Pearson correlation exceeding 90% is achieved. The results are encouraging.

1 INTRODUCTION

Diabetes Mellitus, or commonly known as diabetes, is a chronic disease where the body is unable to properly and efficiently regulate the use and storage of glucose in the blood, leading to prolonged periods of high (hyperglycemia) or low (hypoglycemia) plasma glucose concentration. Chronic hyperglycemia causes severe damage to the eyes, kidneys, nerves, heart and blood vessels of the diabetic patients [Rubin et al. (1992)] while severe hypoglycemia can deprive the human body of its primary energy source and cause a patient to lose consciousness, which may be life threatening [Cryer (1992)]. Many of the diabetes related medical complications, fortunately, can be prevented through the tight control of the diabetic blood glucose levels [DCCT (1995)].

The current standard treatment of diabetes primarily involves insulin medication coupled with strict dietary control. The insulin hormone can be administered through discrete insulin injections or continuous insulin delivery via an insulin pump. The key component to the successful management of diabetes, however, is essentially to develop the ability to maintain a long-term near-normoglycaemia state of the patient [Rosenstock (2001)]. Hence, discrete insulin injections are not therapeutically ideal for the treatment of diabetes as the regulation of the insulin hormone is an open-loop process. Continuous insulin infusion through a programmable insulin pump, on the other hand, offers an effective approach to normalize the diabetic blood glucose level due to the controllable insulin infusion rate [Fletcher et al. (2001)].

Generally, the programmable insulin pumps are algorithmically driven and an avalanche of regulatory techniques of these insulin pumps have been proposed for diabetes treatment [Hovorka (2005); Fisher (1991)]. The fundamental objective of these insulin pumps and their closed-loop systems is to artificially re-create (via variable insulin delivery) the healthy insulin profiles in a diabetic patient so as to regulate the diabetic blood glucose level within the

homeostatic range of 60-110 mg/dl. Therefore, the performances of such pumps to manage diabetes correlate to their capability in replicating the insulin response of a healthy person. However, the majority of these insulin pumps currently employ static mathematical models of the human glucose metabolic process (obtained from data fitting of patient records, compartmentalized differential/difference equations, statistical or machine learning approaches) to compute the amount of insulin required by a diabetic patient. These models, however, often require manual tuning to cater for the metabolic biodiversity of the diabetic patients, as well as the intra and inter-day variability in the glucose metabolic rates of each specific patient [Makroglou (2006); Bellazzi et al. (2001); Parker et al. (2001)]. Consequently, these closed-loop blood glucose regulatory systems are developed with fixed insulin regimes and require strict patient compliance to function properly.

This paper proposes the use of the Pseudo Self-Evolving Cerebellar Model Arithmetic Computer (PSECMAC) network as a novel brain-inspired approach to model the healthy insulin response to external disturbances such as food intake. The human cerebellum is responsible for many sub-conscious but precise cognitive and behavioral manifestations [Kandel et al. (2000)]. Therefore, the functional principles of the human cerebellum can be harnessed in a computational framework (i.e. PSECMAC) to model the biological autonomic decision processes of the pancreatic secretion of insulin to replicate the healthy insulin profile for the treatment of diabetes. In this paper, the PSECMAC network is employed as a computational beta-cell to functionally model the biological decision process of insulin secretion in response to serum glucose fluctuations due to food ingestion. The proposed approach has a distinct advantage. The PSECMAC insulin model can be easily adapted and customized to capture the intra- and inter-day variability of the glucose metabolic process among the different individuals in the diverse population.

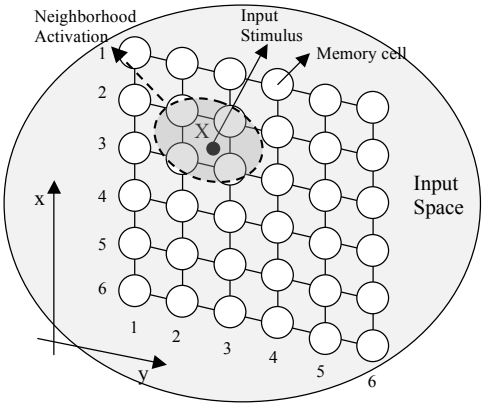
The rest of this paper is organized as follows. Section 2 briefly describe the architecture of the PSECMAC network and highlights the cerebellar-inspired memory formation and knowledge acquisition process of the network. In Section 3, the patient profile and the dietary models employed in the study are first described. Subsequently, Section 4 presents the proposed PSECMAC modeling of the healthy insulin response of the specified patient profile. The experimental results and analysis of the performances of the proposed PSECMAC insulin model are presented in Section 5. Finally, Section 6 concludes this paper.

2 THE PSECMAC NETWORK

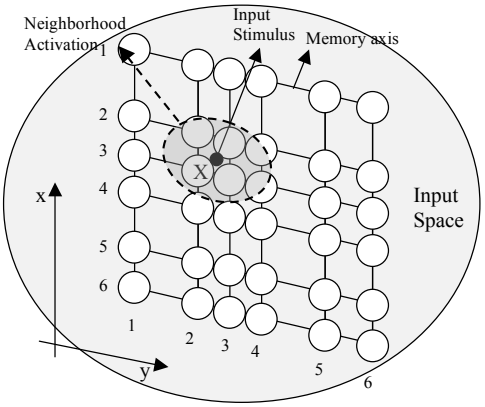
The cerebellum constitutes a part of the human brain that is important for motor control and cognitive functions [Middleton and Strick (1998)], including motor learning and memory. The human cerebellum is postulated to function as a movement calibrator [Albus (1989)], which is involved in the detection of movement error and the subsequent coordination of the appropriate skeletal responses to reduce the error. It functions by performing *associative mappings* between the input sensory information and the cerebellar output required for the production of temporal-dependent precise behaviors [Kandel et al. (2000)]. The human cerebellum has been classically modelled by the Cerebellar Model Articulation Controller (CMAC) [Albus (1975)]. As a computational model of the human cerebellum, CMAC manifests as an associative memory network, where the memory cells are uniformly quantized to cover the entire input space. The CMAC network operation is characterized by the table lookup access of its memory cells. This allows for advantages such as localized generalization and rapid algorithmic computation.

This paper proposes the use of a brain-inspired cerebellar-based learning memory model named PSECMAC as a generic functional model of the human cerebellum for solving approximation, modeling, control and classification problems. This architecture differs from the CMAC network in *two* aspects. Firstly, the PSECMAC network employs *one* layer of network cells, but maintained the computational principles of the layered-based CMAC network by adopting a neighborhood activation of its computing cells to facilitate: (1) smoothing of the computed output; (2) distributed learning paradigm; and (3) activation of highly correlated computing cells in the input space. Secondly, instead of uniform partitioning of the memory cells, the PSECMAC network employs the PSEC clustering technique [Ang and Quek (2005)] to form an experience-driven adaptive memory quantization mechanism of its network cells. Figure 1 illustrates this fundamental architectural distinction.

The adaptive quantization process of the PSECMAC network is performed in per dimension basis. The non-uniform quantization of the PSECMAC memory structure is inspired by the neurophysiological properties of the brain development, where the precise wiring in the adult brain is a result of experience-dependent refinement of initial architecture through repeated exposures to external stimuli. This experience-dependent plasticity is also observed in the human cerebellum [Federmeier et al. (2002)], and is incorporated to the PSECMAC network through the PSEC clustering algorithm. Each training data



(a) CMAC



(b) PSECMAC

Figure 1. Comparison of CMAC and PSECMAC memory quantization for 2D input problem

point is a learning episode to the network. In each input dimension, the PSEC clustering algorithm is used to compute clusters of data density, and the memory axes in each dimension are allocated based on the observed density profile of the training data. Thus, more memory cells are allocated to the densely populated regions of the input space. The details on the adaptive quantization algorithm is reported in [Teddy et al. (2007)].

The PSECMAC network employs a *Weighted Gaussian Neighborhood Output* (WGNO) computational process, where a set of neighborhood-bounded computing cells is activated to derive an output response to the input stimulus. For each input stimulus $\mathbf{X}$, the computed output is derived as follows:

1. *Step 1: Determine the region of activation*
   Each input stimulus $\mathbf{X}$ activates a neighborhood of PSECMAC computing cells. The neighborhood size is governed by the neighborhood constant parameter N, and the activated neighborhood is centered at the input stimulus (see Fig 1(b)).
2. *Step 2: Compute the Gaussian weighting factors*
   Each activated cell has a varied degree of activation that is inversely proportional to its distance from the input stimulus. These degrees of activation functioned as weighting factors to the memory contents of the active cells.
3. *Step 3: Retrieve the PSECMAC output*
   The output is the weighted sum of the memory contents of the active cells.

Following this, the PSECMAC network adopts a modified *Widrow-Hoff learning rule* [Widrow and Stearns (1985)] to implement a *Weighted Gaussian Neighborhood Update* (WGNU) learning process. The network update process is briefly described as follows:

1. *Step 1: Computation of the network output*
   The output of the network corresponding to the input stimulus $\mathbf{X}$ is computed based on the WGNO process.
2. *Step 2: Computation of learning error*
   The learning error is defined as the difference between the expected output and the current output of the network.
3. *Step 3: Update of active cells*
   The learning error is subsequently distributed to all of the activated cells based on their respective weighting factors.

3 THE SUBJECT PROFILE

The first step into the modeling of the healthy insulin response is to determine the subject profile to be employed in the study. Due to the lack of real-life patient data and the logistical difficulties and ethical issues involving the collection of such data, a well-known web-based simulator known as *GlucoSim* [GlucoSim] from the Illinois Institute of Technology is employed to simulate a person subject to generate the blood glucose and insulin data that is needed for the construction of the healthy and diabetic patient models. For this purpose, a human profile for the simulated subject (Subject A) is created and described in Table 1. The simulated person, Subject A, is a typical middle-aged Asian male. His body mass index (BMI) is 23.0 and within the recommended range for Asian.

Based on the profile of Subject A, his recommended daily allowance (RDA) of carbohydrate intake from meals is computed using an applet from the website of

Table 1. The profile of Subject A

Attribute	Value
Sex	Male
Age	40 years old
Race	Asian
Weight	67 kg (147.71 lbs)
Height	1.70 m (5 ft 7 in)
BMI	23 (Recommended for Asian)
Lifestyle	Typical office worker with moderate physical activities such as walking briskly, leisure cycling and swimming.

the Health Promotion Board of Singapore [HPBSg]. According to his sex, age, weight and lifestyle, the recommended daily carbohydrate intake for Subject A is approximately 346.9g per day.

4 THE PSECMAC INSULIN MODEL

It has been established in Matschinsky (1996) that plasma glucose is the most effective physiological nutrient stimulus of the pancreatic insulin secretion. Therefore, in this study, the PSECMAC network is employed to capture the plasma insulin response of Subject A to prior food ingestion based on the current and past plasma glucose information. Let $I_{H(A)}$ denotes the insulin profile of the healthy Subject A. The insulin relationship to be modelled by the PSECMAC network is formalized as eq. (1),

$$\hat{I}_{H(A)}(t+1) \quad = \quad \mathfrak{F}\left(\left\{Z_{H(A)}(t)\right\}\right) \qquad (1)$$

where $\hat{I}_{H(A)}(t+1)$ is the predicted blood insulin concentration at time $t+1$; $\left\{Z_{H(A)}(t)\right\}$ denotes the information set that characterizes the glucose metabolic process of the healthy Subject A due to a normal diet at time t; and $\mathfrak{F}(\cdot)$ is a nonlinear function that implements the insulin model mapping from the input metabolic variables $\left\{Z_{H(A)}(t)\right\}$ to the desired output, that is, the blood insulin concentration at the next sampling instance $I_{H(A)}(t+1)$.

The GlucoSim simulator is employed to generate a total of eight days of glucose and insulin data based on the profile of Subject A and his normal dietary habit. The carbohydrate contents and the timings of the daily meals are varied from day-to-day during the data collection phase. The GlucoSim simulator requires 10 different inputs, which consists of the body weight, the simulation period, and both the time and carbohydrate content of each of the assumed daily four meals, namely: breakfast, lunch, afternoon snack, and dinner respectively. This is to account for the inter- and intra-day variability of the eating habits of Subject A and to ensure that the PSECMAC insulin model is not being trained on a cyclical dataset but elicits the inherent relationships between food intakes and the insulin response of a healthy person. The collected metabolic data is subsequently partitioned into two groups: the first 4-days data is used for training the PSECMAC network, while the remaining 4-days data is used for the evaluation of the trained network. A sampling interval of 5 minutes is adopted to discretize the measurements of the blood glucose and insulin concentrations.

Based on the collected glucose metabolic data, a total of 18 glucose variables (consisting of the current and past blood glucose measurements and its derivatives) are extracted as inputs to model the healthy insulin profile of Subject A. These variables are outlined as Table 2. Due to the large number of input features available (18 variables), a novel feature selection algorithm named Monte Carlo Evaluative Selection (MCES) [Quah and Quek (2007)] is employed to identify the prominent features that best characterize the insulin response of a healthy person. That is, given by eq. (2),

$$\hat{I}_{H(A)}(t+1) \quad = \quad \mathfrak{F}\left(\mathfrak{R}\left(\left\{Z_{H(A)}(t)\right\}\right)\right) \qquad (2)$$

where $\mathfrak{R}$ = MCES denotes the MCES feature selection process. The reduced set of inputs/features for the normal diet is subsequently denoted by eq (3).

$$\left\{z^{H(A)}_{\text{MCES, normal}}(t)\right\} \quad = \quad \mathfrak{R}\left(\left\{Z_{H(A)}(t)\right\}\right) \qquad (3)$$

The MCES method has the advantages of (1) low computational cost; (2) the ability to identify both *correlated* and *irrelevant* features based on weight ranking; (3) being applicable to both classification and regression tasks; and (4) is independent of the underlying induction algorithm used to perform the feature selection process.

The MCES algorithm is executed independently for 50 times, where in each run, 50 iterations on the training set (first 4-days of metabolic data) is performed. The feature ranking results for 50 independent executions of the MCES algorithm are aggregated to determine the relevant features for the insulin modeling task. The salient/prominent features are identified based on their rankings and associated weights (evaluative feedback values). The top four features, namely: the current glucose level ($G(t)$), the 4-point exponential moving average (EMA) of the glucose level ($G_{\text{MA}_M}(t)$), the delta change in the glucose level over the last 5 minutes ($dG(t)$), and the 2-point EMA of the glucose level ($G_{\text{MA}_S}(t)$) are selected as the glucose indicators/inputs to the PSECMAC insulin model.

5 EXPERIMENTS AND RESULTS

A PSECMAC network with a memory size of 8 cells per dimension is constructed to model the insulin

Table 2. The glucose variables extracted to model the healthy insulin response

Feature	Definition
$G(t)$	the current blood glucose level (at t)
$G(t-1)$	the blood glucose level at $t-1$
$G(t-2)$	the blood glucose level at $t-2$
$G(t-3)$	the blood glucose level at $t-3$
$dG(t)$	$dG(t) = G(t) - G(t-1)$
$dG(t-1)$	$dG(t-1) = G(t-1) - G(t-2)$
$dG(t-2)$	$dG(t-2) = G(t-2) - G(t-3)$
$ddG(t)$	$ddG(t) = dG(t) - dG(t-1)$
$ddG(t-1)$	$ddG(t-1) = dG(t-1) - dG(t-2)$
$G_{\mathrm{MA}_S}(t)$	the 2-point exponential moving average (EMA) of the blood glucose level $G(t)$
$G_{\mathrm{MA}_M}(t)$	the 4-point EMA of the blood glucose level $G(t)$
$G_{\mathrm{MA}_L}(t)$	the 7-point EMA of the blood glucose level $G(t)$
$dG_{\mathrm{MA}_1}(t)$	$dG_{\mathrm{MA}_1}(t) = G_{\mathrm{MA}_S}(t) - G_{\mathrm{MA}_L}(t)$
$dG_{\mathrm{MA}_2}(t)$	$dG_{\mathrm{MA}_2}(t) = G_{\mathrm{MA}_S}(t) - G_{\mathrm{MA}_M}(t)$
$dG_{\mathrm{MA}_3}(t)$	$dG_{\mathrm{MA}_3}(t) = G_{\mathrm{MA}_M}(t) - G_{\mathrm{MA}_L}(t)$
$ddG_{\mathrm{MA}_1}(t)$	$ddG_{\mathrm{MA}_1}(t) = dG_{\mathrm{MA}_1}(t) - \mathrm{MA}_{N=3}(dG_{\mathrm{MA}_1}(t))$
$ddG_{\mathrm{MA}_2}(t)$	$ddG_{\mathrm{MA}_2}(t) = dG_{\mathrm{MA}_2}(t) - \mathrm{MA}_{N=3}(dG_{\mathrm{MA}_2}(t))$
$ddG_{\mathrm{MA}_3}(t)$	$ddG_{\mathrm{MA}_3}(t) = dG_{\mathrm{MA}_3}(t) - \mathrm{MA}_{N=3}(dG_{\mathrm{MA}_3}(t))$

profile of the healthy Subject A. A neighborhood size (N) of 0.1 and a Gaussian width constant (γ) of 0.3 have been empirically determined to give the optimal modeling performance. As benchmarks, the insulin modeling task is also performed using various well-established empirical models. The benchmarking models studied in this work are the basic CMAC network [Albus (1975)] and a fuzzy CMAC variant named the Fuzzy CMAC with Yager Inference Scheme (FCMAC-Yager) [Sim et al. (2006)]; a well-established neuro-fuzzy system termed the Generic Self-Organizing Fuzzy Neural Network with the Compositional Rule of Inference reasoning schema (GenSoFNN-CRI) [Tung and Quek (2004)]; as well as the classical machine learning models of the Radial Basis Function (RBF) network [WEKA] and the Multi-Layered Perceptron (MLP). The parameters for the FCMAC-Yager and the GenSoFNN-CRI systems have all been empirically optimized for best performances. There are two network structures of the MLP, each having one and two hidden layers respectively. These have also been empirically determined. The RBF network is initialized to contain 50 hidden layer nodes. In addition, the size of the CMAC network has been defined as 8 cells per dimension for a fair comparison with the PSECMAC insulin model.

Table 3 lists the *recall* (in-sample testing) and the *generalization* (out-of-sample testing) performances of the various benchmarked insulin models. *RMSE* denotes the root-mean-squared-error between the set of computed and expected insulin levels; and *PC* is the Pearson correlation coefficient, a statistical measure reflecting the goodness-of-fit between the computed and expected insulin dynamics. A *performance index* (PI_1) measure is used to combine the RMSE and the PC values of the benchmarked networks as described in eq. (5).

$$\begin{aligned} \mathrm{PI}_1 &= \frac{\mathrm{PC}}{1+\mathrm{RMSE}} \times 100 \\ \mathrm{PI}_1 &\in [-100, 100] \end{aligned} \tag{4}$$

such that a higher PI_1 value corresponds to a better overall prediction performance of the insulin model. In addition, the generalization results are also reported in terms of the *mean-absolute-error* (MAE) and the *mean-squared-error* (MSE) values of the computed insulin response. The MSE measure magnifies the larger errors between the computed and the actual insulin concentrations; hence the impact of these errors is pronounced for this measure. Together with the MAE value, this would allow one to discern amongst the insulin models that give consistent but minute errors from the insulin models that provide highly accurate predictions at most of the sampled points but with occasional large errors. The MSE and MAE measures are subsequently combined as shown in eq. (6).

$$\begin{aligned} \mathrm{PI}_2 &= \frac{\mathrm{MSE}}{1+\mathrm{MAE}} \\ \mathrm{PI}_2 &\in [0, \infty] \end{aligned} \tag{5}$$

such that a lower PI_2 value implies a more consistent prediction performance of the insulin model.

As shown in Table 3, the PSECMAC network achieved the best generalization performances among all the benchmarked models. The generalization evaluation of the PSECMAC network results in the highest PI_1 value and the lowest PI_2 value, which

Table 3. Simulation results for the various insulin models

	Recall			Generalization					
Network	**RMSE**	**PC**	**PI_1**	**RMSE**	**PC**	**PI_1**	**MAE**	**MSE**	**PI_2**
PSECMAC	**6.3011**	**0.9918**	**13.58**	**4.0737**	**0.9948**	**19.61**	**2.1187**	**16.595**	**5.32**
CMAC	4.4990	0.9958	18.11	6.6692	0.9880	12.88	4.6351	44.478	7.89
FCMAC-Yager	6.7013	0.9929	12.89	6.8474	0.9899	12.61	6.0575	46.887	6.64
GenSoFNN-CRI	6.6710	0.9944	12.96	5.8942	0.9953	14.44	4.7014	34.742	6.09
MLP (4-120-1)	26.337	0.8861	3.24	24.291	0.8552	3.38	20.666	590.05	27.23
MLP (4-20-4-1)	23.450	0.8908	3.64	21.757	0.8607	3.78	18.637	473.37	24.11
RBF	6.4141	0.9915	13.37	5.3977	0.9906	15.48	3.4419	29.135	6.56

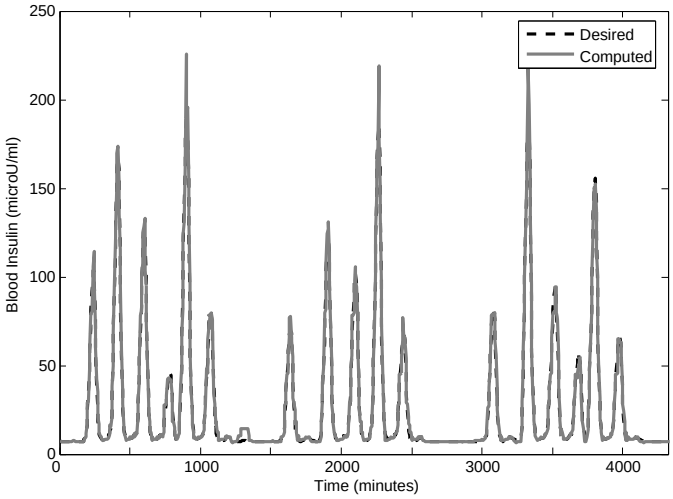


Figure 2. 3-days generalization performances of the PSECMAC networks in modeling the insulin profile of a healthy person

demonstrate the accuracy and consistency in its predicted insulin responses. The generalization results of the PSECMAC network outperformed those of the benchmarked cerebellar-based architectures (i.e. the CMAC and FCMAC-Yager networks), thereby demonstrating the effectiveness of the PSECMAC network as a cerebellar-based insulin model. While the uniform quantization process of the CMAC network results in a lower accuracy of the computed output, the FCMAC-Yager network is a Mamdani fuzzy rule-based system that adopts trapezoidal-shaped fuzzy sets as membership functions. This often leads to a low output accuracy due to the coarse granularity of the membership functions.

In addition, the PSECMAC insulin model achieved a 26.7% higher $((19.61 - 15.48)/15.48)$ PI_1 value and a 18.9% $((6.56-5.32)/5.32)$ lower PI_2 value over the best performing benchmarked non-cerebellar-based model (i.e. RBF) for the generalization evaluation. The PSECMAC network has comprehensively outperformed the benchmarked GenSoFNN-CRI neuro-fuzzy system and the classical machine learning technique-based (i.e. MLP, RBF) insulin models. The simulation results outlined in Table 3 have also demonstrated the inability of the MLP network in capturing the underlying relationships between the selected glucose indicators and the desired insulin responses. Both the 3-layers and 4-layers MLPs reported the poorest recall and generalization performances amongst the benchmarked systems.

Figure 2 depicts a 3-days snapshot of the generalization performances of the PSECMAC insulin models. Simulation results shown in Figure 2 and Table 3 have sufficiently demonstrated the highly encouraging accuracy of the PSECMAC insulin model in predicting the correct insulin response based on the selected glucose indicators.

6 CONCLUSIONS

This paper presents a cerebellar-based approach to the modeling of the healthy human insulin response to food ingestion. Motivated by the function approximation capability of the human cerebellum, this study proposed the use of the PSECMAC network, which is a computational model of the human cerebellum, to model the healthy human insulin dynamics based on the plasma glucose fluctuations. Such an insulin model can subsequently be employed in a closed-loop glucose regulatory system to control the insulin infusion rate for the

treatment of diabetes. The proposed PSECMAC-based insulin model is applied to model the insulin profile of a simulated healthy Subject A. The modeling performances of the PSECMAC speaker models are evaluated against those of the basic CMAC, FCMAC-Yager and GenSoFNN networks as well as the classical machine learning models of MLP and RBF networks. The experimental results have sufficiently demonstrated the superior modeling accuracy of the PSECMAC insulin model to the benchmarked systems.

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