

(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
31 July 2008 (31.07.2008)

PCT

(10) International Publication Number  
WO 2008/089649 A1

- (51) International Patent Classification:  
A61B 5/145 (2006.01) G01N 33/49 (2006.01)  
A61B 5/083 (2006.01)
- (21) International Application Number:  
PCT/CN2008/000064
- (22) International Filing Date: 10 January 2008 (10.01.2008)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:  
60/881,265 19 January 2007 (19.01.2007) US
- (71) Applicant (for all designated States except US): THE UNIVERSITY OF HONG KONG [CN/CN]; G18, Eliot Hall, Pokfulam Road, Hong Kong (CN).
- (72) Inventors; and
- (75) Inventors/Applicants (for US only): LEE, Chiyeung [CN/CN]; 9D, Hon Kwong Mansion, 25-29 Hankow Road, Tsim Sha Tsui, Kowloon, Hong Kong (CN). CHEUNG, Yingsheung [GB/CN]; Flat 9B, Block 6, Villa Rhapsody,

Symphony Bay, Sai Kung, New Territories, Hong Kong (CN). LAM, Siuling, Karen [GB/CN]; Block F, 10th Floor, Fulham Garden, 84 Pokfulam Road, Hong Kong (CN). LI, Onkwok, Vicotr [US/CN]; 28B, Tower 2, 14 Tregunter Path, Mid-Levels, Hong Kong (CN).

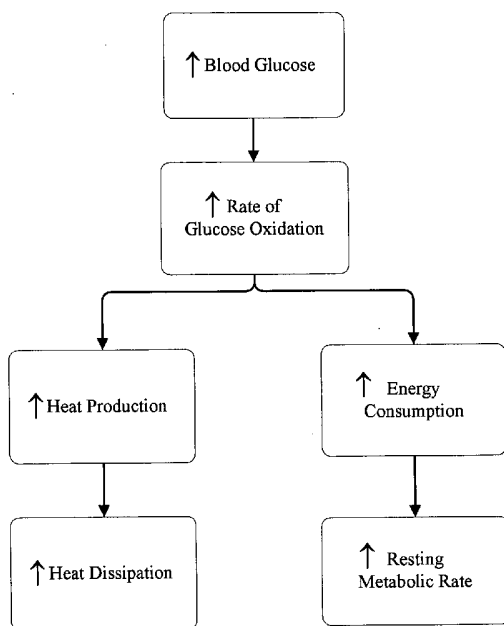
(74) Agent: CHINA PATENT AGENT (H.K.) LTD.; 22/F, Great Eagle Centre, 23 Harbour Road, Wanchai (HK).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH,

[Continued on next page]

(54) Title: NONINVASIVE METHOD TO ESTIMATE VARIATION OF BLOOD GLUCOSE LEVELS USING METABOLIC MEASUREMENTS



(57) Abstract: A method to estimate the variation of blood glucose concentration in a patient without blood sampling. The method can be implemented by measuring metabolic parameters including heat dissipation by conduction, percentage oxygen content of expired air and volume per minute of expired air. These parameters are used to calculate estimated blood glucose variation.

WO 2008/089649 A1



GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

**Published:**

— *with international search report*

## A NONINVASIVE METHOD TO ESTIMATE VARIATION OF BLOOD GLUCOSE LEVELS USING METABOLIC MEASUREMENTS

### FIELD OF THE INVENTION

5 This invention relates to a method for measuring the variation of human blood glucose concentration without blood sampling, and more particularly to a method that uses measurable body parameters to estimate the variation in blood glucose concentration.

### BACKGROUND OF THE INVENTION

10 The amount of glucose in blood directly affects the glucose oxidation rate. It has been shown that hyperglycemia significantly increases the carbohydrate (CHO) oxidation rate in normal and type 2 diabetic human beings [1, 2, 3].

Glucose oxidation is an exothermic chemical reaction. Biological glucose oxidation produces heat energy [4]. This probably explains the experimental results indicating facial and sublingual temperature rises after intravenous glucose injection in diabetic subjects [5].

15 It has been discovered that human energy expenditure increases after oral glucose load [6]. A Weir equation was derived to determine metabolic rate, which is a measure of human energy expenditure [7]. Later, an alternative version of the Weir equation was provided using data that focus on glucose oxidation [8]. The equation indicates that metabolic rate depends on percentage oxygen content of expired air and volume per minute of expired air.

A metabolic heat conformation (MHC) method for noninvasive blood glucose measurement has been proposed [9, 10], [11, 12, 13]. This method makes use of thermal and optical techniques to measure body glucose metabolic effects at an extremity's tip, such as a forefinger tip. A multiple linear regression equation was formed based on the measured parameters. The apparatus was designed by hard-coding the regression equation to a ROM unit based on the measured results of only 8 subjects (2 normal + 6 diabetic). The population of sample subjects is small, so that variations of the measured parameters due to variations of body properties (e.g., skin thickness) among different subjects were not indicated. Thus, the results are far from conclusive, and do not appear to constitute an accurate predictive model from the measured parameters.

25  
30

Therefore, a novel noninvasive reliable and accurate method to estimate the variation of human blood glucose concentration is needed.

### SUMMARY OF THE INVENTION

5 The present invention provides methods of estimating the variation of blood glucose in a subject without blood sampling. In a preferred embodiment, the subject invention provides a method that can be implemented by measuring metabolic parameters related to glucose oxidation including, for example, heat dissipation, oxygen content of expired air, and the rate of air expiration (e.g. volume per minute of expired air).

10 A further aspect of the subject invention is the development of a classification model based on measurements from a clinical trial. The methods of the subject invention obtain results that are sufficiently accurate to grade the variation of blood glucose into, for example, five classes according to the classification model, without blood sampling. Based on this model, estimation of blood glucose variation can be performed. Advantageously, the variation  
15 of blood glucose can be accurately determined using the method of the present invention.

A further aspect of the subject invention is a device that facilitates taking simple metabolic measurements in order to implement the method of the subject invention.

Owing to its noninvasive and easy-to-use features, self-monitoring of blood glucose (SMBG) according to the subject invention is made possible for home use. Thus, not only can  
20 this method lead to better control of blood glucose level, but it can also help facilitate a healthy lifestyle for normal, pre-diabetic and type 2 diabetic persons.

### BRIEF DESCRIPTION OF THE DRAWINGS

Further features and advantages of the invention will become apparent upon review of  
25 the following detailed description of the preferred embodiments thereof in conjunction with the drawings in which:

**FIG. 1** is a schematic diagram of the method of the present invention;

**FIG. 2** shows the calibration process of the method of FIG. 1;

**FIG. 3** shows the estimation process of blood glucose variation;

30 **FIG. 4** presents a scattered plot of the estimated blood glucose variation against the reference blood glucose variation using multiple linear regression analysis; and

**FIG. 5** presents the classification results by the inventive method using 3 regions.

### DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

In accordance with the subject invention, it is possible to analyze and determine the extent of blood glucose variation in a patient using noninvasive metabolic measurements. The measurements used according to the subject invention, optionally used in conjunction with the classification model described herein, is able to obtain results with sufficient accuracy for home-used blood glucose monitoring. The methods and devices of the subject invention can be used to monitor blood glucose variation and/or for lifestyle education for normal, pre-diabetic and type 2 diabetic persons.

The present invention provides methods of estimating the variation of blood glucose in a subject without blood sampling. In a preferred embodiment, the subject invention provides a method that can be implemented by measuring metabolic parameters related to glucose oxidation including, for example, heat dissipation, the oxygen content of expired air, and the rate of air expiration.

Heat dissipation may be measured at an extremity. Preferably heat dissipation is measured at a fingertip. In a preferred embodiment, the oxygen content of air expired by the patient is measured as a percentage of the gases expired by the patient. Furthermore, preferably, the rate of air expiration is measured as a volume of air expired per minute.

A further aspect of the subject invention is the development of a classification model based on measurements from a clinical trial. The methods of the subject invention obtain results that are sufficiently accurate to grade the variation of blood glucose into, for example, five classes according to the classification model, without blood sampling. Based on this model, estimation of blood glucose variation can be performed. Advantageously, the variation of blood glucose can be accurately determined using the method of the present invention.

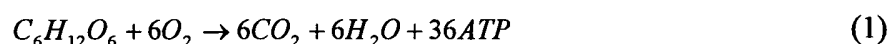
A further aspect of the subject invention is a device that facilitates taking simple metabolic measurements in order to implement the method of the subject invention.

Owing to its noninvasive and easy-to-use features, self-monitoring blood glucose (SMBG) according to the subject invention is made possible for home use. Thus, not only can this method lead to better control of blood glucose level, but it can also help facilitate a healthy lifestyle for normal, pre-diabetic and type 2 diabetic persons.

The subject invention further pertains to devices whereby the methods of the subject invention can be carried out utilizing a portable or non-portable apparatus that measures parameters and/or makes calculations relevant to blood glucose concentration. The device of

the subject invention can be used by a patient, remain at a patient's home, or be in a physician's office, a laboratory or hospital. The device can measure, for example, heat dissipation, the oxygen content of expired air and/or the rate of air expiration.

Blood glucose is a fuel to produce necessary energy for living bodies. Such energy is produced through a chemical reaction called glucose oxidation, which can be simply expressed in the following chemical equation (1):



In glucose oxidation, oxygen in blood is consumed and heat is produced ( $\Delta H = -686 \text{ kcal/mol}$ ). Therefore, oxygen is consumed for energy production. When the concentration of blood glucose increases, the rate of glucose oxidation also increases. This, in turn, causes an increase both heat dissipation and energy expenditure, which can be measured by resting metabolic rate (*RMR*). These biological relationships are shown in **FIG. 1**.

*RMR* can be calculated using the revised Weir equation (2):

$$RMR = (1.039 - 0.05O_e) \cdot V \quad (2)$$

where  $O_e$  is percentage oxygen content of expired air, and  $V$  is volume per minute of expired air.

Based on the concept of glucose metabolism, a method has been proposed to estimate blood glucose variation noninvasively with the following assumptions:

1. Blood glucose can be estimated based on heat production and energy expenditure;
2. The amount of heat production and the amount of heat dissipation are equal;
3. The amount of heat dissipation can be determined at an extremity's tip by a conduction method;
4. Energy expenditure is represented by *RMR*, which is dependent on  $O_e$  and  $V$ ;
5. Measurements are taken from the subjects under resting condition;
6. Artifacts are avoided before measurements; and
7. Subjects do not have fever, hand trauma and respiratory diseases.

**FIG. 2** shows the steps of the calibration process. In step 210, raw metabolic parameters (i.e. conduction heat loss at the extremity's tip,  $O_e$  and  $V$ ) are measured. Blood glucose level is also measured using finger-pricking method for reference purpose. In step 220, the measured parameters are converted to metabolic features (i.e. heat dissipation by conduction and  $RMR$ ). In step 230, for each subject, variations of metabolic features and variation of blood glucose level are computed by subtracting the previously measured values. This can account for the variations of different subjects since they have different biological properties and thus, different offset metabolic values. In step 240, the variations of metabolic features are tested whether they are feasible to become features of the classification model. Multiple linear regression analysis using least-squares method is carried out. In step 250, the feasible variations of features and the corresponding reference blood glucose variation are used to train and develop a classification model for future estimation of blood glucose variation. Linear discriminant classifier is adopted to obtain the best performance and classification accuracy.

**FIG. 3** describes the estimating process of blood glucose variation once the classification model has been developed. In step 310, conduction heat flow,  $O_e$  and  $V$  are measured. In step 320, these measured parameters are converted to heat dissipation by conduction and  $RMR$ . In step 330, for each subject, variations of metabolic features are computed by subtracting the previously measured values in order to account for subject variability. In step 340, the variations of metabolic features are input to the classifier. After classification, the extent of blood glucose variation is obtained.

Multiple linear regression using least-squares method is adopted to test the feasibility of features' variation to become features of the classification model. Suppose that  $n$  is number of samples taken,  $X_1$  is variation of heat dissipation by conduction,  $X_2$  is  $RMR$  variation,  $y$  is reference blood glucose variation,  $Y$  is estimated blood glucose variation and  $e$  is the error with respect to a measured value  $y_k$  ( $k = 1, \dots, n$ ) using finger-pricking method, the regression equation (3) is written such that values of coefficient  $\alpha_i$  ( $i = 0, 1, 2$ ) are going to be determined using least-squares method:

$$y = a_0 + a_1 X_1 + a_2 X_2 + e \quad (3)$$

Since  $n$  samples are taken, equation (3) is expanded to  $n$  equations, which can be summarized with equation (4):

$$5 \quad \mathbf{y} = \mathbf{X}\mathbf{a} + \mathbf{e} \quad (4)$$

where  $\mathbf{y}$  is a  $n \times 1$  vector consisting of  $y_k$ 's ( $k=1, \dots, n$ ),  $\mathbf{X}$  is a  $n \times 3$  matrix consisting of  $[1 \ X_{1k} \ X_{2k}]$  ( $k=1, \dots, n$ ),  $\mathbf{a}$  is a  $3 \times 1$  vector which is equal to  $[a_0 \ a_1 \ a_2]^t$  and  $\mathbf{e}$  is a  $n \times 1$  vector consisting of  $e_k$ 's ( $k=1, \dots, n$ ).

10 Let  $J_s(\mathbf{a})$  be the sum-of-squared-error criterion function with respect to  $\mathbf{a}$ :

$$J_s(\mathbf{a}) = \|\mathbf{e}\|^2 = \|\mathbf{y} - \mathbf{X}\mathbf{a}\|^2 = \sum_{i=1}^n (y_i - \mathbf{a}^t \mathbf{X}_i)^2 \quad (5)$$

The first-order derivative of equation (5) is expressed in equation (6):

$$\nabla J_s = -\sum_{i=1}^n 2(y_i - \mathbf{a}^t \mathbf{X}_i) \mathbf{X}_i = 2\mathbf{X}^t (\mathbf{X}\mathbf{a} - \mathbf{y}) \quad (6)$$

15 To minimize the sum-of-squared-error criterion function, its first-order derivative is set to be zero. Therefore,  $\mathbf{a}$  can be solved using equation (7):

$$\begin{aligned} \nabla J_s &= 0 \\ \Rightarrow 2\mathbf{X}^t (\mathbf{X}\mathbf{a} - \mathbf{y}) &= 0 \\ \Rightarrow \mathbf{X}^t \mathbf{X}\mathbf{a} &= \mathbf{X}^t \mathbf{y} \\ 20 \quad \Rightarrow \mathbf{a} &= (\mathbf{X}^t \mathbf{X})^{-1} \mathbf{X}^t \mathbf{y} \end{aligned} \quad (7)$$

As a result,  $\mathbf{Y}$ , a  $n \times 1$  vector consisting of estimated values  $Y_k$ 's ( $k=1, \dots, n$ ), can be calculated using equation (8).

$$\mathbf{Y} = \mathbf{X}\mathbf{a} \quad (8)$$

25

A classification model is designed and carried out using linear discriminant analysis (LDA). Assume the sample points are normally distributed, Bayes formula is defined in equation (9) where  $\mathbf{x}$  is a  $d$ -component column vector,  $\omega_i$  represents the state of nature for



region  $i$  ( $R_i$ ) such that  $R_i$  and  $R_j$  are adjacent to each other,  $c$  is the number of regions,  $P(\omega_i | \mathbf{x})$  is the posterior probability,  $p(\mathbf{x} | \omega_i)$  is the likelihood,  $P(\omega_i)$  is the prior probability and  $p(\mathbf{x})$  is the evidence factor defined in equation (10). Equation (11) expresses the general multivariate normal likelihood in  $d$  dimensions where  $\boldsymbol{\mu}_i$  is the  $d$ -component mean vector with respect to region  $i$  and  $\Sigma_i$  is the  $d$ -by- $d$  covariance matrix with respect to region  $i$ :

$$P(\omega_i | \mathbf{x}) = \frac{p(\mathbf{x} | \omega_i)P(\omega_i)}{p(\mathbf{x})} \text{ for } i = 1, 2, \dots, c \quad (9)$$

$$\text{where } p(\mathbf{x}) = \sum_{k=1}^c p(\mathbf{x} | \omega_k)P(\omega_k) \quad (10)$$

$$\text{and } p(\mathbf{x} | \omega_i) = \frac{1}{(2\pi)^{\frac{d}{2}} |\Sigma_i|^{\frac{1}{2}}} \exp\left[-\frac{1}{2}(\mathbf{x} - \boldsymbol{\mu}_i)' \Sigma_i^{-1} (\mathbf{x} - \boldsymbol{\mu}_i)\right] \text{ for } i = 1, 2, \dots, c \quad (11)$$

10 According to the Bayes decision theory, the classification decision depends on the discriminant function  $g(\cdot)$  defined below:

Decide  $\omega_i$  if  $P(\omega_i | \mathbf{x}) > P(\omega_j | \mathbf{x}) \quad \forall j \neq i$

$$\Rightarrow \text{Decide } \omega_i \text{ if } \frac{p(\mathbf{x} | \omega_i)P(\omega_i)}{p(\mathbf{x})} > \frac{p(\mathbf{x} | \omega_j)P(\omega_j)}{p(\mathbf{x})} \quad \forall j \neq i$$

$$\Rightarrow \text{Decide } \omega_i \text{ if } p(\mathbf{x} | \omega_i)P(\omega_i) > p(\mathbf{x} | \omega_j)P(\omega_j) \quad \forall j \neq i$$

$$15 \Rightarrow \text{Decide } \omega_i \text{ if } \ln p(\mathbf{x} | \omega_i) + \ln P(\omega_i) > \ln p(\mathbf{x} | \omega_j) + \ln P(\omega_j) \quad \forall j \neq i$$

$$\Rightarrow \text{Decide } \omega_i \text{ if } g_i(\mathbf{x}) > g_j(\mathbf{x}) \quad \forall j \neq i \text{ where } \begin{cases} g_i(\mathbf{x}) = \ln p(\mathbf{x} | \omega_i) + \ln P(\omega_i) \\ g_j(\mathbf{x}) = \ln p(\mathbf{x} | \omega_j) + \ln P(\omega_j) \end{cases} \quad (12)$$

Substitute equation (11) into  $g_i(\mathbf{x})$  in equation (12) becomes:

$$20 \begin{aligned} g_i(\mathbf{x}) &= \ln p(\mathbf{x} | \omega_i) + \ln P(\omega_i) \\ &= -\frac{1}{2}(\mathbf{x} - \boldsymbol{\mu}_i)' \Sigma_i^{-1} (\mathbf{x} - \boldsymbol{\mu}_i) - \frac{d}{2} \ln(2\pi) - \frac{1}{2} \ln |\Sigma_i| + \ln P(\omega_i) \end{aligned} \quad (13)$$

Assume all the regions have identical covariance matrices (i.e.  $\Sigma_i = \Sigma$ ), the terms that are independent of  $i$  are eliminated. Equation (13) thus becomes:

$$\begin{aligned}
g_i(\mathbf{x}) &= -\frac{1}{2}(\mathbf{x} - \boldsymbol{\mu}_i)' \boldsymbol{\Sigma}^{-1}(\mathbf{x} - \boldsymbol{\mu}_i) - \underbrace{\frac{d}{2} \ln(2\pi) - \frac{1}{2} \ln|\boldsymbol{\Sigma}|}_{\text{Independent of } i} + \ln P(\omega_i) \\
&= -\frac{1}{2}(\mathbf{x} - \boldsymbol{\mu}_i)' \boldsymbol{\Sigma}^{-1}(\mathbf{x} - \boldsymbol{\mu}_i) + \ln P(\omega_i) \\
&= -\frac{1}{2} \left( \underbrace{\mathbf{x}' \boldsymbol{\Sigma}^{-1} \mathbf{x}}_{\text{Independent of } i} - 2\boldsymbol{\mu}_i' \boldsymbol{\Sigma}^{-1} \mathbf{x} + \boldsymbol{\mu}_i' \boldsymbol{\Sigma}^{-1} \boldsymbol{\mu}_i \right) + \ln P(\omega_i) \\
5 \quad &= \boldsymbol{\mu}_i' \boldsymbol{\Sigma}^{-1} \mathbf{x} - \frac{1}{2} \boldsymbol{\mu}_i' \boldsymbol{\Sigma}^{-1} \boldsymbol{\mu}_i + \ln P(\omega_i) \\
&= \mathbf{w}_i' \mathbf{x} + \omega_{i0}
\end{aligned}$$

where

$$\mathbf{w}_i = \boldsymbol{\Sigma}^{-1} \boldsymbol{\mu}_i \text{ and } \omega_{i0} = -\frac{1}{2} \boldsymbol{\mu}_i' \boldsymbol{\Sigma}^{-1} \boldsymbol{\mu}_i + \ln P(\omega_i) \quad (14)$$

10 The calculation of  $g_j(\mathbf{x})$  is similar. A linear decision boundary can therefore be obtained as follows:

$$\begin{aligned}
g_i(\mathbf{x}) &= g_j(\mathbf{x}) \\
&\Rightarrow \mathbf{w}_i' \mathbf{x} + \omega_{i0} = \mathbf{w}_j' \mathbf{x} + \omega_{j0} \\
15 \quad &\Rightarrow (\mathbf{w}_i' - \mathbf{w}_j') \mathbf{x} + (\omega_{i0} - \omega_{j0}) = 0 \\
&\Rightarrow \mathbf{w}' \mathbf{x} + \omega_0 = 0 \text{ where } \begin{cases} \mathbf{w} = \mathbf{w}_i - \mathbf{w}_j = \boldsymbol{\Sigma}^{-1}(\boldsymbol{\mu}_i - \boldsymbol{\mu}_j) \\ \omega_0 = \omega_{i0} - \omega_{j0} \end{cases} \quad (15)
\end{aligned}$$

20

## TRIAL DESIGN

The apparatus used are all noninvasive and commercially available. They are as follows:

- 25 1. Data Harvest EasySense Advanced Datalogger, which was used to measure conduction heat loss at the extremity's tip;

2. Teledyne AX300 Oxygen Analyzer with R-17 MED Oxygen Sensor, which was used to measure percentage oxygen content of expired air at the mouth cavity;
3. Vitalograph Micro Spirometer, which was used to measure volume per minute of expired air; and
- 5 4. Medisense Optium Xceed Meter, which was used to measure blood glucose level for calibration and reference purposes.

The clinical trial was done with informed consent by the subjects and ethical approval by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (HKU/HA HKW IRB) at Queen Mary Hospital (QMH). A total of 190  
10 subjects (31 normal and 159 type 2 diabetic), aged from 23 to 86, participated in this trial.

The trial protocol is as follows:

1. Patient should report to the clinic fasting (at least 12 hours, no food or drink except water), having not taken their morning study medication dose.
- 15 2. Patient should sit down and rest for 15 minutes.
3. Patient should have a blood glucose measurement taken as usual.
4. Patient should have a conduction heat loss measurement taken.
5. Patient should have a percentage oxygen content of expired air measurement taken.
6. Patient should have a volume per minute of expired air measurement taken.
- 20 7. The patient should complete eating a meal (standard meal is not necessary).
8. Step 3 to 6 should be repeated 45 minutes after the start of the meal.

## RESULTS

25 **FIG. 4** presents the scattered plot of the estimated blood glucose variation ( $Y$ ) versus the reference blood glucose variation ( $y$ ) using multiple linear regression analysis where  $n = 190$ . It can be seen that a good correlation is obtained with correlation coefficient ( $R$ ) equals to 0.88. Thus, variation of heat dissipation by conduction and  $RMR$  variation can be used as features of the classification model.

30 The classifier has been tested 100 times by randomly choosing half of the samples as training set and half of them as testing set. **FIG. 5** presents the LDA classification results using 3 regions. The classification accuracy is 84.26%. When 4 and 5 regions were used, the

classification accuracy is 71.98% and 71.82% respectively. The result shows that the method of the subject invention can be used to estimate blood glucose variation.

Having thus described at least illustrative embodiments of the invention, various modifications and improvements will readily occur to those skilled in the art and are intended to be within the scope of the invention. Accordingly, the foregoing detailed description is by way of example only and is not intended as limiting. The invention is limited only as defined in the following claims and the equivalents thereto.

## REFERENCES

1. Chevaux et al., "Study by Indirect Calorimetry of the Oxidation Rate of Carbohydrate in Man at Two Different Plasma Insulin Levels" (abstract), *Diabetologia*, 12, 383 (1976).
2. Felber et al., "Carbohydrate and Lipid Oxidation in Normal and Diabetic Subjects", *Diabetes*, 26, 693-699 (1977).
3. Meyer et al., "Modifications of Glucose Storage and Oxidation in Nonobese Diabetics, Measured by Continuous Indirect Calorimetry", *Diabetes*, 29, 752-756 (1980).
4. Scott, "Contribution of anaerobic energy expenditure to whole body thermogenesis", *Nutrition & Metabolism*, 2, 14 (2005).
5. Hillson et al., "Facial and sublingual temperature changes following intravenous glucose injection in diabetics", *Diabetes & Metabolism*, 8, 15-19 (1982).
6. Rousselle et al., "Relationship Between Glucose Oxidation and Glucose Tolerance in Man", *Metabolism*, 31(9), 866-870 (1982).
7. Weir, "New methods for calculating metabolic rate with special reference to protein metabolism", *The Journal of Physiology*, 109, 1-9 (1949).
8. Mansell et al., "Reappraisal of the Weir equation for calculation of metabolic rate", *American Journal of Physiology*, 258(6 Pt 2), R1347-1354 (1990).
9. Ko et al., "Body Metabolism Provides a Foundation for Noninvasive Blood Glucose Monitoring", *Diabetes Care*, 27, 1211-1212 (2004).
10. Cho et al., "Noninvasive Measurement of Glucose by Metabolic Heat Conformation Method", *Clinical Chemistry*, 50, 1894-1898 (2004).

11. O. K. Cho and B. Holzgreve, "Process and device for non-invasive determination of glucose concentration in parts of the human body," United States Patent 5,795,305, Aug. 18, 1998.
12. O. K. Cho and B. Holzgreve, "Process and device for detecting the exchange of heat between the human body and the invented device and its correlation to the glucose concentration in human blood," United States Patent 5,924,996, Jul. 20, 1999.
13. O. K. Cho, Y. O. Kim, N. Sato, and H. Mitsumaki, "Optical measurement apparatus and blood sugar level measuring apparatus using the same," United States Patent Application Publication 20060094941, May 4, 2006.

## CLAIMS

We claim:

1. A method for estimating blood glucose variation in a patient based on metabolic parameters, comprising:
  - a) measuring, in a patient, conduction heat loss of an extremity, the oxygen content of expired air, and the rate of air expiration; and
  - b) calculating blood glucose variation for the patient with an algorithm that uses the metabolic parameters measured in part a) to estimate blood glucose concentration.
2. The method of claim 1, wherein a classification model takes the metabolic parameters as inputs and provides the extent of blood glucose variation as an output.
3. The method of claim 2, wherein the classification model places blood glucose variation into up to five classes.
4. The method of claim 1, wherein metabolic parameters are used to estimate blood glucose concentration.
5. The method of claim 1, wherein multiple regression analysis is used to calculate blood glucose concentration from the metabolic parameters.
6. An apparatus comprising a heat flow sensor and a heat flow analyzer, which respectively are capable of measuring and computing the conduction heat loss at an extremity's tip.
7. The apparatus of claim 6, further comprising an oxygen analyzer, which is capable of measuring the percentage oxygen content of expired air from the mouth.
8. The apparatus of claim 1, further comprising a gas speed-measuring device, which is capable of measuring the expiratory flow rate at the mouth cavity.

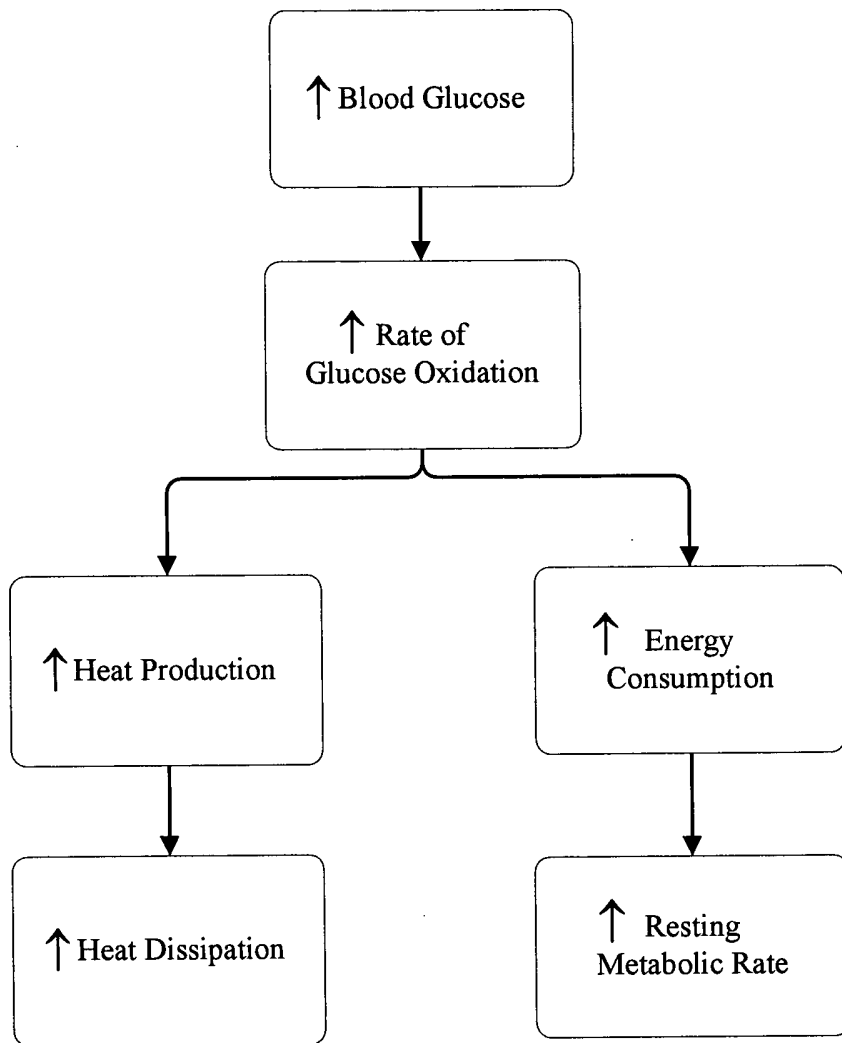


FIG. 1



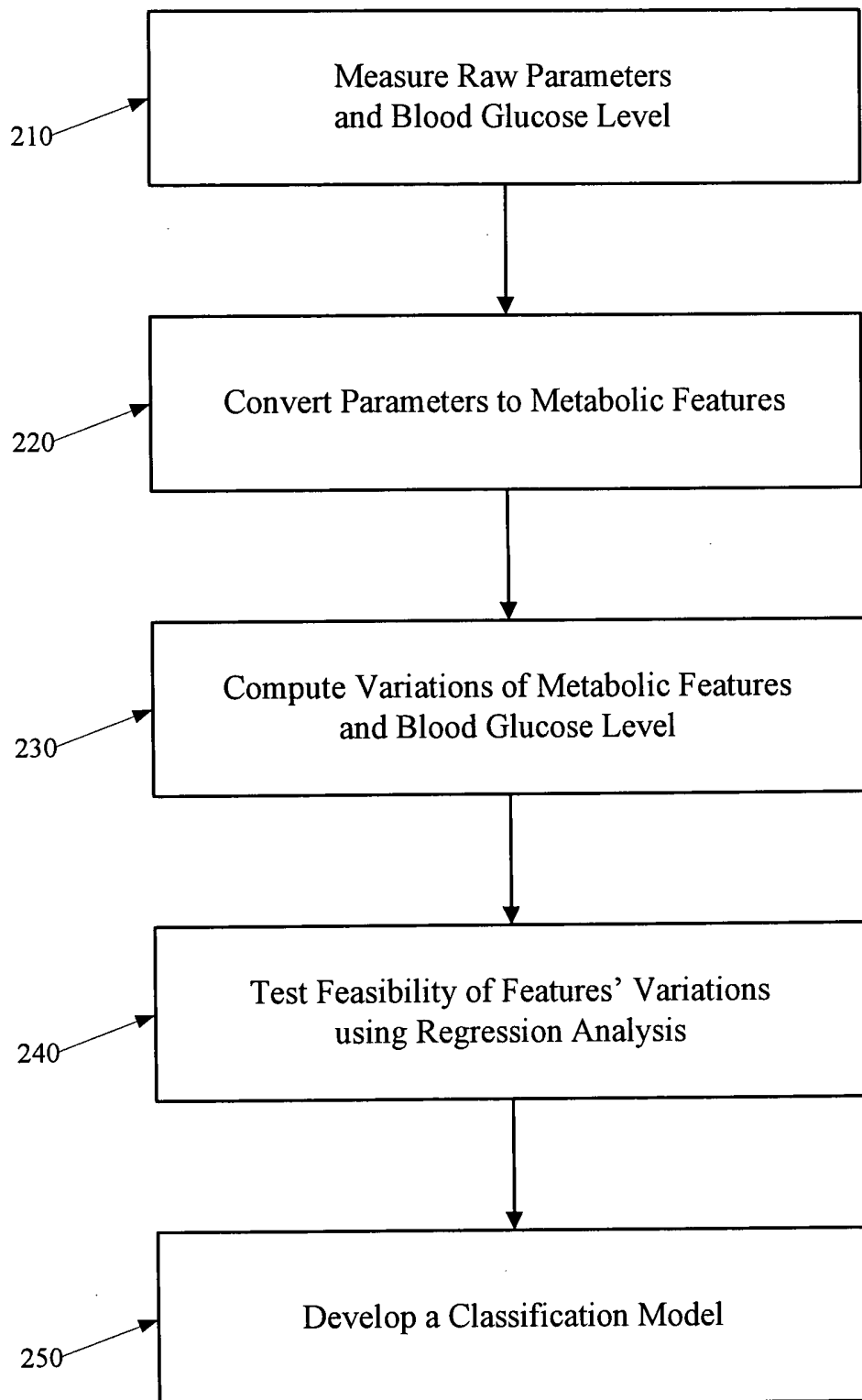


FIG. 2

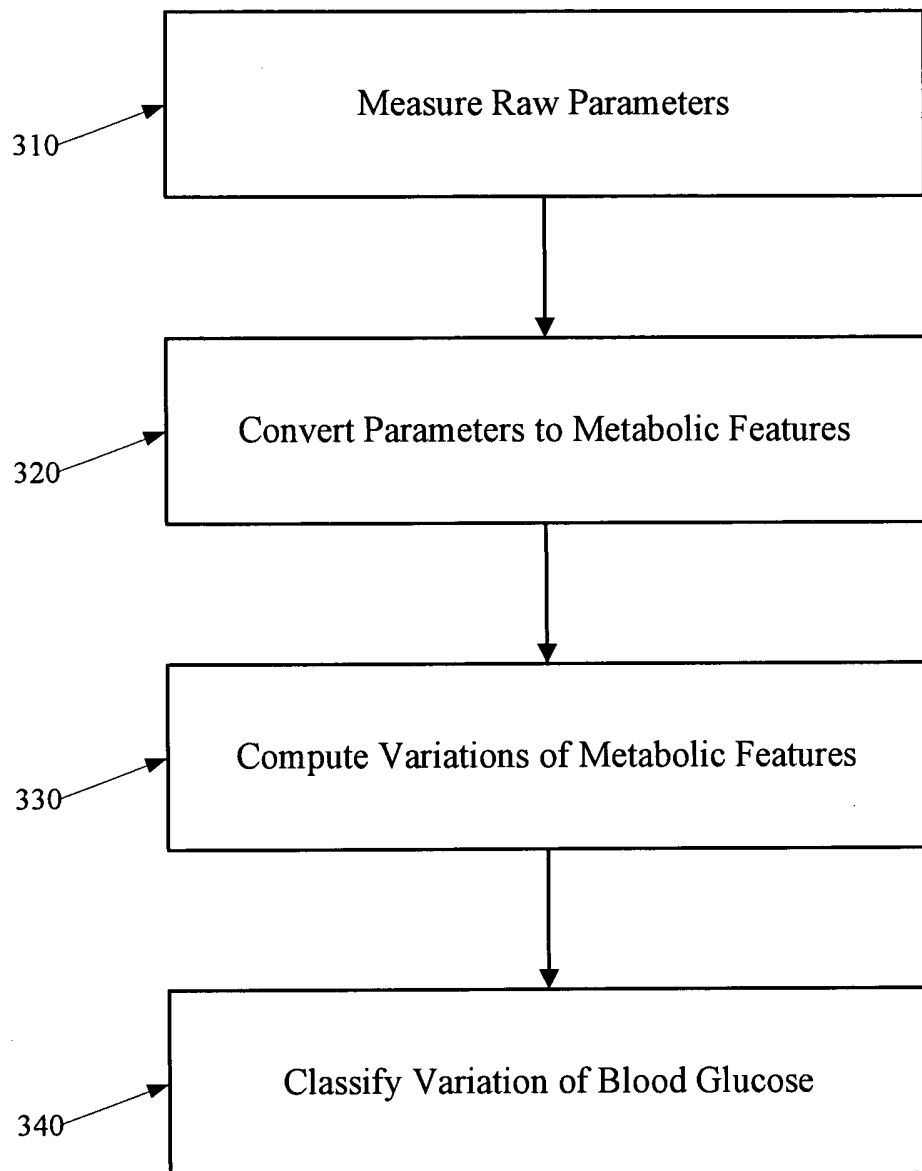


FIG. 3

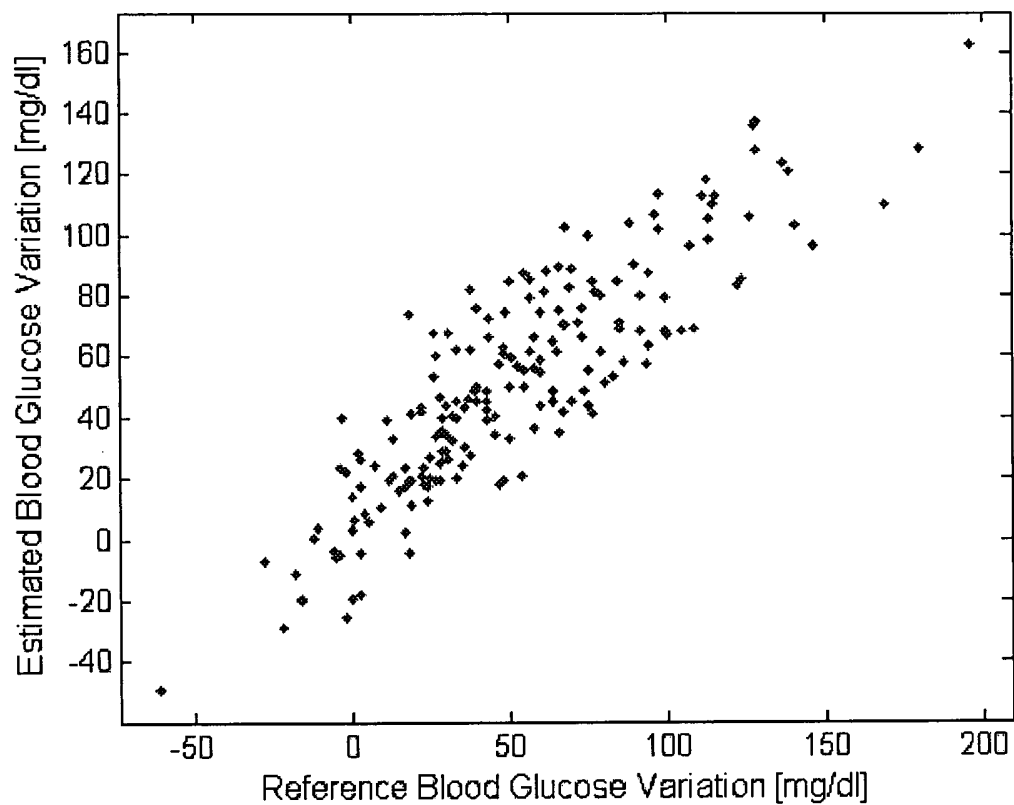


FIG. 4

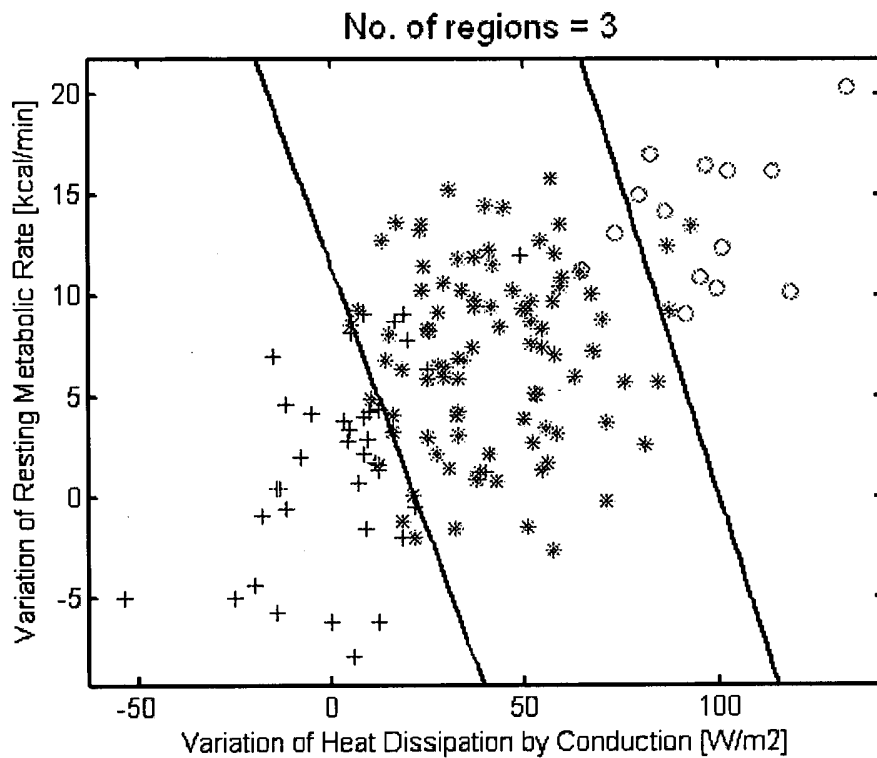


FIG. 5

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/CN2008/000064

**A. CLASSIFICATION OF SUBJECT MATTER**

See extra sheet

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

IPC A61B5 G01N33 G01K17

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI,EPODOC,PAJ,CNPAT

GLUCOSE OR SUGAR, BLOOD, EXPIR??? OR EXPIRATION, BREATH, INVASIVE, WEIR W EQUATION, GAS OR AIR

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CN1754505A (HITACHI LTD), 05 Apr.2006 (05.04.2006), page 5, line 11 to page 6, line 11 in the specification, figs.1-2.	1-8
A	US6599750B2 (ISOTECHNIKA INC), 29 Jul. 2003 (29.07.2003), column 3, line 63 to column 5, line 59 in the specification.	1-8
A	CN1636505A (SYSMEX CORP), 13 Jul.2005 (17.07.2005), the whole document.	1-8
A	US2003208110A1 (HEALTHETECH INC et al), 06 Nov.2003 (06.11.2003), the whole document.	1-8
A	JP2006102035A (MATSUSHITA ELECTRIC IND CO LTD), 20 Apr.2006 (20.04.2006), the whole document.	1-8

Further documents are listed in the continuation of Box C.       See patent family annex.

<p>* Special categories of cited documents:</p> <p>“A” document defining the general state of the art which is not considered to be of particular relevance</p> <p>“E” earlier application or patent but published on or after the international filing date</p> <p>“L” document which may throw doubts on priority claim (S) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>“O” document referring to an oral disclosure, use, exhibition or other means</p> <p>“P” document published prior to the international filing date but later than the priority date claimed</p>	<p>“T” later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>“X” document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</p> <p>“Y” document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art</p> <p>“&amp;”document member of the same patent family</p>
--	--

Date of the actual completion of the international search <b>20 Mar. 2008(20.03.2008)</b>	Date of mailing of the international search report <b>17 Apr. 2008 (17.04.2008)</b>
--	--

Name and mailing address of the ISA/CN The State Intellectual Property Office, the P.R.China 6 Xitucheng Rd., Jimen Bridge, Haidian District, Beijing, China 100088 Facsimile No. 86-10-62019451	Authorized officer <p style="text-align: center;"><b>TIAN, Yunqing</b></p> Telephone No. (86-10)62085631
--	---

**INTERNATIONAL SEARCH REPORT**  
Information on patent family members

International application No.

PCT/CN2008/000064

Patent Documents referred in the Report	Publication Date	Patent Family	Publication Date
CN1754505A	05.04.2006	EP1642524A1	05.04.2006
		JP2006094992A	13.04.2006
		US2006079742A1	13.04.2006
US6599750B2	29.07.2003	WO9956790A2	11.11.1999
		AU3725199A	23.11.1999
		EP1075286A2	14.02.2001
		ES2161669T1	16.12.2001
		US2002042143A1	11.04.2002
		JP2002513911T	14.05.2002
		US6461870B2	08.10.2002
		US6468802B1	22.10.2002
		US2003044993A1	06.03.2003
		US2003049853A1	13.03.2003
		US6602715B2	05.08.2003
		US2004038412A1	26.02.2004
		US6878550B2	12.04.2005
		US2005147560A1	07.07.2005
		CA2331812C	22.08.2006
US7118919B2	10.10.2006		
JP2007192831A	02.08.2007		
CN1636505A	17.07.2005	EP1552782A1	13.07.2005
		US2005177037A1	11.08.2005
US2003208110A1	06.11.2003	JP2005218855A	18.08.2005
		WO0189368A2	29.11.2001
		AU6502201A	03.12.2001
		EP1284642A2	26.02.2003
JP2006102035A	20.04.2006	JP2003533318T	11.11.2003
		None	

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/CN2008/000064

## A. CLASSIFICATION OF SUBJECT MATTER

A61B5/145 ( 2006.01 ) i

A61B5/083 ( 2006.01 ) i

G01N33/49 ( 2006.01 ) i