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Real-time Detection of Nocturnal Hypoglycemic Episodes using a Novel Non-invasive Hypoglycemia Monitor

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Abstract— **Hypoglycemia or low blood glucose is a common and serious side effect of insulin therapy in patients with diabetes. Hypoglycemia is unpleasant and can result in unconsciousness, seizures and even death. HypoMon is a real-time non-invasive monitor that measures relevant physiological parameters continuously to provide detection of hypoglycemic episodes in Type 1 diabetes mellitus patients (T1DM). Based on heart rate and corrected QT interval of the ECG signal, we have continued to develop effective algorithms for early detection of nocturnal hypoglycemia. From a clinical study of 24 children with T1DM, associated with natural occurrence of hypoglycemic episodes at night, their heart rates increased (1.021±0.264 vs. 1.068±0.314, P<0.053) and their corrected QT intervals increased significantly (1.030±0.079 vs. 1.052±0.078, P<0.002). It is interesting to note that QT interval and heart rate are less correlated when the patients experienced hypoglycemic episodes through natural occurrence compared to when clamp studies were performed. The overall data were organized into a training set (12 patients) and a test set (another 12 patients) randomly selected. Using the optimal Bayesian neural network which was derived from the training set with the highest log evidence, the estimated blood glucose profiles produced a significant correlation (P<0.02) against measured values in the test set.**

I. Introduction

THE Diabetes Control and Complications Trial (DCCT) Research Group in 1993 [1] has highlighted the significant benefits of intensive treatment that improves glycemic control and reduces substantially the long-term complications of diabetes. Results of the DCCT showed that intensive insulin therapy for a mean of six years (maintaining glycemic levels to a target HbA_{1c} level of 7%) as opposed to conventional therapy (with resultant mean HbA_{1c} level of 9%) significantly lowered the risk for retinopathy by 47%, nephropathy by 54%, and neuropathy by 60% [1-2].

On the other hand, episodes of hypoglycemia, especially at night, were common among people treated for T1DM, largely because usual insulin preparations do not adequately mimic the normal patterns of endogenous insulin secretion [2]. In the DDCT, patients assigned to intensive therapy experienced a threefold-increase incidence of severe hypoglycemic episodes over those receiving conventional therapy [1,3]. In that report, severe hypoglycemic episodes are defined as those in which the patient required assistance to treat the event and had documented blood glucose levels < 2.8 mmol/l (50 mg/dl). Thus, hypoglycemia proved to be a limiting factor in achieving improved diabetes control.

In T1DM patients undergoing intensive insulin therapy, falling plasma glucose concentrations often do not elicit counter-regulatory responses at normal glycemic thresholds, allowing glucose levels to drop to dangerously low values. Symptoms of hypoglycemia arise from the activation of the autonomous central nervous system (autonomic symptoms) and from reduced cerebral glucose consumption (neuroglycopenic symptoms), some of the latter being potentially life threatening. Nocturnal hypoglycemia is particularly dangerous because sleep reduces and may obscure autonomic counter-regulatory responses, so that an initially mild episode may become severe. The risk of severe hypoglycemia is high at night, with at least 50% of all severe episodes occurring during that time [4-5]. Even with modest insulin elevations, deficient glucose counter-regulation may also lead to severe hypoglycemia.

During hypoglycemia, the most profound physiological changes are caused by activation of the sympathetic nervous system. Among the strongest responses are sweating and increased cardiac output [6-8]. Sweating is mediated through sympathetic cholinergic fibres, while the change in cardiac output is due to an increase in heart rate and increase in stroke volume [8]. Tattersall and Gill [9] raised the possibility of hypoglycemia-induced arrhythmias, and experimental hypoglycemia has been shown to prolong QT intervals and dispersion in both non-diabetic subjects and in those with T1DM and T2DM [10].

In the past few years, we developed Bayesian neural network algorithms for the detection of hypoglycemic episodes in T1DM children using physiological parameters such as heart rate, corrected QT interval and skin impedance. Using the data from 25 children with T1DM for the 4-hour glucose clamp study, we found that hypoglycemic episodes in T1DM children can be detected non-invasively and continuously under glucose clamp conditions [11-13]. Recently, we have developed an optimal Bayesian neural network algorithm for the detection of natural occurrence of hypoglycemic episodes in 16 children with T1DM and confirmed that it is possible to detect hypoglycemic episodes under natural occurrence conditions [14].

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In this paper, we explore further the relevance of the detection of natural occurrence hypoglycemic episodes at night by observing relevant physiological parameters in more children with T1DM. We aim to observe the essential difference between the detection of hypoglycemic episodes under clamp and natural occurrence conditions. In addition, apart from the continued development of Bayesian neural network algorithms for early detection of hypoglycemic episodes, we are also interested in the estimation of blood glucose profiles arisen from these algorithms.

Section II provides an overview of the method used for non-invasive and continuous detection of hypoglycemia. Section III presents the development and results of an optimal Bayesian neural network algorithm used for the early detection of nocturnal hypoglycemic episodes in T1DM children. Section IV provides a conclusion for this study.

II. METHODS

A. Non-Invasive Hypoglycemia Monitor

There is a limited number of non-invasive blood glucose monitoring systems currently available but each has specific drawbacks in terms of functioning, cost, reliability and obtrusiveness. Recently, GlucoWatch G2 Biographer from Cygnus Inc was designed to measure glucose levels up to 3 times per hour for 12 hours. The AutoSensor (the disposable component) which was attached to the back of the GlucoWatch monitor and adhered to the skin will provide 12 hours of measurement. The product used reverse iontophoresis to extract and measure glucose levels non-invasively using interstitial fluid. It had to be calibrated before each measurement period and required a two-hour warm-up period. It required costly disposable components, the gel pads must be replaced after each use, sweating might cause skipped readings, and the measurement had a time delay of about 10-15 minutes. As a result of these limitations this device is no longer available.

Intensive research has been devoted to the development of hypoglycemia alarms, exploiting principles that range from detecting changes in skin conductance (due to sweating) to measurements, by glucose sensors, of subcutaneous tissue glucose concentrations [15]. However, none of these have proved sufficiently reliable or unobtrusive.

Although real-time continuous glucose monitoring systems (CGMS) are now available to give real-time estimations of glucose levels, these lack the sensitivity to be used as alarms. For the MiniMed Medtronic (Northridge, CA) CGMS, the median error was reported as 10%–15% at a plasma glucose of 4–10 mmol/l [16-18] and the low efficacy of CGMS (79.1% sensitivity) in detecting unrecognised hypoglycemia has been confirmed [19]. For the Abbott Freestyle Navigator CGMS, the sensor accuracy was lowest during hypoglycemia (3.9 mmol/l), with the median absolute relative difference (ARD) reported as 26.4% [20]. As these are median values, the errors may be significantly greater and, as a result, the manufacturers do not recommend their use as an alarm.

We have developed a continuous non-invasive hypoglycemia monitor which uses physiological responses [11-14]. HypoMon® (Hypoglycemia Monitor) from AIMedics Pty Ltd is a non-invasive monitor that measures physiological parameters continuously to provide detection of hypoglycemic episodes in T1DM patients. Associated with this device, the US patent 7,450,986 was granted in November 2008. The system consists of a battery-powered chest belt that houses a set of bio-sensor electrodes for monitoring physiological parameters and a wireless hand-held receiver computer. An alarm system is available for warning various stages of hypoglycemia.

B. Bayesian Neural Network

Bayesian neural networks were firstly introduced by MacKay as a practical and powerful means to improve the generalization of neural networks [21-24]. Bayesian learning of multi-layer perceptron neural networks is performed by considering Gaussian probability distributions of the weights which can give the best generalization [21-22]. In particular, the weights w in network X are adjusted to their most probable values given the training data D. Specifically, the posterior distribution of the weights can be computed using Bayes' rule as follows:

$$p(w \mid D, X) = \frac{p(D \mid w, X)p(w \mid X)}{p(D \mid X)} \quad (1)$$

where $p(D \mid w, X)$ is the likelihood function, which contains information about the weights from observations and the prior distribution $p(w \mid X)$ contains information about the weights from background knowledge. The denominator, $p(D \mid X)$, is known as the evidence for network X.

Regularization can be used to prevent any weights becoming excessively large, which can lead to poor generalization. For a multi-layer perceptron neural network classifier with G groups of weights and biases, a weight decay penalty term proportional to the sum of squares of the weights and biases is added to the data error function E_D to obtain the cost function:

$$S = E_D + \sum_{g=1}^{G} \xi_g E_{W_g}, \; E_{W_g} = \frac{1}{2}\left\| w_g \right\|^2 \; (g = 1,...,G) \quad (2)$$

where S is called the cost function, ξ_g is a non-negative scalar, sometimes knows as a *hyperparameter*, ensuring the distribution of weights and biases in group g and w_g is the vector of weights and biases in group g.

In network training, the hyperparameters are initialized to be arbitrary small values. The cost function is then minimized using an advanced optimization technique. When the cost function has reached a local minimum, the

hyperparameter ξ_g ($g = 1,...,G$) must be re-estimated. The number of 'well-determined' weights γ_g in group g is calculated based on the old value of ξ_g as follows [24]

$$\gamma_g = W_g - \xi_g tr\left(A^{-1} I_g\right),\ \xi_g = \frac{\gamma_g}{2E_{W_g}} \quad (g = 1,...,G) \quad (3)$$

The hyperparameters need to be re-estimated several times until the cost function value ceases to change significantly between consecutive re-estimation periods. After the network training is completed, the values of parameters γ_g and ξ_g are then used to compute the log evidence of network X_i having M hidden nodes as follows [23-24] :

$$\ln Ev(X_i) = -S + \sum_{g=1}^{G} \frac{W_g}{2} \ln \xi_g - \frac{1}{2} \ln|A| + \ln M! + M \ln 2 + \sum_{g=1}^{G} \frac{1}{2} \left(\frac{4\pi}{\gamma_g} \right) - G \ln(\ln \Omega) \quad (4)$$

where W_g is the number of weights and biases in group g, and Ω is set to be 10^3. The best network will be selected with the highest log evidence.

C. Study

Twenty-four (24) children with T1DM volunteered for the 10-hour overnight hypoglycemia study at the Princess Margaret Hospital for Children in Perth, Australia. Each patient was monitored overnight for the natural occurrence of nocturnal hypoglycemia. Data were collected with approval from Women's and Children's Health Service, Department of Health, Government of Western Australia, and with informed consent. In this group of children, severe hypoglycemia occurred at a rate of 20 episodes per 100 patient years. All experienced occasional mild hypoglycemia, as is usual during the course of treatment in adolescents with type 1 diabetes.

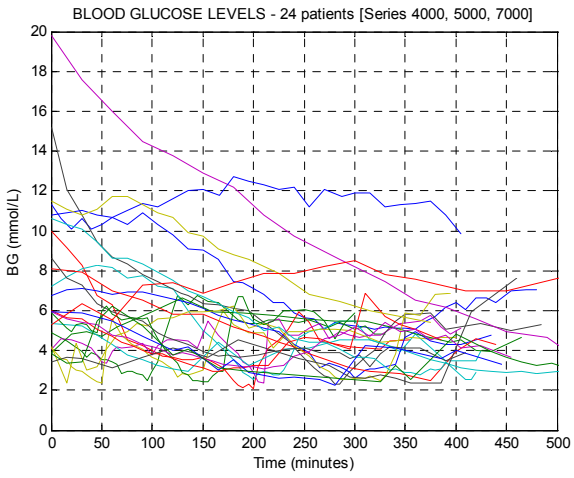

Fig. 1. Actual blood glucose level profiles in 24 T1DM children

III. RESULTS

HypoMon was used to measure the required physiological parameters, while the actual blood glucose (BG) levels were collected as reference using Yellow Spring Instruments. The four skin-surface bio-sensor electrodes are multiplexed to measure both skin impedance and ECG signals in real-time. The skin impedance circuit uses a variable frequency constant-current sinusoidal signal to generate a voltage which represents the skin impedance of the patient. The QRS detection intervals are applied to obtain average real-time heart rate values and the data acquisition sequence allows the calculation of corrected QT intervals.

The responses from 24 T1DM children exhibit significant changes during the hypoglycemia phase against the non-hypoglycemia phase. The actual blood glucose profiles are shown in Fig. 1. Normalization was used to reduce patient-to-patient variability and to enable group comparison by dividing the patient's heart rate, corrected QT interval and skin impedance by corresponding values at time zero.

The study shows that associated with hypoglycemic episodes (natural occurrence) in 24 T1DM children, using normalized values, their heart rates increase (1.021±0.264 vs. 1.068±0.314, P<0.053) and their corrected QT intervals increase significantly (1.030±0.079 vs. 1.052±0.078, P<0.002). In this clinical study of hypoglycemic detection, the reduction of skin impedance was again not strong.

It should be noted that in our previous 4-hour glucose clamp study which involved 25 patients [12], associated with hypoglycemic episodes (clamp conditions), stronger correlations for both heart rate and corrected QT interval were achieved (heart rate: 1.035±0.108 vs. 1.152±0.157, P<0.0001; QTc: 1.020±0.062 vs. 1.088±0.086, P<0.0001). This is understandable, as blood glucose profiles in T1DM patients are more predictable under clamp conditions.

The detection of hypoglycemic episodes (BG<=60 mg/dl) using these variables is based on an optimal Bayesian neural network algorithm developed from the obtained clinical data. This neural network has a multilayer feed-forward neural network structure with one hidden node layer and one output node layer. In effect, it estimates the presence of hypoglycemia at sampling period k based on the basis of the data at sampling period k and the previous data at sampling period k-1. In general, the sampling period is 5 minutes and approximately 30 data points are used for each patient.

The overall data set consisted of a training set and a test set, each with 12 patients randomly selected. For these, the whole data set which included both hypoglycemia data part and non-hypoglycemia data part were used. For optimal robustness of the evaluation, we applied the evidence framework for Bayesian inference to the training set and found the feed forward neural network architecture with 5 hidden nodes yielded the highest evidence as shown in Fig. 2. The final feed-forward multi-layer neural network had heart rate, corrected QT interval as inputs, 5 hidden nodes and 1 output node (estimated blood glucose level).

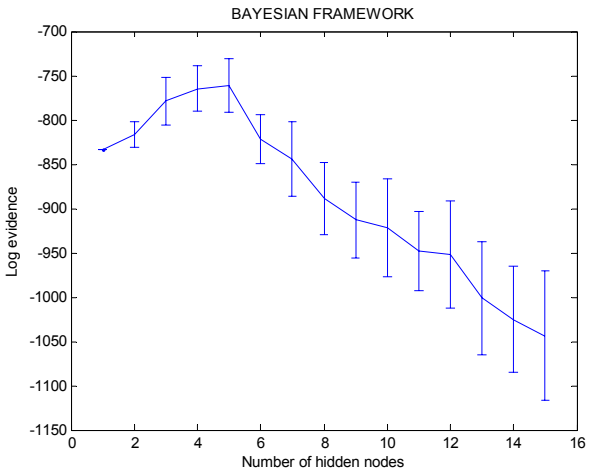

Fig. 2. Evidence framework for Bayesian inference

From the optimal neural network which was derived from the training set with the highest log evidence, estimated blood glucose profiles were produced for the test set. These estimated blood glucose values were found to be correlated significantly ($P<0.02$) to the actual blood glucose values obtained for the test set.

IV. Conclusion

The above results indicate that natural occurrence hypoglycemic episodes at night in T1DM children can be detected non-invasively and continuously from real-time physiological responses measured by HypoMon. It is noted that the relevant physiological parameters such as QTc interval and heart rate are less correlated to the actual blood glucose levels when the patients experienced hypoglycemic episodes through natural occurrence compared to when clamp studies were performed. Nevertheless, these parameters are still significant to be used effectively for early detection of nocturnal hypoglycemia episodes.

We are continuing to develop advanced algorithms to improve the overall accuracy of this real-time hypoglycemia monitor. In the future, relevant algorithms will have a real-time adaptation capability at specific times which would allow the monitor to predict hypoglycemic episodes in certain T1DM patients more accurately.

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