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(54) **A NON-INVASIVE METHOD AND APPARATUS FOR DETERMINING ONSET OF PHYSIOLOGICAL CONDITIONS**

NICHT-INVASIVES VERFAHREN UND GERÄT ZUR BESTIMMUNG DES EINSETZENS PHYSIOLOGISCHER ZUSTÄNDE

METHODE ET DISPOSITIF NON INVASIFS PERMETTANT DE DETERMINER L'APPARITION D'ETATS PHYSIOLOGIQUES

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Description

Field of the invention

[0001] The present invention relates to the modelling and design of early warning systems using physiological responses. In particular such systems can be used for early detection of medical conditions, a non-invasive hypoglycaemia monitor for example. Although this specification concentrates on a system and method for the detection of hypoglycaemia, it should be understood that the invention has wider application.

Background of the invention

[0002] Hypoglycaemia is the most common complication experienced by patients with insulin dependent diabetes mellitus. Its onset is characterised by symptoms which include sweating, tremor, palpitations, loss of concentration and tiredness. Although the majority of patients can use these symptoms to recognise the onset of hypoglycaemia and take corrective action, a significant number of patients develop hypoglycaemic unawareness and are unable to recognise the onset of symptoms.

[0003] Concerning hypoglycaemia, the blood glucose in men can drop to 3 mmol/L after 24 hrs of fasting and to 2.7 mmol/L after 72 hrs of fasting. In women, glucose can be low as 2 mmol/L after 24 hrs of fasting. Blood glucose levels below 2.5 mmol/L are almost always associated with serious abnormality. Hypoglycaemia in diabetic patients has the potential to become dangerous. In many cases of hypoglycaemia, the symptoms can occur without the awareness of the patient and at any time, eg. while driving or even during deep sleep. In severe cases of hypoglycaemia, the patient can lapse into a coma and die. Nocturnal episodes are also potentially dangerous and have been implicated when diabetic patients have been found unexpectedly dead in bed. Hypoglycaemia is one of the complications of diabetes most feared by patients, on a par with blindness and renal failure.

[0004] Current technologies used for diabetes diagnostic testing and self-monitoring are known. For example, glucose meter manufacturers have modified their instruments to use as little as 2 μl of blood and produce results in under a minute. However, devices which require a blood sample are unsatisfactory in that the sample is painful to obtain, and continuous monitoring is not possible.

[0005] There are only a few manufacturers who have produced non-invasive blood glucose monitoring systems. The Diasensor 1000 from Biocontrol Technology Inc. uses near-infrared technology and multivariate regression to estimate blood glucose levels. The system is very expensive, it has to be individually calibrated to each patient, it has to be recalibrating every three months, and the calibration process takes up to seven days. The GlucoWatch monitor from Cygnus is designed to measure glucose levels up to three times per hour for 12 hours. The AutoSensor (the disposable component) which is attached to the back of the GlucoWatch monitor and adheres to the skin will provide 12 hours of measurement. The product uses reverse iontophoresis to extract and measure glucose levels non-invasively using interstitial fluid. It requires 12 hours to calibrate, only provides 12 hours of measurement, requires costly disposable components, and the measurement has a time delay of 15 minutes. Another device, the Sleep Sentry, monitors perspiration and a drop in body temperature to alert the patient to the onset of hypoglycaemia. In studies of patients admitted for overnight monitoring it was found to be unreliable in between 5% and 20% of cases.

[0006] During hypoglycaemia, the most profound physiological changes are caused by activation of the sympathetic nervous system. Among the strongest responses are sweating and increased cardiac output. Sweating is centrally mediated through sympathetic cholinergic fibres, while the change in cardiac output is due to an increase in heart rate and increase in stroke volume.

[0007] WO 97/41772 A1 discloses an apparatus and method for monitoring a system or patient to provide information regarding the status of the system. The apparatus comprises a means of transforming measured values of more than one parameter of the system using a function dependent on at least baseline and critical values of the parameters. The apparatus further includes mapping means for mapping the function to a sequence of reference values and generating a deviation indicator for each parameter. The deviation indicators are analyzed by an analyzer to generate information concerning that status of the system or patient.

[0008] US-A-4,981,139 describes a system for monitoring the vital signs of a patient. The system includes a plurality of sensing units for sensing a plurality of physiologic conditions of a patient connected to a microprocessor that is responsive to the sensing units for providing an alarm signal in response to a deviation of a condition to an alarm state from a predetermined norm, a voice enunciating alarm responsive to an alarm signal for generating a voice sound identifying the physiological condition reaching an alarm state, an infrared transmitter having an omni-directional antenna for transmitting certain vital sign sounds and the voice sound, and a portable infrared receiver for receiving and producing the vital sign sounds and the voice sound for enabling remote monitoring of the physiological conditions.

[0009] GB 2,281,780 A describes a patient monitoring system which displays the trend of a measured parameter. The system may execute the steps of measuring values representative of a physiological parameter of a patient, determining whether the parameter values are within safe zone limits, initiating calculation of a trend vector that is a function of changes in the parameter values, when the parameter values go outside the safe zone limits, comparing the trend vector with an alarm limit function and issuing an alarm when the trend vector exceeds the alarm limit function. The alarm limit function typically varies with time after initiating calculation of the trend vector. The trend vector is calculated for each measured value until an alarm is issued or the parameter value returns to within the safe zone limits.

[0010] WO 97/15227 describes a continuous monitoring of diabete-related blood constituents according to the preamble of claim 1.

[0011] It is an object of the invention to provide a non-invasive method of detecting medical conditions in patients, which is relatively accurate and relatively inexpensive to use, and will trigger an alarm signal within an acceptable time delay from when a condition which is being monitored for presents itself.

[0012] This object is achieved by a method of claim 1 and by an apparatus of claim 7.

Summary of the Invention

[0013] According to a first aspect of the invention there is provided a non-invasive method of determining the presence or onset of a physiological condition in a person comprising the steps of:

continuously monitoring at least two of the following parameters of the patient: skin impedance, heart rate, QT interval, and mean or peak frequency of the alpha wave;
establishing whether one or more of those monitored parameters changes, and if so, the rate of change of that parameter or parameters;
feeding data obtained in the first two steps into a neural network processor programmed with a fast learning algorithm; and
causing an alarm signal to be triggered either when said neural network establishes conditions which suggest the presence or imminent onset of said physiological condition, or when said neural network has estimated the value of said physiological condition.

[0014] The monitoring of the heart rate and QT interval is preferably done with a ECG. The monitoring of the alpha wave is preferably done with an EEG. The fast learning algorithm may have either a magnified gradient function, or an optimal gradient function, or may be a robust sliding mode learning algorithm.

[0015] The invention extends to apparatus for generating an alarm when a physiological condition is present or imminent in a person, said apparatus comprising:

sensors for sensing at least two of the skin impedance, heart rate, QT interval, and mean or peak frequency of the alpha wave;
means for establishing when one or more of the sensed parameters changes and when so established, the rate of change of said changed parameters,
a neural network linked to said sensors and said means so as to receive a substantially continuous data stream from said sensors and said means, the neural network being programmed with a fast learning algorithm and adapted to establish when the sensed parameters, and any change to those parameters, for a particular person are such as to indicate the presence or imminent onset of said physiological condition,
and alarm means linked to said neural network adapted to be triggered when the presence or imminent onset of said physiological condition is established.

[0016] The apparatus may include a magnified gradient function, an optimal gradient function, or is a robust sliding mode learning algorithm.

Brief Description of the Drawings

[0017]

Figure 1 shows the basic structure of a two-layer feed forward neural network.
Figure 2 shows blood glucose level estimations using multiple regression (left) and neural network (right) for three diabetic patients.

Detailed Description of the Invention

[0018] In the development of the device, analysis of the effectiveness of skin impedance, ECG (in particular heart rate and QT interval) and EEG by means of a robust neural network provides a novel basis for early detection of a medical condition such as hypoglycaemia as well as an indirect measurement of blood glucose levels. There are numerous factors which can affect the accuracy with which a medical condition is precluded such as environment conditions, stress, and the like. The device should be capable of differentiating between effects caused by environmental conditions and those which indicate the presence of or onset of a particular medical condition.

[0019] The possibility of hypoglycaemia induced arrythmias, and experimental hypoglycaemia has been shown to prolong QT intervals and dispersion in both non-diabetic subjects and in those with Type 1 and Type 2 diabetes. Another important physiological change is that a slowing of the α rhythm in EEG (8-13 Hz) in response to hypoglycaemia appears at blood glucose values of approximately 2.5 mmol/L and is the earliest abnormality.

[0020] In broad terms, a device which is capable of initiating and correctly interpreting a wide range of physiological signals could be used for the detection of conditions such as hypoglycaemia, hyperglycaemia, or may be used to provide indirect measurement of blood glucose levels. It may also be used for the detection of sudden infant death syndrome, chronic stress, sleep disorders and driver fatigue for example. Indeed, other medical conditions which present themselves by a range of different physiological indications could be detected using the method and apparatus of the invention. Because physiological signals differ from patient to patient it is important that a device is able to "learn" when a particular set of signals represent the onset or presence of a medical condition in a particular patient, and disregard false signals which might be caused by environmental or other factors.

[0021] There are many different ways to implement the signal sensing and signal conditioning for the device. One implementation strategy can be described as follows.

[0022] Skin moisture (sweating) can be measured using skin impedance monitoring. A concentric type electrode may be used which contains an outer passive electrode (10mm inner and 20mm outer diameter) and an inner electrode (5mm diameter). A sinusoidal constant current source of 100kHz 10μA may be applied by a Wien bridge oscillator to the inner electrodes, and a voltage produced in accordance to the skin impedance, at the outer electrode. The signal from the outer electrode may be amplified by an instrumentation amplifier, passed through a Butterworth low-pass filter (cut-off freq = 140kHz) and fed through an AC-DC converter to produce a DC signal proportional to the skin impedance.

[0023] The ECG may be achieved by placing three Ag-AgCl electrodes in a LeadII configuration on the patient's chest. The signal obtained from the electrodes may then be amplified using an instrumentation amplifier with gain of 10 and CMRR > 100dB at 100Hz. This feeds through a high-pass filter with cutoff frequency of 0.5Hz. A second stage non-inverting amplifier may be added to provide a gain of 100. To obtain a reliable heart rate of the patient, a bandpass filter may be used, to detect the QRS complex of the ECG signal. A threshold circuit together with a comparator may be used to reliably detect the R slope. The QT interval, on the other hand is a clinical parameter which can be derived from the ECG signal. During hypoglycaemia, the QT interval increases. QT measurement requires the identification of the start of QRS complex and the end of the T wave. The intersection of the isoelectric line and a tangent to the T wave can be used to measure the QT interval.

[0024] EEG signals may be obtained using a pair of Ag-AgCl electrodes on O_1 and O_2 sites on the posterior cortex. The conditioning circuitry includes a two op-amp instrumentation amplifier to obtain high overall gain. Low voltage and current noise CMOS amplifiers may be used for EEG recordings to reproduce these signals for diagnostic purposes. In this instrumentation amplifier configuration, an integrator in the feedback loop provides a low overall gain for the low-frequency input signals. For high resolution, the digital sampling rate per channel may be 256 Hz and data may be stored in one-second epochs. Signals may be analysed using Fast Fourier Transform (FFT). The mean frequency or the peak frequency of the α wave in EEG can then be derived.

[0025] The monitoring for hypoglycaemia and blood glucose level is difficult because of imperfections caused by possible conflicting or reinforcing responses from skin impedance, ECG and EEG. This conflicting information is handled in the framework of a robust neural network in order to obtain accurate determinations from a complex uncertain non-linear physiological system.

[0026] For hypoglycaemia detection using a combination of four variables (skin impedance, heart rate, QT interval and mean or peak frequency of the α wave) the analysis is akin to a black box belonging to a given class of nonlinear systems. A neuro-estimator is suitable for complex estimates. A neuro-estimator may be embedded in an EEPROM of the system to monitor hypoglycaemia episodes in patients. This neural network has a multilayer feedforward neural network structure with one input layer, one hidden layer and one output layer as shown in Figure 1. Essentially, this neural network is trained using a learning algorithm in which synaptic strengths are systematically modified so that the response of the network will increasingly approximate the blood glucose status given by the available qualitative data.

[0027] The back-propagation (BP) algorithm is a widely applied multilayer neural-network learning algorithm. Unfortunately, it suffers from a number of shortcomings. One such shortcoming is its slow convergence. A preferred system will implement real-time learning so as to be able to adapt to the physiological signals of individual patients.

[0028] The learning algorithms for updating the weight matrices may be based on a magnified gradient algorithm or a sliding mode strategy. The gradient descent back-propagation (BP) learning algorithm for updating the weight matrices, the error signal terms for output layer and hidden layer respectively can be found from:

$$\delta_k = -\frac{\partial E}{\partial v_k} = (R_k - z_k)\frac{\partial z_k}{\partial v_k} \qquad \bar{\delta}_j = -\frac{\partial E}{\partial \bar{v}_j} = \frac{\partial y_j}{\partial \bar{v}_j}\sum_{k=1}^{K}\delta_k w_{kj}$$

$$\mathbf{W}^* = \mathbf{W} - \eta\frac{\partial E}{\partial \mathbf{W}} = \mathbf{W} + \eta\delta\mathbf{y}' \qquad \overline{\mathbf{W}}^* = \overline{\mathbf{W}} - \eta\frac{\partial E}{\partial \overline{\mathbf{W}}} = \overline{\mathbf{W}} + \eta\bar{\delta}\mathbf{x}'$$

[0029] For faster network convergence suitable for real-time learning, a magnified gradient function (MGF) in adaptive learning can be used, where the error signal terms for output layer and hidden layer can be magnified with a constant S (usually between 1 and 5):

$$\delta_j = -\frac{\partial E}{\partial \bar{v}_k} = (R_k - z_k)\left(\frac{\partial z_k}{\partial v_{kj}}\right)^{\frac{1}{S}} \qquad \bar{\delta}_j = -\frac{\partial E}{\partial \bar{v}_j} = \left(\frac{\partial y_j}{\partial \bar{v}_j}\right)^{\frac{1}{S}}\sum_{k=1}^{K}\delta_k w_{kj}$$

$$\left|\left(\frac{\partial E}{\partial t}\right)_{MGF}\right| - \left|\left(\frac{\partial E}{\partial t}\right)_{BP}\right| > 0$$

[0030] MGF-PROP retains the gradient-descent property and the convergence rate of MGF-PROP is faster than that of BP. This algorithm can be implemented in real-time relatively easily.

[0031] Similar to the above solution, it is also possible to develop a back propagation algorithm based on sliding mode for updating the weight matrices. This type of algorithm should be faster as the rate of convergence can be controlled, and is more robust against parameter uncertainty and strong disturbances, as the error will be forced to slide along a pre-determined hyperplane.

[0032] In order to detect hypoglycaemia episodes reliably, it is not a simple matter of just using a combination of the above-mentioned parameters: skin impedance, heart rate, QT interval, mean or peak frequency of the α wave. The main difficulty is different patients have different base values of these parameters. In addition, these base values may vary from day to day.

[0033] False detection may arise from other environmental or personal conditions which could cause similar variations in sweating and heart rate such as the occurrence of nightmares, sudden change in weather, etc. Avoidance of false detection is important if the system is to be relied on by sufferers of acute or life threatening conditions.

[0034] As a consequence, the main parameters used for the detection of hypoglycaemia are not only skin impedance, heart rate, QT interval or mean/peak frequency of the α wave, but also their rates of change. The additional parameters are the rates of change in skin impedance, heart rate, QT interval and mean/peak frequency of the α wave. Other important parameters are the time constants associated with these physiological responses. Rates of changes and the time constants inherent in physiological responses are important factors which can be used to reject or minimise false detection.

[0035] It is possible to model the dynamic neural network which is used to estimate blood glucose levels as:

$$\frac{d\mathbf{x}}{dt} = f(\mathbf{x}) + g(\mathbf{x}).\mathbf{u}$$

$$z = \sigma[\mathbf{W}.\phi(\overline{\mathbf{W}}\mathbf{x})]$$

where x is the state of the neural network and σ and ϕ are sigmoidal vector functions. Note that x contains the skin impedance, heart rate, QT interval, peak frequency of the α wave, and their rates of changes. The nonlinear functions *f*(x) skin impedance, heart rate, QT interval, and peak α frequency respond to a reduction of blood glucose levels.

[0036] The above model also allows the identification of model variations and disturbances to ensure that the convergence of the learning algorithm is assured. This is important for providing real-time neural network adaptation to a specific patient for the detection of a physiological condition such as hypoglycaemia under various conditions.

[0037] Using the above important main parameters for hypoglycaemia detection, the learning algorithms for updating the weight matrices based on a magnified gradient algorithm or a sliding mode strategy allows the neural network to adapt on-line to a particular patient very effectively or to provide robust estimation in the presence of disturbances (initial state, system and observation noises) to minimise false detection.

[0038] A combination or all of these parameters are fed into a generic neural network for the detection of hypoglycaemia or the estimation of blood glucose levels. Figure 2 shows the estimation of blood glucose levels using only skin impedance and heart rate for three diabetic patients. In Figure 2, the result of a multiple regression technique used to evaluate corresponding blood glucose levels is shown on the left with good correlation (R^2 = 0.792), and the result of a trained neural network is shown on the right with a very strong correlation (R^2 = 0.977).

[0039] It is envisaged that the device, once properly trained, should be capable of not only determining the onset or presence of a condition, but also able to assign a value to that condition. Thus, for example, if the device is able to accurately estimate actual blood glucose levels, then the patient should be able to use that estimation to modify quantum and timing of medication.

[0040] In practice, a trained neural network would be obtained off-line for many patients, but the described neural network should have the ability to adapt to a particular patient. This hypoglycaemia monitor can quickly fine tune the neural network for better estimation of blood glucose levels or hypoglycaemia conditions, using either the magnified gradient function back propagation technique (MGF-PROP) or the sliding mode back propagation technique (SM-PROP). Both of these two techniques can be implemented in real-time with very fast convergence.

[0041] It is envisaged that communication between the sensors and the processor may be via a telemetric system. Radio frequency transmitters and receivers or transceivers (typically 433 MHz or 2.4GHz) may be used.

[0042] The alarm may be of any convenient type, and might comprise a simple radio alarm, a signal transmitted to a monitoring station, or the like.

[0043] It is also preferred that data transmitted from the sensors will be continuously logged. The system may be interfaced with a PC which will continuously log the relevant data using a data management system such as Labview.

[0044] Clearly the invention can vary from that described herein without departing from the scope of the invention. In particular the fast learning algorithm need not be of the type described herein, but any fast learning algorithm that is able to provide substantially real time analysis of multiple data streams in the manner described herein could be used.

Claims

1. A non-invasive method of determining the presence or onset of a hypoglycaemic condition in a patient known to be susceptible to hypoglycaemia comprising the steps of:

   continuously monitoring at least two parameters of the patient from the set comprising skin impedance, heart rate, QT interval, and mean or peak frequency of an alpha wave;
   establishing whether one or more of those monitored parameters changes, and if so, establishing the rate of change of that parameter or parameters; **characterized in that** said method further comprises the steps of
   feeding data obtained by said monitoring and establishing steps into a neural network processor programmed with a fast learning algorithm that adapts a neural network for detection of the hypoglycaemic condition of the patient; and
   causing a signal to be generated when said neural network establishes conditions which suggest the presence or imminent onset of said hypoglycaemic condition for the patient.

2. A non-invasive method according to claim 1 wherein the monitoring of the heart rate and QT interval is done with an ECG.

3. A non-invasive method according to either of the preceding claims wherein the monitoring of the alpha wave is done with an EEG.

4. A non-invasive method according to any preceding claim wherein the fast learning algorithm has either a magnified gradient function or an optimal gradient function.

5. A non-invasive method according to any one of claims 1 to 3 wherein the fast learning algorithm is a robust sliding mode algorithm.

6. A non-invasive method according to any one of the preceding claims wherein the neural network processor is adapted to estimate a blood glucose level of the patient and the method comprises:

   causing a signal to be generated when said neural network has estimated the blood glucose level.

7. Apparatus for generating an alarm when hypoglycaemia is present or imminent in a patient known to be susceptible to hypoglycaemia, said apparatus comprising:

   sensors for sensing at least two of the patient's parameters from the set comprising skin impedance, heart rate, QT interval, and mean or peak frequency of an alpha wave;
   means for establishing when one or more of the sensed parameters changes and when so established, a rate of change of said changed parameters, **characterized in that** said apparatus further comprises
   a neural network linked to said sensors and said means so as to receive a substantially continuous data stream from said sensors and said means, the neural network being programmed with a fast learning algorithm that adapts the neural network to establish when the sensed parameters, and any change to those parameters, for a particular person are such as to indicate the presence or imminent onset of a hypoglycaemic condition, and
   alarm means linked to said neural network adapted to be triggered when the presence or imminent onset of said hypoglycaemic condition is established.

8. Apparatus according to claim 7 wherein the fast learning algorithm has either a magnified gradient function or an optimal gradient function.

9. Apparatus according to claim 7 wherein the fast learning algorithm is a robust sliding mode algorithm.

10. Apparatus according to any one of claims 7 to 9 wherein an ECG is used to obtain the data for the heart rate and QT interval.

11. Apparatus according to any one of claims 7 to 10 wherein an EEG is used to obtain the data for the mean or peak alpha wave.

12. Apparatus according to any one of claims 7 to 11 wherein data is transmitted between the sensors and the neural network by a radio-frequency telemetric system.

13. Apparatus according to any one of claims 7 to 12 wherein the device is adapted to estimate an actual value of a hypoglycaemic condition of a patient.

14. Apparatus according to claim 13 wherein the hypoglycaemic condition which the device is adapted to estimate is the blood glucose level of the patient.

Patentansprüche

1. Ein nicht invasives Verfahren zum Bestimmen des Vorhandenseins oder Einsetzens eines hypoglykämischen Zustands bei einem Patienten, der bekanntermaßen unter Hypoglykämie leidet, das folgende Schritte aufweist:

   kontinuierliches Überwachen von zumindest zwei Parametern des Patienten aus dem Satz, der Hautimpedanz, Herzfrequenz, QT-Intervall und Mittel- oder Spitzen-Frequenz einer Alphawelle umfasst;
   Bestimmen, ob sich einer oder mehrere dieser überwachten Parameter ändern, und wenn ja, Bestimmen der Änderungsrate dieses Parameters oder dieser Parameter;
   dadurch gekennzeichnet, dass das Verfahren ferner folgende Schritte aufweist
   Zuführen von Daten, die durch den Schritt des Überwachens und Bestimmens erhalten werden, in einen Neurales-Netz-Prozessor, der mit einem schnell lernenden Algorithmus programmiert ist, der ein neurales Netz zur Erfassung des hypoglykämischen Zustands des Patienten anpasst; und
   Verursachen, dass ein Signal erzeugt wird, wenn das neurale Netz Zustände bestimmt, die das Vorhandensein oder das direkt bevorstehende Einsetzen des hypoglykämischen Zustands für den Patienten nahelegen.

2. Ein nicht invasives Verfahren gemäß Anspruch 1, bei dem das Überwachen der Herzfrequenz und des QT-Intervalls mit einem EKG ausgeführt wird.

3. Ein nicht invasives Verfahren gemäß einem der vorangehenden Ansprüche, bei dem das Überwachen der Alphawelle mit einem EEG ausgeführt wird.

4. Ein nicht invasives Verfahren gemäß einem der vorangehenden Ansprüche, bei dem der schnell lernende Algorithmus entweder eine Vergrößerter-Gradient-Funktion oder eine Optimaler-Gradient-Funktion aufweist.

5. Ein nicht invasives Verfahren gemäß einem der Ansprüche 1 bis 3, bei dem der schnell lernende Algorithmus ein Robust-Gleitmoden-Algorithmus ist.

6. Ein nicht invasives Verfahren gemäß einem der vorangehenden Ansprüche, bei dem der Neurales-Netz-Prozessor angepasst ist, um einen Blutzuckerspiegel des Patienten zu schätzen und das Verfahren folgenden Schritt aufweist:

   Verursachen, dass ein Signal erzeugt wird, wenn das neurale Netz den Blutzuckerspiegel geschätzt hat.

7. Vorrichtung zum Erzeugen eines Alarms, wenn eine Hypoglykämie vorhanden oder direkt bevorstehend ist bei einem Patienten, der bekanntermaßen für Hypoglykämie anfällig ist, wobei die Vorrichtung folgende Merkmale aufweist:

   eine Vorrichtung zum Erfassen von zumindest zwei Parametern des Patienten aus dem Satz, der Hautimpedanz, Herzfrequenz, QT-Intervall und Mittel- oder Spitzen-Frequenz einer Alphawelle umfasst;
   eine Einrichtung zum Bestimmen, wenn sich einer oder mehrere dieser überwachten Parameter ändern, und wenn dies der Fall ist, Bestimmen einer Änderungsrate der veränderten Parameter; **dadurch gekennzeichnet, dass** die Vorrichtung ferner folgendes Merkmal aufweist
   ein neurales Netz, das mit den Sensoren und der Einrichtung verbunden ist, um einen im Wesentlichen kontinuierlichen Datenstrom von den Sensoren und der Einrichtung zu erhalten, wobei das neurale Netz mit einem schnell lernenden Algorithmus programmiert ist, der das neurale Netz anpasst, um zu bestimmen, wann die erfassten Parameter und jegliche Änderungen an diesen Parametern für eine bestimmte Person derart sind, dass sie das Vorhandensein oder das bevorstehende Einsetzen eines hypoglykämischen Zustands anzeigen, und
   eine Alarmeinrichtung, die mit dem neuralen Netz verbunden ist und angepasst ist, um ausgelöst zu werden, wenn das Vorhandensein oder das direkt bevorstehende Einsetzen der hypoglykämischen Bedingung bestimmt wird.

8. Vorrichtung gemäß Anspruch 7, bei der der schnell lernende Algorithmus entweder eine Vergrößerter-Gradient-Funktion oder eine Optimaler-Gradient-Funktion aufweist.

9. Vorrichtung gemäß Anspruch 7, bei der der schnell lernende Algorithmus ein Robust-Gleitmoden-Algorithmus ist.

10. Vorrichtung gemäß einem der Ansprüche 7 bis 9, bei der ein EKG verwendet wird, um die Daten für die Herzfrequenz und das QT-Intervall zu erhalten.

11. Vorrichtung gemäß einem der Ansprüche 7 bis 10, bei der ein EEG verwendet wird, um die Daten für die mittlere oder Spitzen-Alphawelle zu erhalten.

12. Vorrichtung gemäß einem der Ansprüche 7 bis 11, bei der Daten zwischen den Sensoren und dem neuralen Netz durch ein Hochfrequenz-Telemetriesystem übertragen werden.

13. Vorrichtung gemäß einem der Ansprüche 7 bis 12, bei der das Bauelement angepasst ist, um einen tatsächlichen Wert eines hypoglykämischen Zustands eines Patienten zu schätzen.

14. Vorrichtung gemäß Anspruch 13, bei der der hypoglykämische Zustand, an den das Bauelement angepasst ist, um diesen zu schätzen, der Blutzuckerspiegel des Patienten ist.

Revendications

1. Procédé non invasif pour déterminer la présence ou l'apparition d'un état hypoglycémique dans un patient connu comme étant susceptible à l'hypoglycémie, comprenant les étapes consistant à:

surveiller en continu au moins deux paramètres du patient parmi l'ensemble comprenant l'impédance de la peau, le rythme cardiaque, l'intervalle QT, et la fréquence moyenne ou de pointe d'une onde alpha;
établir si l'un ou plusieurs de ces paramètres surveillés changent et, dans l'affirmative, établir le taux de changement de ce paramètre ou ces paramètres;

caractérise par le fait que ledit procédé comprend par ailleurs les étapes consistant à:

alimenter les données obtenues par lesdites étapes de surveillance et d'établissement vers un processeur de réseau neural programmé avec un algorithme d'apprentissage rapide qui adapte un réseau neural pour la détection de l'état hypoglycémique du patient; et
faire générer un signal lorsque ledit réseau neural établit des états qui suggèrent la présence ou l'apparition imminente dudit état hypoglycémique pour le patient.

2. Procédé non invasif selon la revendication 1, dans lequel la surveillance du rythme cardiaque et de l'intervalle QT s'effectue à l'aide d'un ECG.

3. Procédé non invasif selon l'une ou l'autre des revendications précédentes, dans lequel la surveillance de l'onde alpha s'effectue à l'aide d'un EEG.

4. Procédé non invasif selon l'une ou l'autre revendication précédente, dans lequel l'algorithme d'apprentissage rapide présente soit une fonction de gradient amplifié, soit une fonction de gradient optimal.

5. Procédé non invasif selon l'une quelconque des revendications 1 à 3, dans lequel l'algorithme d'apprentissage rapide est un algorithme de mode de glissement robuste.

6. Procédé non invasif selon l'une quelconque des revendications précédentes, dans lequel le processeur de réseau neural est adapté pour estimer un niveau de glucose dans le sang du patient et le procédé comprend:

faire générer un signal lorsque ledit réseau neural a estimé le niveau de glucose dans le sang.

7. Appareil pour générer une alarme lorsque de hypoglycémie est présente ou apparaît dans un patient connu comme étant susceptible à l'hypoglycémie, ledit appareil comprenant:

des capteurs destinés à capter au moins deux des paramètres du patient parmi un ensemble comprenant l'impédance de la peau, le rythme cardiaque, l'intervalle QT, et la fréquence moyenne ou de pointe d'une onde alpha;
un moyen destiné à établir le moment où un ou plusieurs des paramètres détectés changent et, lorsque cela est établi, un taux de changement desdits paramètre changés,

caractérisé par le fait que ledit appareil comprend par ailleurs:

un réseau neural connecté auxdits capteurs et audit moyen, de manière à récevoir un flux de données sensiblement continu desdits capteurs et dudit moyen, le réseau neural étant programmé avec un algorithme d'apprentissage rapide qui adapte le réseau neural pour établir le moment ou les paramètres détectés, et tout changement de ces paramètres pour une personne particulaire sont tels qu'ils indiquent la présence ou l'apparition imminente d'un état hypoglycémique, et
un moyen d'alarme connecté audit réseau neural adapté pour être déclenché lorsqu'est établie la présence ou l'apparition imminente dudit état hypoglycémique.

8. Appareil selon la revendication 7, dans lequel l'algorithme d'apprentissage rapide présente soit une fonction de gradient amplifié, soit une fonction de gradient optimal.

9. Appareil selon la revendication 7, dans lequel l'algorithme d'apprentissage rapide est un algorithme de mode de glissement robuste.

10. Appareil selon l'une quelconque des revendications 7 à 9, dans lequel un EEG est utilisé pour obtenir les données pour le rythme cardiaque et l'intervalle QT.

11. Appareil selon l'une quelconque des revendications 7 à 10, dans lequel un EEG. est utilisé pour obtenir les données pour l'onde alpha moyenne ou de pointe.

12. Appareil selon l'une quelconque des revendications 7 à 11, dans lequel les données sont transmises entre les capteurs et le réseau neural par un système télémétrique à haute fréquence.

13. Appareil selon l'une quelconque des revendications 7 à 12, dans lequel le dispositif est adapté pour estimer une valeur réelle d'un état hypoglycémique d'un patient.

14. Appareil selon la revendication 13, dans lequel l'état hypoglycémique pour l'estimation duquel le dispositif est adapté est le niveau de glucose dans le sang du patient.

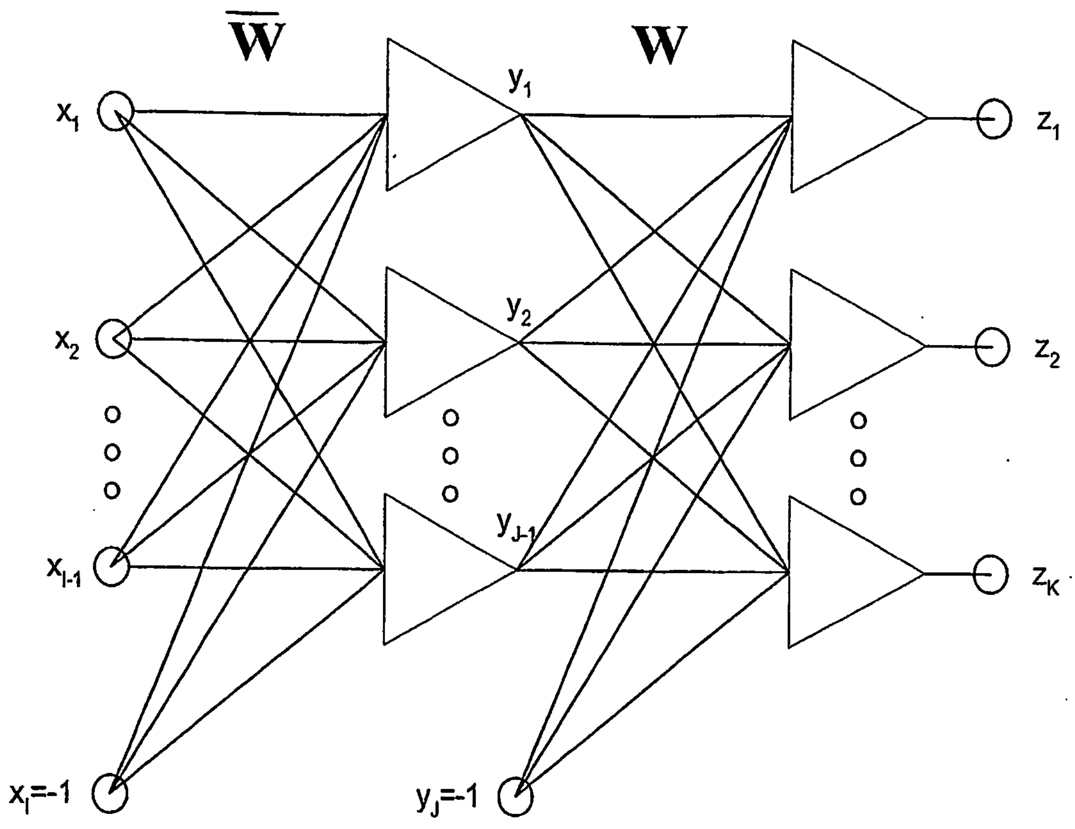
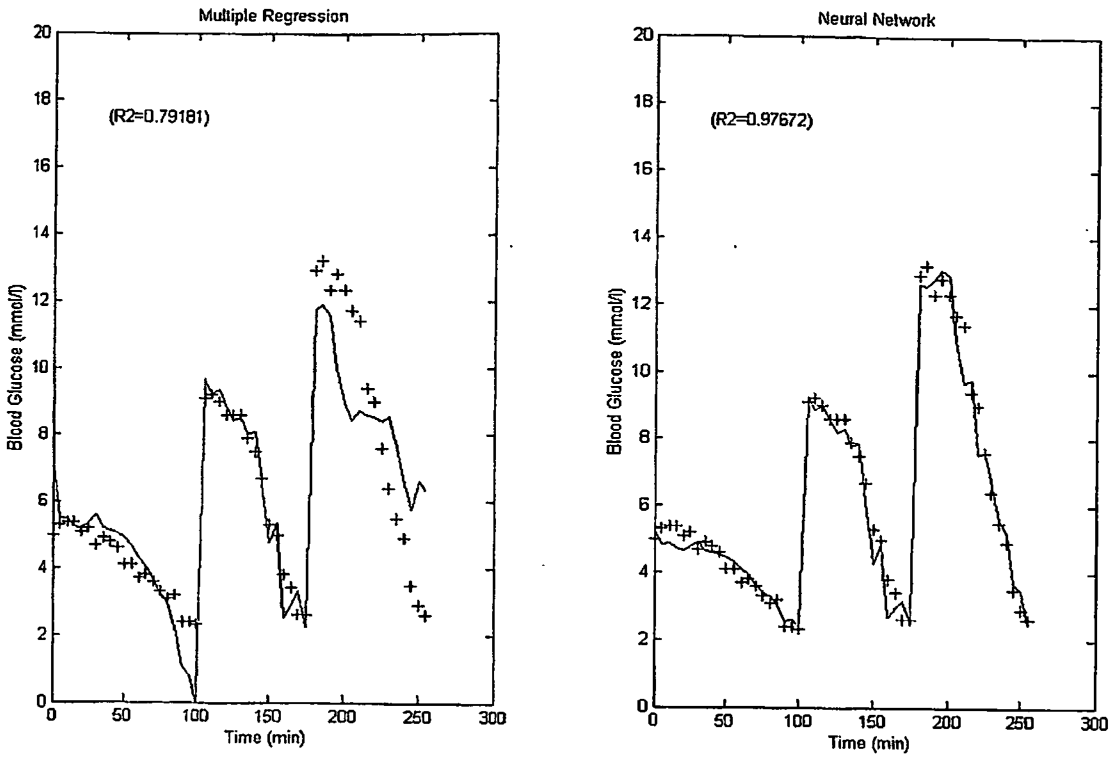


Figure 1

Figure 2


Multiple Regression
(R2=0.79181)
Blood Glucose (mmol/l)
Time (min)
0
2
4
6
8
10
12
14
16
18
20
0
50
100
150
200
250
300
Neural Network
(R2=0.97672)
Blood Glucose (mmol/l)
Time (min)

REFERENCES CITED IN THE DESCRIPTION

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Patent documents cited in the description

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- US 4981139 A **[0008]**
- GB 2281780 A **[0009]**
- WO 9715227 A **[0010]**

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摘要(译)

本发明涉及使用生理响应检测医疗状况的早期预警系统的建模和设计。该装置包括用于监测生理参数的传感器，例如患者的皮肤阻抗，心率和QT间期，用于确定何时这些参数改变的装置，参数的变化率，以及用于处理由所获得的信息获得的信息的神经网络处理器。传感器。神经网络处理器用快速学习算法编程。当神经网络确定患者中存在生理状况时，将产生警报信号。本发明扩展到使用利用快速学习算法编程的神经网络对人进行无创监测的方法。具体描述了非侵入性低血糖监测器。

$$\delta_k = -\frac{\partial E}{\partial v_k} = (R_k - z_k)\frac{\partial z_k}{\partial v_k} \qquad \delta_j = -\frac{\partial E}{\partial v_j} = \frac{\partial y_j}{\partial v_j}\sum_{k=1}^{K}\delta_k w_{kj}$$