

A NEUROLOGICALLY INSPIRED CEREBELLAR MODEL OF THE HUMAN BLOOD GLUCOSE METABOLIC PROCESS

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Abstract: Diabetes Mellitus or diabetes is a chronic disease where the body is unable to regulate the plasma glucose level within tight physiological bounds. Intensive insulin therapy to maintain long-term near-normoglycaemia is of key importance to the management of diabetes. Continuous delivery of insulin via an algorithmic-driven insulin pump offers the potential for close-looped regulation of the plasma glucose level in the presence of disturbances. However, an efficient model of the blood glucose dynamics is crucial to the derivation of a suitable pump control regime. Many of the classical control algorithms for insulin pumps proposed in the literature are often static and are unable to account for the variability of the glucose metabolism of a patient, especially in the presence of disturbances. On the other hand, the brain is the biological structure responsible for learning and memory. Neurophysiological studies have established that the cerebellum is a primary biological controller of motor movements and is important for a number of cognitive functions. This paper proposes the use of a neurologically inspired cerebellar-based learning memory model (HCAQ-CMAC) for the modeling of the human blood glucose metabolic process. The modeling capability of the HCAQ-CMAC network has been evaluated with the glucose metabolic data of a healthy person and a Pearson correlation exceeding 90% is achieved. The results are encouraging.

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. This resulted in large perturbations of the plasma glucose level, leading to hyperglycemia (elevated glucose level) or hypoglycemia (depressed glucose level). Chronic hyperglycemia causes severe damage to the eyes, kidneys, nerves, heart and blood vessels of the patients while severe hypoglycemia can deprive the body of energy and causes one to lose consciousness and can eventually become life threatening [1]. Currently, the treatment of diabetes is based on a two-pronged approach: strict dietary control and insulin medication. The objective of insulin therapy is to artificially re-create the insulin profiles of a diabetic patient and to regulate the blood glucose level

within tight physiological limits (typically 60-110 mg/dl) [2].

Insulin can be administered subcutaneously, intravenously or peritoneally, and it can take the form of discrete insulin injections or continuous insulin delivery via an insulin pump. Extensive studies on the advantages, disadvantages and peripheral issues regarding these insulin delivery approaches have been performed and reported in the literature [3][4].

The key importance to a successful management of diabetes is essentially the ability to maintain long-term near-normoglycaemia level of the patient. In line with this interest, the therapeutic effect of discrete insulin injections is not ideal for the treatment of diabetes as the regulation of the insulin is an open-looped process [5]. Continuous insulin infusion through an insulin pump, on the other hand, is a more viable approach to a better management of the blood glucose level due to its controllable infusion rate [6]. The workings of such insulin pumps are algorithmic-driven, with an avalanche of techniques proposed, investigated and reported in the literature over the years [7][8]. Classical control methods and advanced algorithms using implicit knowledge or explicit models (empirical, fundamental, or "gray-box") of the diabetic patient have been studied and examined in [9]-[11]. All such proposed methods required some form of modeling of the glucose metabolic process of the diabetic patient before a suitable control regime can be devised.

However, the use of classical modeling techniques (data fitting, compartmentalized differential/difference equations, statistical or machine learning approaches etc) [12]-[14] to describe the dynamics of the impaired diabetic metabolism process generally results in a rigid system, which is neither dynamically evolving nor responsive to the inter- and intra-day variability of the patient's metabolic profile.

The motivation of this paper is therefore to approach the dynamic modeling of the human blood glucose cycle; as the first step towards the regulation and control of insulin by means of an insulin pump for diabetic treatment using a brain inspired learning memory model (HCAQ-CMAC Neural Network [15]).

Materials and Methods

The first step into constructing a model of the human glucose metabolic process is to determine the patient profile to be modeled. 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* [16] (Figure 1) from Illinois Institute of Technology is employed to simulate a person subject to generate the blood glucose data that is needed for the construction of the patient model. The objective of the study is to apply the brain-inspired computational models of the cerebellar memory system to the modeling of the glucose metabolism of a healthy subject. A person profile for the simulated healthy subject is created as in Table 1.

Figure 1: The healthy person model in GlucoSim.

Table 1: Person profile of the simulated healthy subject in the research project

Profile name	Subject A
Sex	Male
Age	40 years old
Race	Asian
Weight	67 kg (147.71 lbs)
Height	1.70 m (5 ft 7 in)
BMI	23.0 (Recommended for Asian)
Lifestyle	Typical office worker with moderate physical activities such as walking briskly, leisure cycling and swimming.

The simulated healthy person, Subject A, is a typical middle-aged Asian male. His body mass index (BMI) is at 23.0, within the recommended range for Asian. Based on the person profile of Subject A, his recommended daily allowance (RDA) of carbohydrate intake from meals is computed using an applet from the website of the Health Promotion Board of Singapore [17]. According to his sex, age, weight and lifestyle, the recommended daily carbohydrate intake for subject A is approximately 346.9g per day. A total of 100 days of

glucose metabolic data for Subject A are collected. Refer to [18] for the details on the data collection.

Figure 2 illustrates a sample output from GlucoSim for Subject A. This output consists of six elements: blood glucose, blood insulin, intestinal glucose absorption rate, stomach glucose, total glucose uptake rate and liver glucose production rate of Subject A respectively over a simulated time period of 24 hours.

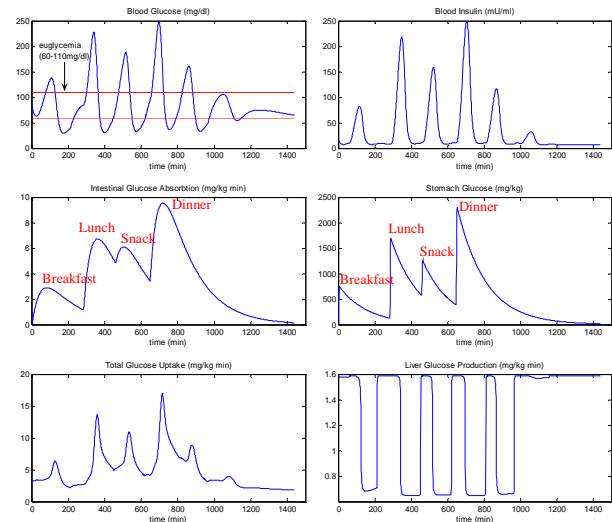


Figure 2: Sample glucose data output from the GlucoSim simulator based on a set of ten generated inputs as shown in Figure 1.

The peaks in the stomach glucose subplot of Figure 2 coincide with the timings of the assumed daily four meals (i.e. breakfast, lunch, afternoon snack and dinner) while those peaks in the intestinal glucose absorption rate subplot reflect a delay effect (response) of food intake on the blood glucose level of Subject A. The subplots of blood glucose and blood insulin illustrate the insulin-glucose regulatory mechanism in a healthy person such as Subject A and depict the dynamics of the metabolic process when subjected to disturbances such as food intake.

Since the glucose metabolic process depends on its own current (and internal) states as well as exogenous inputs (or disturbances) such as food intake, it is hypothesized that the blood glucose level at any given time is a non-linear function of prior food intakes and the historical traces of the insulin and blood glucose levels. To properly account for the effect of prior food ingestion to the blood glucose level, a historical window of six hours is adopted. To resolve the variability issue in the number of meals (and hence number of inputs) taken within the previous 6 hours, a soft-windowing strategy is adopted to partition the six hours historical windowing and weighting function into three conceptual segments, namely: *Recent Window* (i.e. previous 1 hour), *Intermediate Past Window* (i.e. previous 1 to 3 hour) and *Long Ago Window* (i.e. previous 3 to 6 hour); which are chosen to intuitively represent the human conceptual understanding and perception of time, resulting in only three food history inputs. Based on these windows, three weighting functions are introduced

to compute the carbohydrate content of meal(s) taken within the *recent*, *intermediate past* or *long ago* periods. Figure 3 depicts the weighting function for each of the segmented windows.

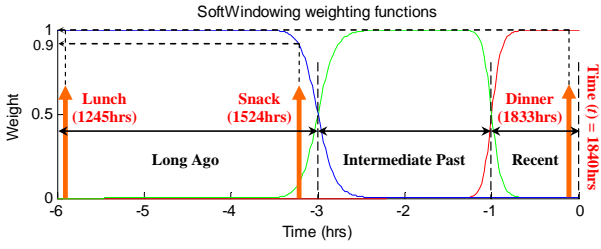


Figure 3: Soft-windowing weighting functions to compute the carbohydrate content of meal(s) in the segmented windows of the 6-hours food history.

As a modeling tool, the HCAQ-CMAC (Hierarchically Clustered Adaptive Quantization Cerebellar Model Arithmetic Computer) Network [15] was developed as a neuro-physiologically inspired enhancement of the well-established CMAC neural network [19]. First proposed in 1975 as a mathematical model of human cerebellum, CMAC is one of the most popular types of associative neural network. It possesses characteristics such as simple computation, fast training, local generalization and ease of hardware implementation. Thus CMAC is particularly suitable for real-time control and optimization [20]-[22].

As an associative memory network, CMAC memory cells are organized in such a way that the cells are evenly distributed throughout the overall input space. Therefore, memory size requirement of the network is of the main concern. The HCAQ-CMAC network solves this problem by effectively allocating the available storage space into perceptually more *important* regions of the input, i.e. regions which contain more information as compared to the rest. Figure 4 shows an example of a CMAC memory structure, as compared to those of HCAQ-CMAC, as depicted in Figure 5.

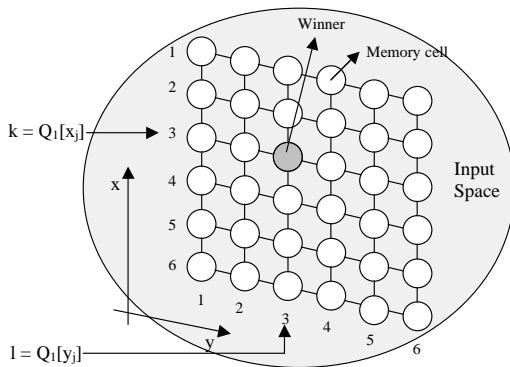


Figure 4: An example of 2D CMAC memory structure

In the HCAQ-CMAC network, agglomerative hierarchical clustering is employed to capture the input distribution and the output variation. More memory cells are allocated to those areas in which rapid changes in the target output are observed, and thereby increasing the resolution of the system.

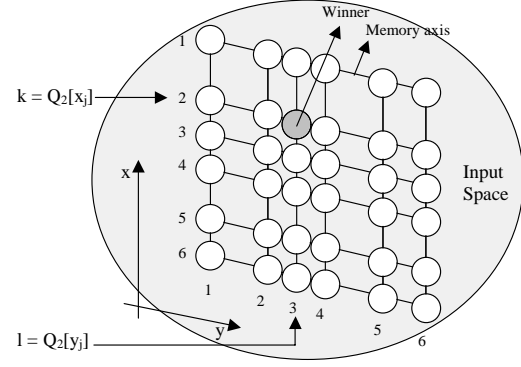


Figure 5: The 2D HCAQ-CMAC memory counterpart

The HCAQ-CMAC neural network is then employed to model and determine the highly nonlinear input-output functional associative mapping of the exogenous input (*food history*), the internal states of the metabolic process (*past blood glucose and insulin values*) and the output which is the current blood glucose level.

Results

Based on the formulated hypothesis and the preprocessed glucose data generated from GlucoSim, the HCAQ-CMAC network is employed to model the glucose metabolic process of the healthy person Subject A. The collected data set is partitioned into 2 groups: 20 days of data as training data, and the remaining 80 days is used to test the performance of the network. The modeling accuracy of the HCAQ-CMAC network is compared to those of the original CMAC and the results are tabulated in Table 2. Figure 6 gives a 3-days snapshot of the modeling accuracy of the HCAQ-CMAC network.

Table 2: Simulation results of the blood glucose modeling using HCAQ-CMAC and CMAC network

Network	Size	RMSE	P. Correlation
HCAQ-CMAC	4	12.8054	0.95797
CMAC	12	17.9334	0.91603

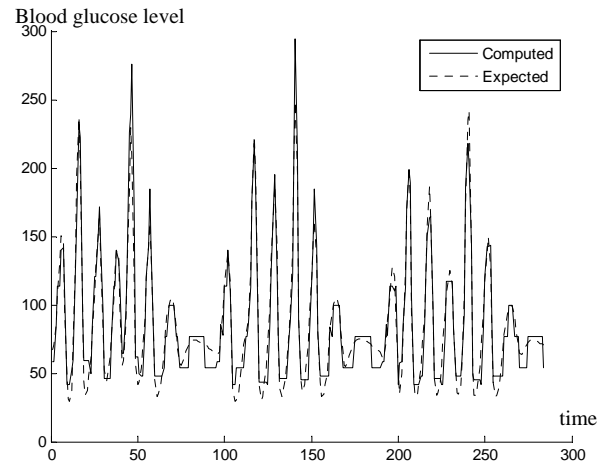


Figure 6: Modeling results of the HCAQ-CMAC system on the glucose metabolic process of Subject A.

The simulation results tabulated in Table 2 clearly justifies the proposed use of the HCAQ-CMAC network for the dynamic modelling of the human blood glucose metabolic cycle. In contrast with its CMAC counterpart, HCAQ-CMAC uses a more efficient memory allocation scheme and hence a smaller resultant network size while enhancing the fidelity of the modelling process.

Conclusions

A brain-inspired dynamically adaptive associative learning memory system as a tool to model the human blood glucose metabolic cycle has been presented in this paper. The modeling capability of the HCAQ-CMAC network has been evaluated with the glucose metabolic data of a healthy person and a Pearson correlation exceeding 90% is achieved. Future work in this direction will include benchmarking against classical modeling techniques and using the resultant HCAQ-CMAC model to the subsequent development of an algorithm-driven insulin-pump to treat diabetes.

References

- [1] Rubin R.J., Altman W.M. & Mendelson D.N. (1992). 'Health Care Expenditures for People with Diabetes Mellitus', *J. Clin. Endocrinology and Metabolism*, **78**: 809A-809F.
- [2] Ashcroft F.M. & Ashcroft S.J.H. (1992): 'Insulin: Molecular Biology to Pathology.' (Oxford University Press, New York).
- [3] Tyagi P. (2002). 'Insulin delivery systems: Present trends and the future direction', *Indian J. Pharm.*, **34**: pp.379-389.
- [4] Cobelli C. & Ruggeri A. (1983). 'Evaluation of portal/peripheral route and of algorithms for insulin delivery in the closed-loop control of glucose in diabetes – A modeling study', *IEEE Trans. Biomed. Eng.*, **30**(2): pp.93-103.
- [5] American Diabetes Association (2001). Internet site address: <http://www.diabetes.org/>
- [6] Fletcher L, Hraban G. & Huang P. *et al.* (2001) 'Feasibility of an implanted, closed-loop, blood-glucose control device', *Immunology* 230.
- [7] Schetky L.M., Jardine P. & Moussy F. (2003). 'A Closed Loop Implantable Artificial Pancreas Using Thin Film Nitinol MEMS Pumps', Proc. Int. Conf. on Shape Memory and Superelastic Technologies (SMST-2003), Pacific Grove, California, USA.
- [8] Sorensen J.T. (1985): 'A Physiologic Model of Glucose Metabolism in Man and its Use to Design and Assess Improved Insulin Therapies for Diabetes.' (PhD dissertation, Dept. of Chemical Engineering, MIT).
- [9] Ollerton R.L. (1989). 'Application of Optimal Control Theory to Diabetes Mellitus', *Int. J. Control*, **50**: pp.2503-22.
- [10] Hovorka R. (2005). 'Management of diabetes using adaptive control', *Int. J. Adapt. Control Signal Process*, **19**: pp.309-325.
- [11] Fisher M.E. (1991). 'A Semiclosed-Loop Algorithm for the Control of Blood Glucose Levels in Diabetics', *IEEE Trans. Biomed. Eng.*, **38**(1): pp.57-61.
- [12] Topp B., Promislow K. & Devries G. *et al.* (2000). 'A Model of β -Cell Mass, Insulin, and Glucose Kinetics: Pathways to Diabetes', *J Theoretical Biol.*, **206**(4): pp.605-620.
- [13] Puckett W.R. & Lightfoot E.N. (1995). 'A Model for Multiple Subcutaneous Insulin Injections Developed from Individual Diabetic Patient Data', *Am. J. Physiol.*, **269** (Endocrinol. Metab. 32), E1115-24.
- [14] Steil G.M., Murray J., & Bergman R.N. *et al.* (1994). 'Repeatability of Insulin Sensitivity and Glucose Effectiveness from the Minimal Model – Implications for Study Design', *Diabetes*, **43**: pp.1365-1371.
- [15] Teddy, S.D. & Lai, E.M-K. (2005) 'Hierarchical Clustering for Effective Memory Allocation in CMAC Neural Network', Proc. 15th International Conference on Artificial Neural Networks: Biological Aspirations – Part II, Warsaw. Poland, 2005. Lecture Notes in Computer Science, Vol.3697, Springer-Verlag, 2005, pp.473-478
- [16] GlucoSim: A Web-Based Educational Simulation Package for Glucose-Insulin Levels in the Human Body, Internet site address: <http://216.47.139.198/glucosim/gsimul.html>
- [17] Health Promotion Board, Internet site address: <http://www.hpb.gov.sg>
- [18] Tung W.L., Teddy S.D. & Zhao G. (2005). 'Neuro-Cognitive Approaches to the Control and Regulation of Insulin for the Treatment of Diabetes Mellitus. Phase 1: Neurologically Inspired Modeling of the Human Glucose Metabolic Process', Technical Report, C2i-TR-05/002, Center for Computational Intelligence, Nanyang Technological University.
- [19] Albus J.S. (1975). 'A new approach to manipulator control: The cerebellar model articulation controller (CMAC)', *J. Dynamic Syst., Measurement, Contr.*, **97**(3): pp.220-227.
- [20] Cetinkunt, S. & Donmez, A. (1993). 'CMAC learning controller for servo control of high precision machine tools,' Proc. American Contr. Conf., San Fransico, CA, 1993, pp. 1976–1980.
- [21] Larsen, G.A., Cetinkunt, S. & Donmez, A. (1995). 'CMAC neural network control for high precision motion control in the presence of large friction,' *J. Dynamic Syst., Measurement, Contr.*, **117**, pp. 415–420, 1995.
- [22] Yamamoto, T. & Kaneda, M. (1999). 'Intelligent controller using CMACs with self-organized structure and its application for a process system,' *IEICE Trans. Fundamentals*, **E82-A**(5), pp. 856–860, May 1999.