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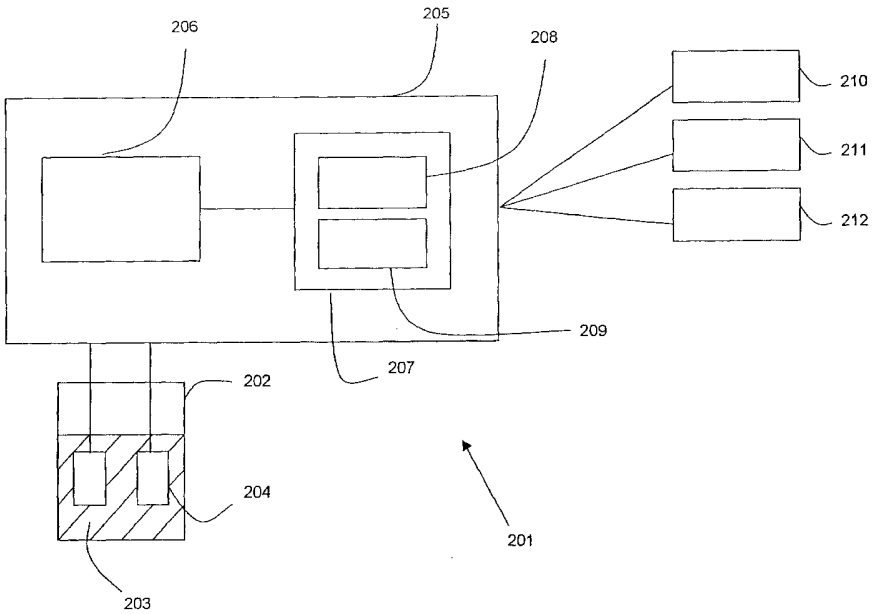
(54) Title: SYSTEM AND METHOD FOR BLOOD ANALYSIS



(57) Abstract: A method for blood analysis, comprising detecting the imaginary part of the complex impedance in a blood sample having an unknown haemoglobin concentration, and directly correlating the imaginary part of the complex impedance with the haemoglobin concentration in said blood sample.

WO 03/019166 A1

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

SYSTEM AND METHOD FOR BLOOD ANALYSIS

The Field of the Invention

The present invention relates to a system and a method for measuring the haemoglobin value in blood, more specifically to measurements in a closed system.

Background of the Invention

Today's techniques for measuring the haemoglobin value in blood often lead to variations in the results of measurement since the analyses are performed on very small blood volumes (approx. 5-20 µl), and therefore the operator's sampling technique is important for the results of the measurement.

Furthermore, these known methods often involve a health risk for the operator, due to exposure to chemicals and contagious blood.

The conventional methods also involve high costs for disposable material and for handling waste of disposable material and chemicals.

Hematocrit values obtained by conventional analyses can most of the time be correlated to the haemoglobin value, but they fail when measuring blood from patients suffering from certain blood anomalies which may cause the blood to contain abnormally large or small blood cells.

Methods for measuring hematocrit values are sometimes used when determining a state of anaemia and are much simpler than a method for measuring the oxygen-carrying component, haemoglobin, directly (see US-4 547 735, EP-0 417 796 and JP-03 099 254).

The above prior arts methods involve measuring the impedance in blood.

Traditional techniques for measuring the hematocrit value involve measuring the packed cell mass in a sample tube containing a blood sample. This measurement is performed after the blood sample having been centrifuged.

In Ackmann et al, *Specific impedance of canine blood*, Ann. Biomed. Eng., 24 (1), 58 (1996), measurements are disclosed where the imaginary part of the complex impedance is correlated with hematocrit value. Frequency intervals of 5 kHz to 1 MHz have been used when analysing canine blood. This measuring technique involves non-direct measurement of the haemoglobin value.

WO/0009996 or its equivalent US-5 792 668 discloses specific determination of glucose in NaCl using a radio frequency spectral analysis method. This method comprises analysing the real and the imaginary part of the complex impedance in the radio frequency range up to 5 GHz.

Summary of the Invention

Thus, there is a great need for a method for directly measuring the haemoglobin value in blood which does not pose a health risk to the user, does not involve high costs for handling of the disposable material used and enables measurements of small volumes of blood with accuracy.

In view of the drawbacks associated with prior art methods it is therefore the object of the present invention to provide a system and a method that yields accurate haemoglobin results for small blood samples. This object is achieved with a method according to claim 1 and a system according to claim 9.

The inventors have developed a technique primarily for determining the haemoglobin value in human blood in a closed system. Thus, the present invention permits safe measurements of the haemoglobin value in blood, eliminating the user's exposure to chemicals and contagious blood.

The present invention also provides a system that presents high reliability in measurement results and that comprises a procedure of analysis that is so simple that only minimal laboratory experience is needed.

Furthermore, the present invention minimises the production of environmentally detrimental waste like plastics and chemicals.

The aim of the invention is also to provide a method that does not involve addition of agents that degrade the blood samples, so that an analysed blood sample can be used for further analyses at for example a central laboratory.

Brief description of the drawings

The present invention will now become more fully understood from the detailed description given herein, wherein reference is made to the accompanying drawings, in which,

Fig. 1 shows a scheme over the haemoglobin measuring system according to the present invention.

Fig. 2 shows a calibration curve that illustrates the measured reference haemoglobin values as a function of its corresponding imaginary part of the complex impedance (values deriving from measurements performed at 400 kHz).

Fig. 3 shows a graph correlating the measured reference haemoglobin values and the haemoglobin values calculated using the inventive method (values originating from measurements of the imaginary part of the complex impedance performed at 400 kHz).

Fig. 4 shows a calibration curve, which shows the measured reference haemoglobin values as a function of its corresponding imaginary part of the complex impedance (values deriving from measurements performed at 500 kHz).

Fig. 5 shows a graph correlating the measured reference haemoglobin values and the haemoglobin values calculated using the inventive method (values originating from measurements of the imaginary part of the complex impedance performed at 500 kHz).

Fig. 6 shows a calibration curve, which shows the measured reference haemoglobin values as a function of its corresponding imaginary part of the complex impedance (values deriving from measurements performed at 600 kHz).

Fig. 7 shows a graph correlating the measured reference haemoglobin values and the haemoglobin values calculated using the inventive method (values originating from measurements of the imaginary part of the complex impedance performed at 600 kHz).

Fig. 8 shows a calibration curve, which shows the measured reference haemoglobin values as a function of its corresponding imaginary part of the complex impedance (values deriving from measurements performed at 700 kHz).

Fig. 9 shows a graph correlating the measured reference haemoglobin values and the haemoglobin values calculated using the inventive method (values originating from measurements of the imaginary part of the complex impedance performed at 700 kHz).

Fig. 10 shows a calibration curve, which shows the measured reference haemoglobin values as a function of its corresponding imaginary part of the complex impedance (values deriving from measurements performed at 800 kHz).

Fig. 11 shows a graph correlating the measured reference haemoglobin values and the haemoglobin values calculated using the inventive method (values originating from measurements of the imaginary part of the complex impedance performed at 800 kHz).

Fig. 12 shows a calibration curve, which shows the measured reference haemoglobin values as a function of its corresponding imaginary part of the complex impedance (values deriving from measurements performed at 900 kHz).

Fig. 13 shows a graph correlating the measured reference haemoglobin values and the haemoglobin values calculated using the inventive method (values originating from measurements of the imaginary part of the complex impedance performed at 900 kHz).

Detailed Description of the Invention

When directly measuring the haemoglobin value in the blood sample according to the present invention, one uses the fact that the blood has an alternating current (A.C.) impedance constituted by a resistive and a reactive part, where the reactive part is constituted by the imaginary part of the complex impedance.

The above-mentioned prior art hematocrit measurements differ from the method according to the present invention in that they do not analyse the resistive and/or the reactive part separately.

If a molecule is exposed to an alternating electrical field, e.g. between two electrodes constituting a capacitor, it is influenced such that a capacity change occurs.

The reactive part of the alternating current impedance of the blood is dependant on the amount of haemoglobin in the blood sample. The electrical complex impedance of the blood sample can then be measured and the magnitude of the reactive part, i.e. the imaginary part of the complex impedance, can be correlated with the haemoglobin value in the blood.

In the measurements according to the above-mentioned publication by Ackmann the imaginary part of the complex impedance is correlated with hematocrit value and not haemoglobin value, i.e. haemoglobin is not measured directly. Ackmann uses frequency intervals of 5 kHz to 1 MHz when analysing canine blood.

The present inventors have now identified frequency ranges where correlation between the haemoglobin value and the imaginary part of the complex impedance exists at least over a certain range in Hb concentration.

The results described herein have been obtained by exciting haemoglobin molecules in blood samples by applying an alternating field within a range of 400-900 kHz on the blood sample using two electrodes. This frequency range partly overlaps the frequency range that Ackmann uses.

There are thus several differences between this method and the method according to the present invention.

The system according to the present invention will be described with reference to Fig. 1, in which it is generally described with 1. The system includes electrodes 204, an impedance meter 205, a display unit 210, a keyboard 211 and a memory (RAM/ROM) 212.

The impedance meter 205 comprises a signal generator 206 and a signal-processing unit 207. The signal generator is capable of delivering an alternating current in a frequency range of 50 - 1200 kHz and measuring the impedance at one or more frequencies within the frequency range 50 - 1200 kHz. The signal-processing unit 207 delivers an out-signal in analogue or digital form.

In Fig. 1 there is also shown a sample tube 202 containing a blood sample 203. A septum, a rubber cork or the like seals the tube.

To obtain the raw data from said blood sample, a network analyser (Rohde & Schwarz ZVC) including some additional equipment belonging to it and a measuring device was used. In the development work at The Technical University of Luleå the vector network analyser that was used contained a signal generator 206 and a signal-processing unit 207 (see Fig. 1).

The electrodes are preferably made of a material that does not oxidise, has good conductivity and does not affect the blood sample, e.g. platinum.
Said electrodes are arranged in a tightly sealed tube, preferably in an ordinary sample tube.

The system according to the invention uses only two electrodes 204, a measuring electrode and a reference electrode, but any number of electrodes can be employed in combination.

To prevent air bubbles from interfering with the measuring process, the electrodes 204 of the measuring device are introduced from below into the sealed blood sample tube 202 mounted upside-down, so that the electrodes penetrate the sealing of the

blood sample tube and come into direct contact with the blood without first passing through air.

The signal generator 206 generates the electrical alternating field, which is applied to the blood sample 203 via the electrodes 204, the electrical alternating field preferably having a frequency within the range 50 - 1200 kHz.

The signal from the electrodes is amplified and filtered by the signal-processing unit 207, as a preparation for the transformation from analogue to digital form.

After filtering and amplification the signal-processing unit 207 processes the signal mathematically, whereby the reactive part of the signal is correlated with the haemoglobin value of the blood. This is performed within the frequency range 50 - 1200 kHz, and preferably at about 800 kHz, since the best correlation has been obtained at this frequency.

This information is subsequently prepared for presentation on the display unit 210. From the keyboard 211 a user can interact with the system, such as feeding it with patient information and data, in addition to controlling the system.

Furthermore, the signal-processing unit 207 is coupled to a memory 212, which preferably comprises a RAM and a ROM, wherein measurement data and other information can be saved and read.

The method according to the present invention is based on the discovery that within certain frequency intervals correlation exists between the haemoglobin value in blood within a certain concentration range and its imaginary part of the complex impedance.

In order to perform the method according to the invention, a standard curve must be constructed. The imaginary part of the complex impedance is then measured and correlated with the haemoglobin value using the standard curve.

The standard curve is constructed by first centrifuging a reference blood (arbitrary blood sample) to obtain plasma. The plasma is then used to dilute the reference

blood to five appropriate concentrations in haemoglobin. These concentrations lie in the range of normal human haemoglobin values. This interval is chosen because it matches the interval in which the ordinary measurement will be performed, but it is also chosen because linearity exists in this interval, at least for haemoglobin values of 80 to 180.

The haemoglobin values in these samples are then measured with a reference instrument.

The respective corresponding imaginary parts of the complex impedance are determined at a frequency within the frequency range 50 - 1200 kHz using the above-mentioned network analyser (Rohde & Schwarz ZVC).

The impedance results, obtained at the chosen frequency, are correlated with the haemoglobin results obtained with the reference instrument. The equation of a calibration curve within the above-mentioned range is determined. A ready-to-use system comprises a computer system having one or more of these equations stored in its memory unit. When performing the haemoglobin measurements the computer will then perform the correlation procedure.

The measurement of the imaginary part of the complex impedance in patient blood samples is performed by analysing blood samples from patients using the above-described measuring equipment (Rohde & Schwarz ZVC) at the same frequency within the frequency range 50 - 1200 kHz as mentioned above.

The results obtained from measuring the imaginary part of the complex impedance at the chosen frequency are fed into the equations of the respective calibration curve, yielding calculated corresponding haemoglobin values.

The reproducibility of the described method was determined by analysing several times each of a number of patient samples with the measuring equipment. The variation expressed in %CV was 2,5 or lower at the level 80 - 135 g haemoglobin/l.

Examples

The method will now be described with reference to non-limiting examples.

Example 1. Correlation studies of haemoglobin at 400 kHz

Construction of a standard curve

A reference blood sample (normal sample) was centrifuged and the plasma was separated in order to be used for dilution of the blood sample to 5 different levels of haemoglobin.

The diluted samples were analysed with a reference instrument (SYSMEX SF-3000) at the levels 65, 85, 141, 151 and 179 g/l considering the haemoglobin values.

An alternative way would be to provide a reference blood sample exhibiting a known haemoglobin concentration and then dilute said reference blood sample to obtain a set of reference samples having different known haemoglobin concentrations.

Still another way would be to provide a plurality of reference blood samples exhibiting unknown haemoglobin concentrations and then determine the haemoglobin concentrations in said reference blood samples to obtain a set of reference samples having different known haemoglobin concentrations.

The corresponding imaginary part of the complex impedance for each sample was determined at 400 kHz using the above-mentioned network analyser (Rohde & Schwarz ZVC).

The impedance results obtained at 400 kHz were correlated with the haemoglobin results obtained with the reference instrument. The equation of a calibration curve within the mentioned range (65 - 179 g/l) was determined (see Fig. 2).

The standard curve shows the haemoglobin values (Hb) of the above-mentioned blood samples, as obtained with the reference instrument, as a function of their corresponding imaginary parts of the complex impedance.

The obtained values were correlated and the following equation was drawn up:

$$Y = A + B*X$$

where Y represents the haemoglobin values in the reference blood sample and X their corresponding imaginary parts of the complex impedance.

The factor A and the coefficient B were found to be 32,62 and -1632, respectively.

The R and the R-square values were 0.9955 and 0,9910, respectively (see Fig. 2).

Measurement of a patient sample

Subsequent to the construction of the standard curve 93 patient blood samples were analysed using both the reference instrument and the above-described measuring equipment at 400 kHz.

The results obtained from measuring the imaginary part of the complex impedance were fed into the previously made calibration curve to transform them to haemoglobin values.

The calculated haemoglobin values (X-values), ranging between 80-180 were correlated with the haemoglobin values from the reference instrument (Y-values).

It was found that the factor A and the coefficient B were 12,33 and 0,7868, respectively.

The R and the R-square values were 0.8563 and 0,7333, respectively (see Fig. 3).

Example 2. Correlation studies of haemoglobin at 500 kHz

The standard curve for the measurement performed at 500 kHz was constructed in the same manner as in Example 1, which for this frequency resulted in A and B being 31,60 and -1451, respectively, and R and R-square being 0,9966 and 0,9932, respectively (see Fig. 4).

The correlation studies, which also were performed in the same manner as in Example 1, resulted in A and B being 6,065 and 0,8441, respectively, and R and R-square being 0,8943 and 0,7998, respectively (see Fig. 5).

Example 3. Correlation studies of haemoglobin at 600 kHz

The standard curve for the measurement performed at 600 kHz was constructed in the same manner as in Example 1, which for this frequency resulted in A and B being 30,67 and -1336, respectively, and R and R-square being 0,9974 and 0,9949, respectively (see Fig. 6).

The correlation studies, which also were performed in the same manner as in Example 1, resulted in A and B being 6,119 and 0,8578, respectively, and R and R-square being 0,9030 and 0,8155, respectively (see Fig. 7).

Example 4. Correlation studies of haemoglobin at 700 kHz

The standard curve for the measurement performed at 700 kHz was constructed in the same manner as in Example 1, which for this frequency resulted in A and B being 29,88 and -1255, respectively, and R and R-square being 0,9981 and 0,9961, respectively (see Fig. 8).

The correlation studies, which also were performed in the same manner as in Example 1, resulted in A and B being -0,7240 and 0,9136, respectively, and R and R-square being 0,9453 and 0,8937, respectively (see Fig. 9).

Example 5. Correlation studies of haemoglobin at 800 kHz

The standard curve for the measurement performed at 800 kHz was constructed in the same manner as in Example 1, which for this frequency resulted in A and B being 29,42 and -1200, respectively, and R and R-square being 0,9984 and 0,9968, respectively (see Fig. 10).

The correlation studies, which also were performed in the same manner as in Example 1, resulted in A and B being -1,120 and 0,9088, respectively, and R and R-square being 0,9478 and 0,8983, respectively (see Fig. 11).

Example 6. Correlation studies of haemoglobin at 900 kHz

The standard curve for the measurement performed at 900 kHz was constructed in the same manner as in Example 1, which for this frequency resulted in A and B being 29,13 and -1155, respectively, and R and R-square being 0,9986 and 0,9971, respectively (see Fig. 12).

The correlation studies, which also were performed in the same manner as in Example 1, resulted in A and B being 3,189 and 0,9021, respectively, and R and R-square being 0,9470 and 0,8967, respectively (see Fig. 13).

It should be understood that the detailed description and specific examples, while indicating preferred embodiments of the invention are given by way of example only. Various changes and modifications within the spirit and scope of the invention will become apparent to those skilled in the art from this detailed description.

CLAIMS

1. A method for blood analysis, comprising

detecting the imaginary part of the complex impedance in a blood sample having an unknown haemoglobin concentration, and

directly correlating the imaginary part of the complex impedance with the haemoglobin concentration in said blood sample.

2. Method for blood analysis according to claim 1, wherein the imaginary part of the complex impedance is measured within the frequency range 50-1200 kHz, preferably at about 800 kHz.

3. Method for blood analysis according to claim 2, wherein the imaginary part of the complex impedance is measured at one or more frequencies within said frequency range.

4. Method for blood analysis according to any of claims 1-3, which prior to the step of detecting the imaginary part of the complex impedance, comprises the further steps of:

providing a reference blood sample exhibiting an unknown haemoglobin concentration;

diluting said blood reference sample to obtain a set of reference blood samples having unknown haemoglobin concentrations;

determining the haemoglobin concentrations in said reference blood samples to obtain a set of reference blood samples having known haemoglobin concentrations;

applying an alternating current (A.C.) electrical field to each reference blood sample using electrodes in direct contact with the blood,

measuring the imaginary part of the complex impedance of each of said reference blood sample, at one or more frequencies within the frequency range 50 - 1200 kHz,

correlating the imaginary part of the complex impedance with the haemoglobin value of the blood in each of said reference samples to obtain one or more standard curves.

5. Method for blood analysis according to any of claims 1-3, which prior to the step of detecting the imaginary part of the complex impedance, comprises the further steps of:

providing a plurality of reference blood samples exhibiting unknown haemoglobin concentrations;

determining the haemoglobin concentrations in said reference blood samples to obtain a set of reference samples having different known haemoglobin concentrations;

applying an alternating current (A.C.) electrical field to each reference blood sample using electrodes in direct contact with the blood,

measuring the imaginary part of the complex impedance of each of said reference blood sample, at one or more frequencies within the frequency range 50 - 1200 kHz,

correlating the imaginary part of the complex impedance with the haemoglobin value of the blood in each of said reference samples to obtain one or more standard curves.

6. Method for blood analysis according to any of claims 1-3, which prior to the step of detecting the imaginary part of the complex impedance, comprises the further steps of:

providing a reference blood sample exhibiting a known haemoglobin concentration;

diluting said reference blood sample to obtain a set of reference samples having different known haemoglobin concentrations;

applying an alternating current (A.C.) electrical field to each reference blood sample using electrodes in direct contact with the blood,

measuring the imaginary part of the complex impedance of each of said reference blood sample, at one or more frequencies within the frequency range 50 - 1200 kHz,

correlating the imaginary part of the complex impedance with the haemoglobin value of the blood in each of said reference samples to obtain one or more standard curves.

7. Method for blood analysis according to any of claims 4-6, whereby the correlation comprises feeding the result obtained from measuring the imaginary part of the complex impedance of a blood sample having an unknown haemoglobin concentration at the chosen frequency/frequencies into said calibration curve/curves, to obtain its corresponding calculated haemoglobin concentration based on the imaginary part of the complex impedance of said blood sample.

8. Method for blood analysis according to claim 1, comprising

measuring the impedance in a blood sample having an unknown haemoglobin concentration using an impedance meter at one or more frequencies within the frequency range 50 - 1200 kHz.

9. A system for blood analysis, comprising

at least two electrodes (204) adapted to be introduced into a blood sample (203);

an impedance meter (205) coupled to said electrodes (204) and capable of delivering an alternating current in a frequency range of 50 - 1200 kHz, so as to enable measurement of impedance at one or more frequencies within said frequency range, and to deliver an out-signal in analogue or digital form;

a signal processing unit (207) for processing the impedance signal and calculating a haemoglobin value on the basis of said measured impedance.

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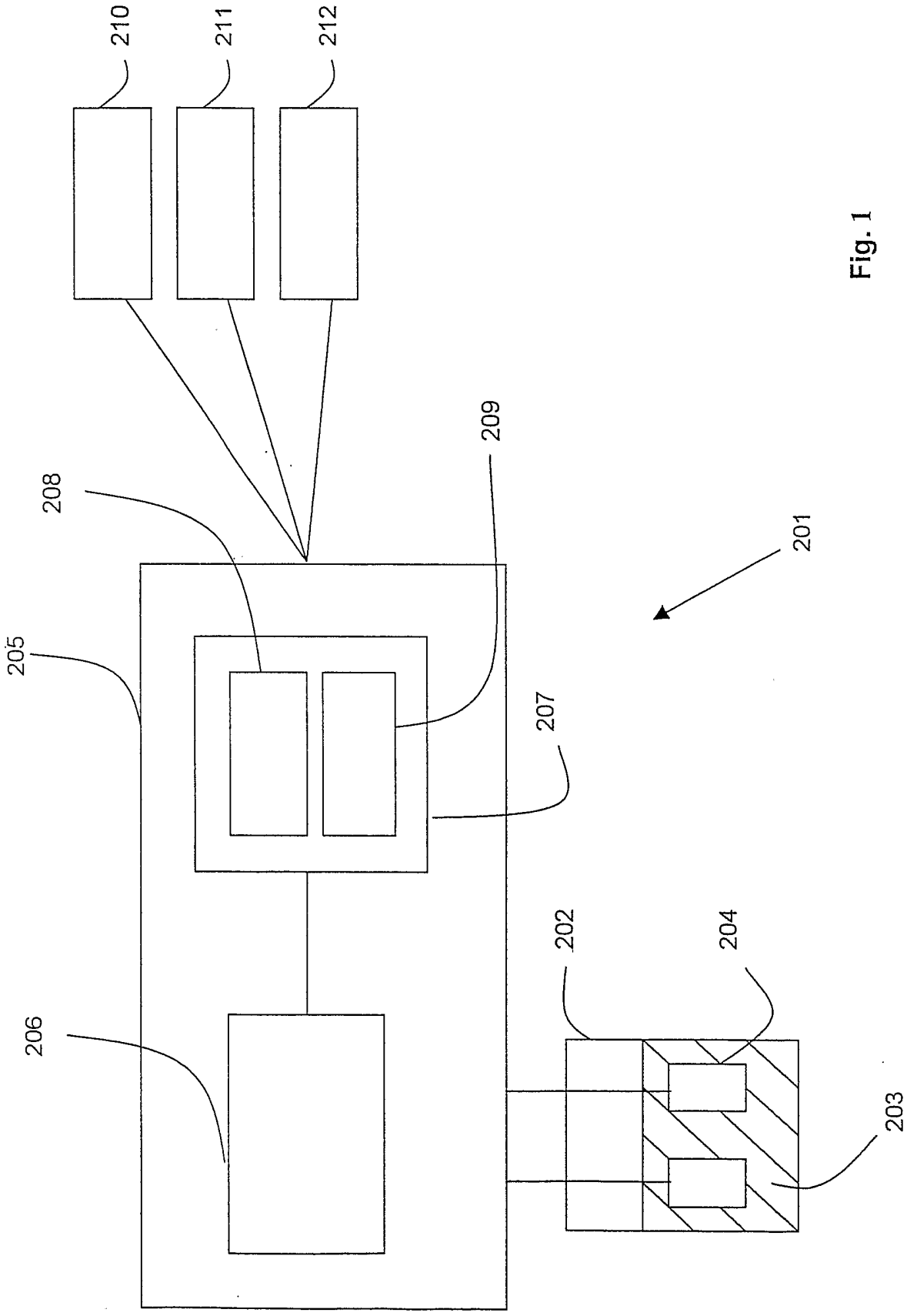
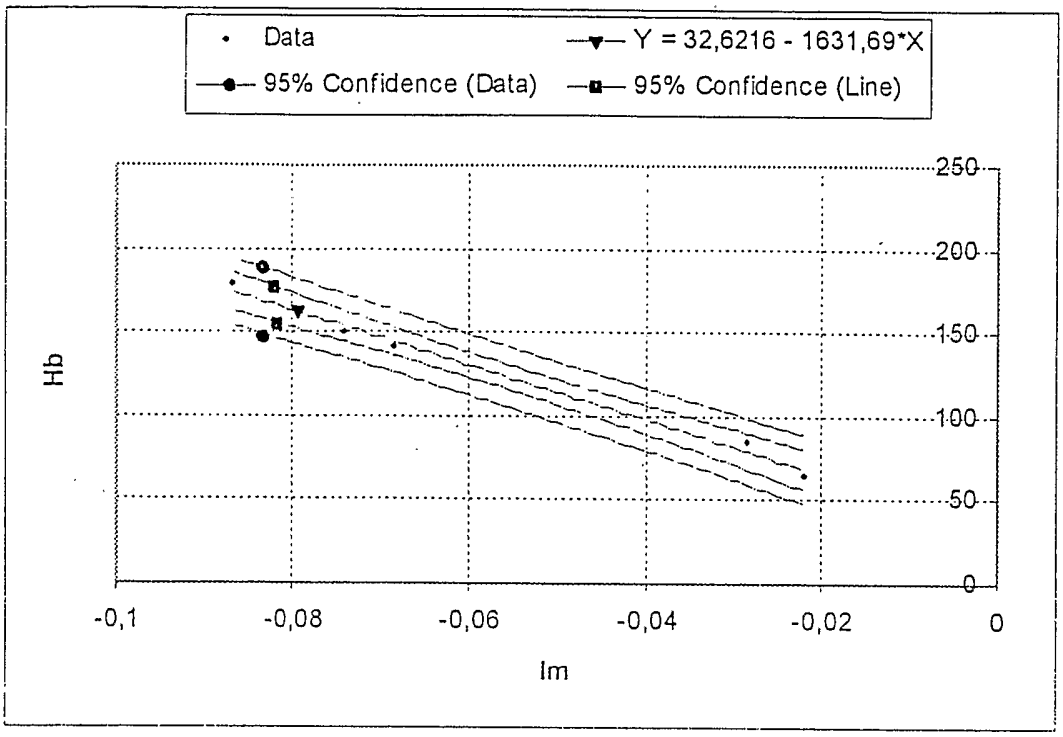


Fig. 1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95% Confidence (Line)
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50
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-0,02
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Im

Fig. 2

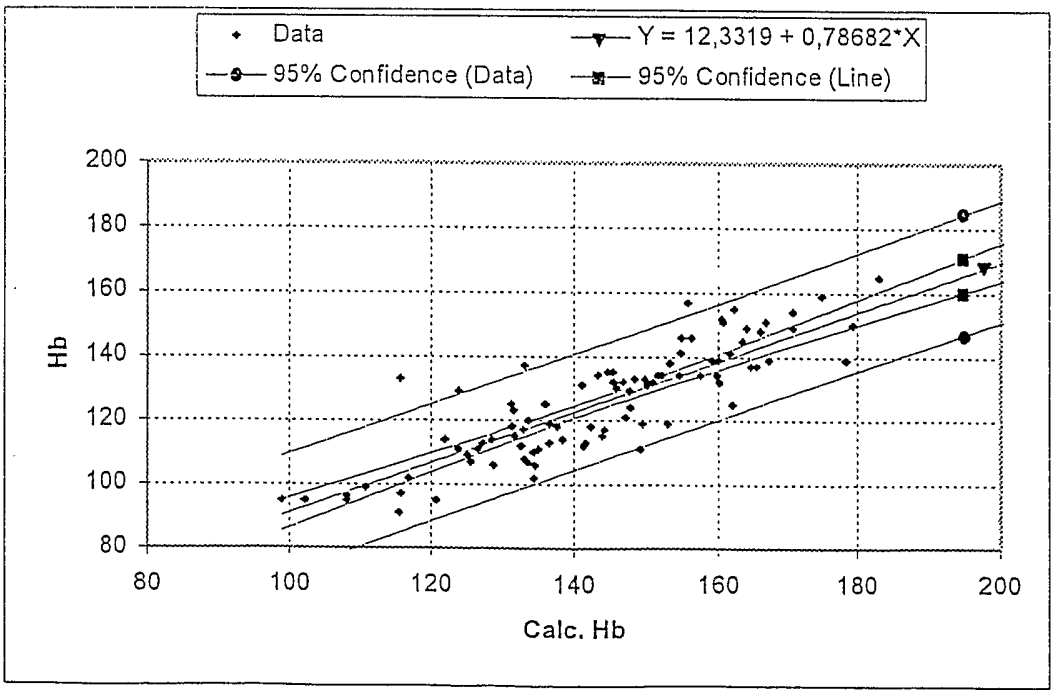
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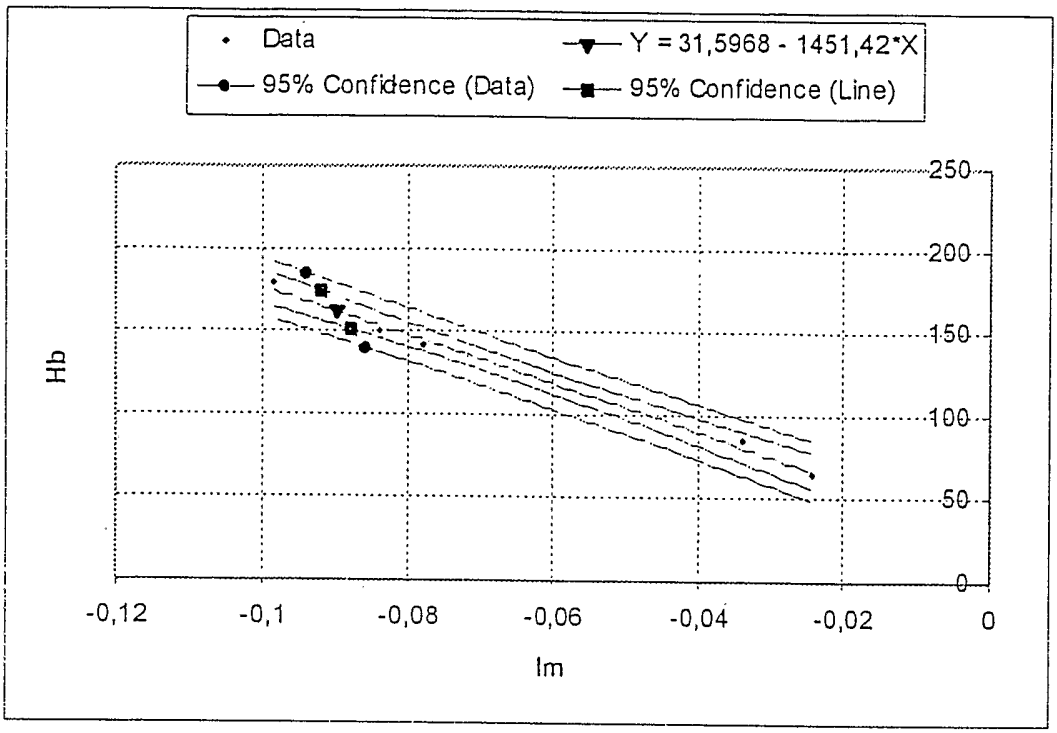
Fig. 3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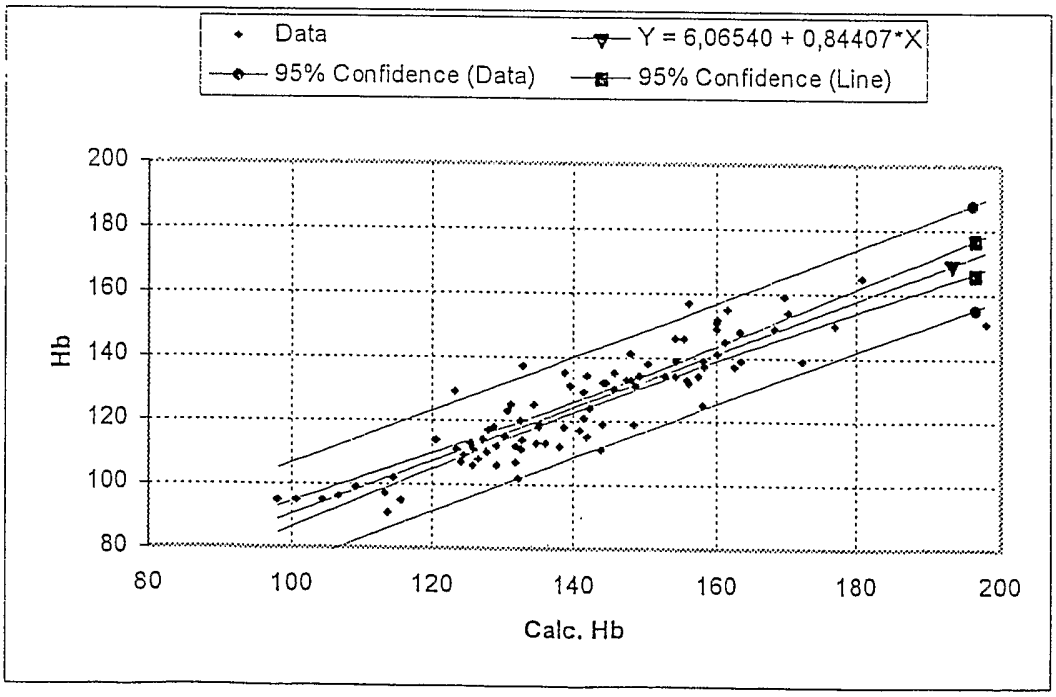
0
Im

Fig. 4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200
Calc. Hb

Fig. 5

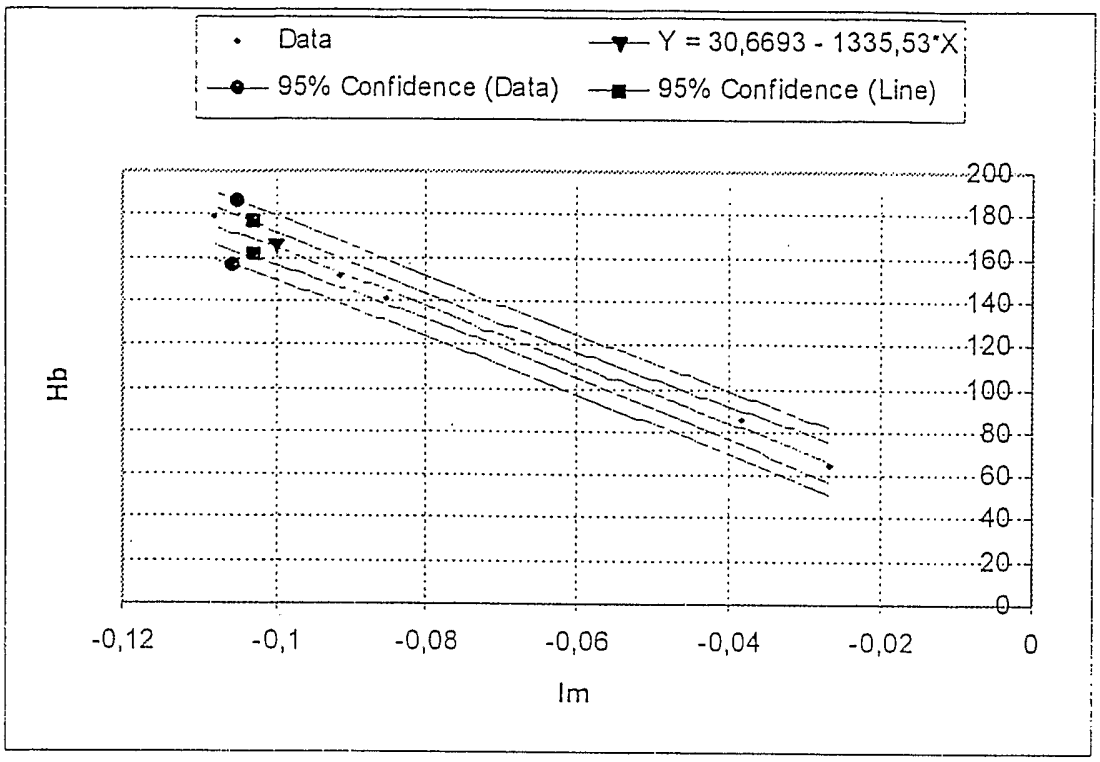
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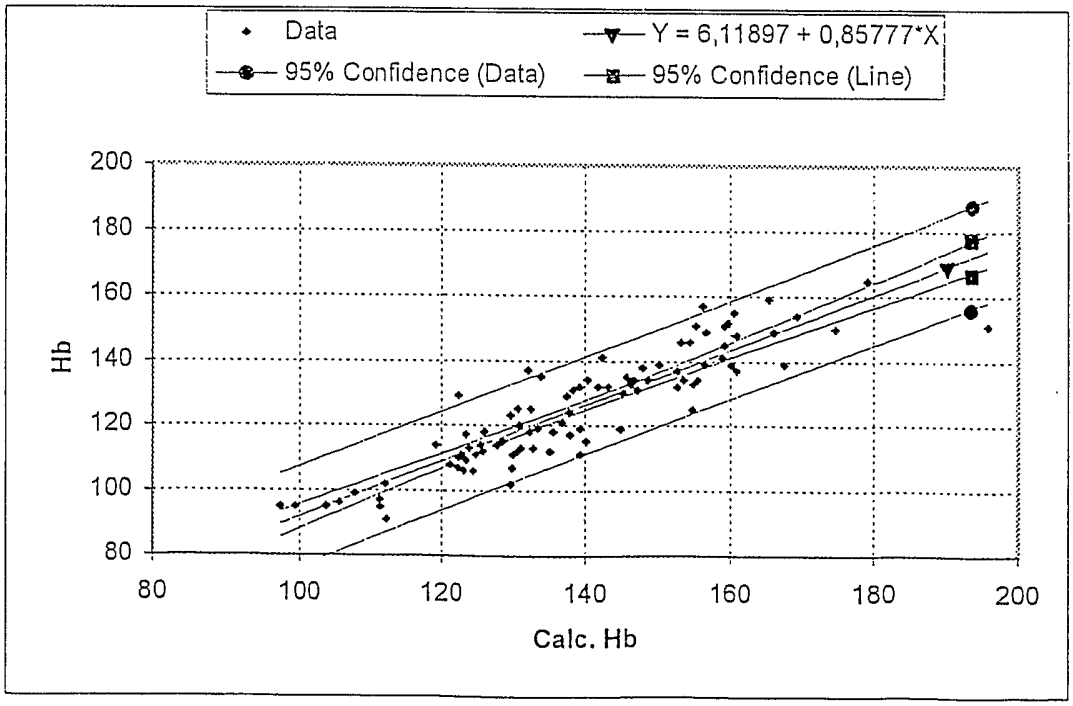
Fig. 6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95% Confidence (Line)
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Calc. Hb

Fig. 7

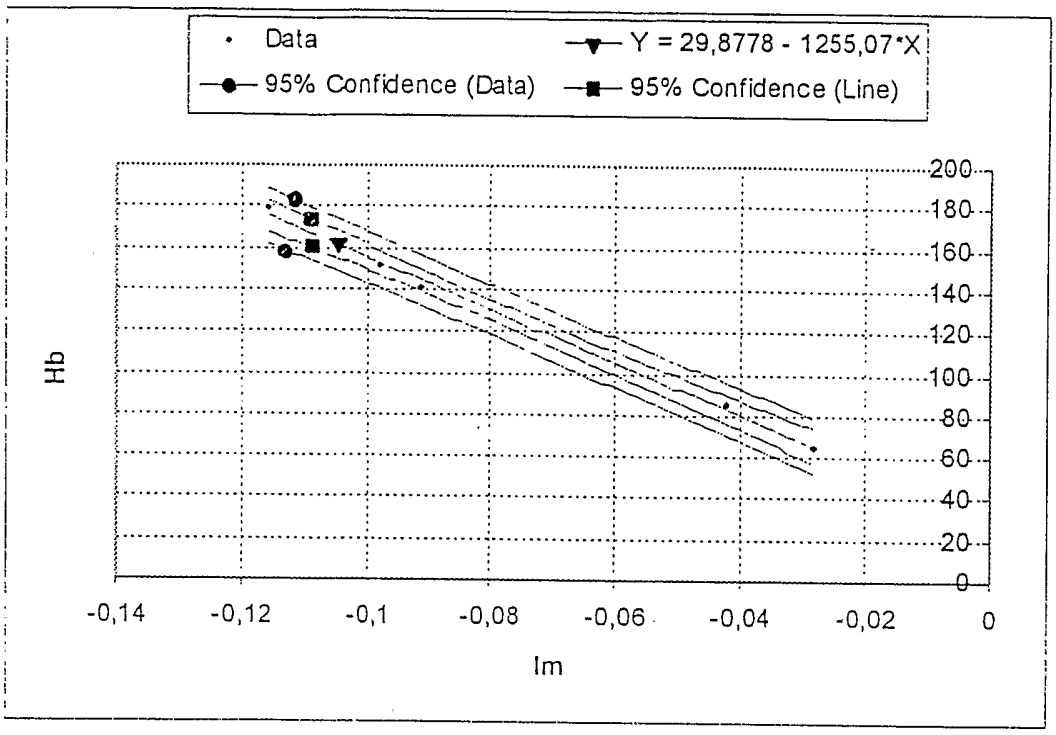
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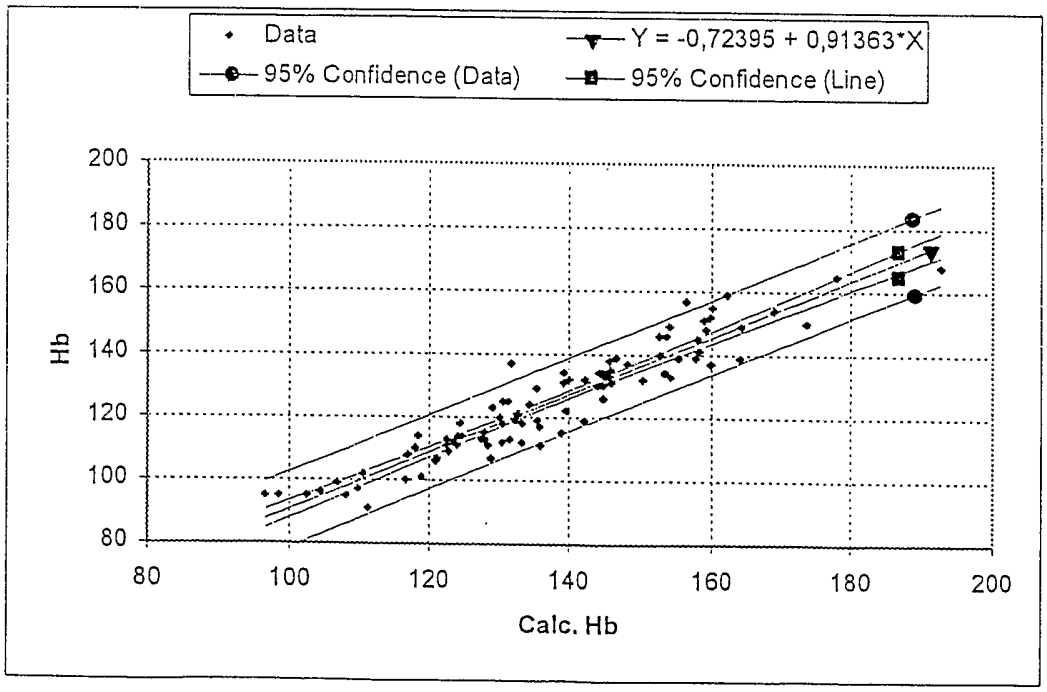
Fig. 8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95% Confidence (Line)
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80
80
100
120
140
160
180
200
Calc. Hb

Fig. 9

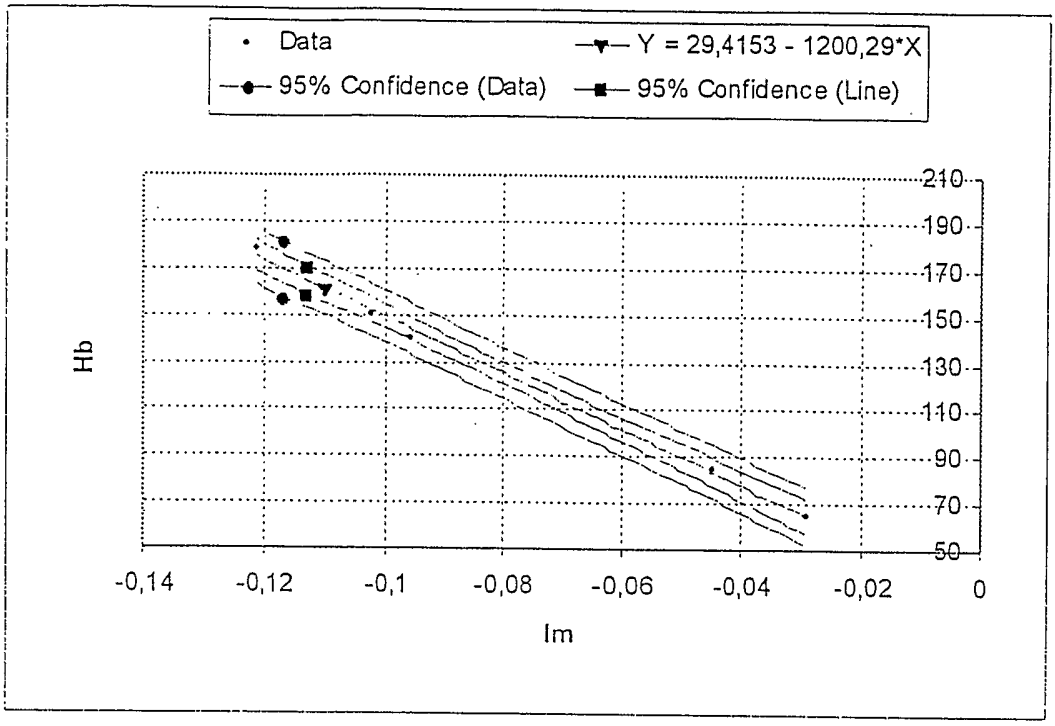
Data
Y = 29,4153 - 1200,29*X
95% Confidence (Data)
95% Confidence (Line)
Hb
210
190
170
150
130
110
90
70
50
-0,14
-0,12
-0,1
-0,08
-0,06
-0,04
-0,02
0
Im

Fig. 10

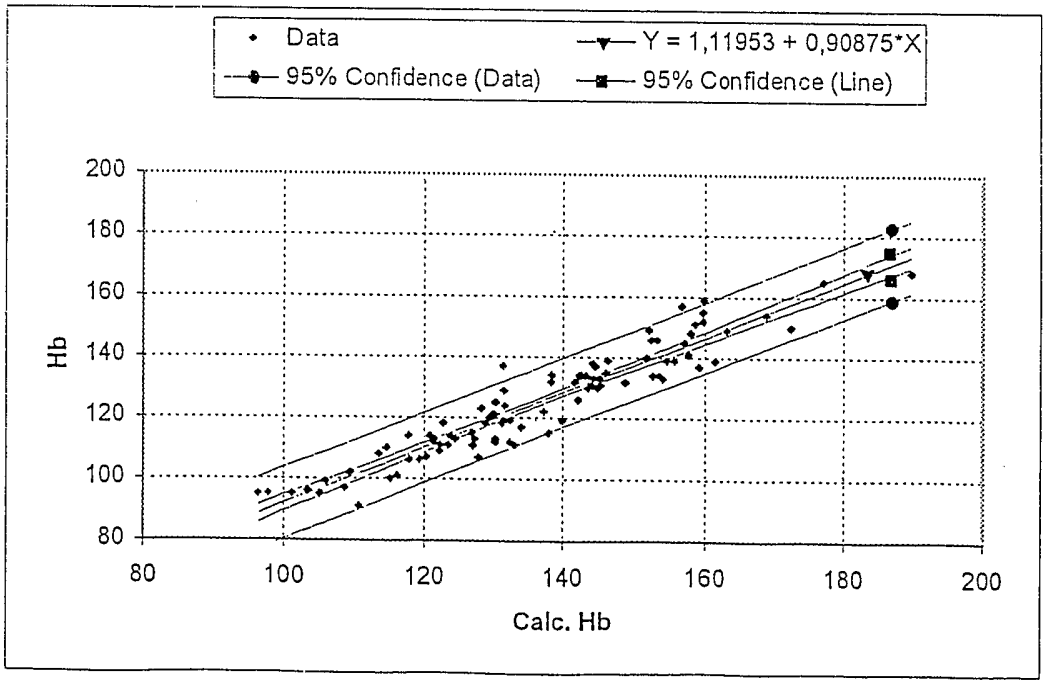
Data
Y = 1,11953 + 0,90875*X
95% Confidence (Data)
95% Confidence (Line)
Hb
200
180
160
140
120
100
80
80
100
120
140
160
180
200
Calc. Hb

Fig. 11

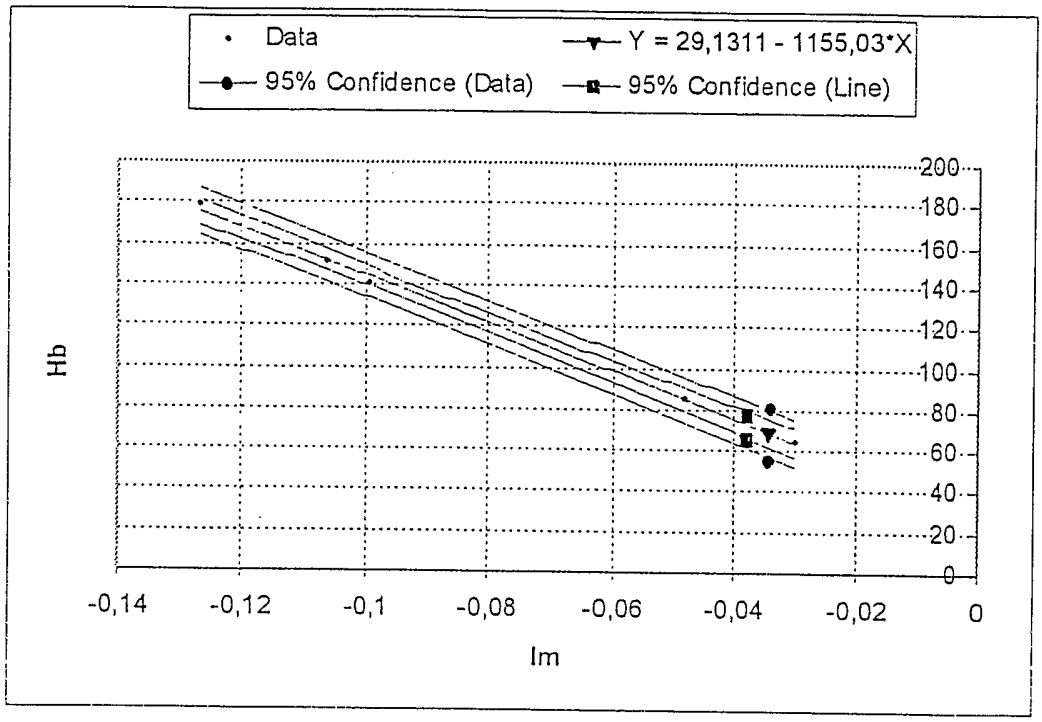
Data
Y = 29,1311 - 1155,03*X
95% Confidence (Data)
95% Confidence (Line)
Hb
200
180
160
140
120
100
80
60
40
20
0
-0,14
-0,12
-0,1
-0,08
-0,06
-0,04
-0,02
0
Im

Fig. 12

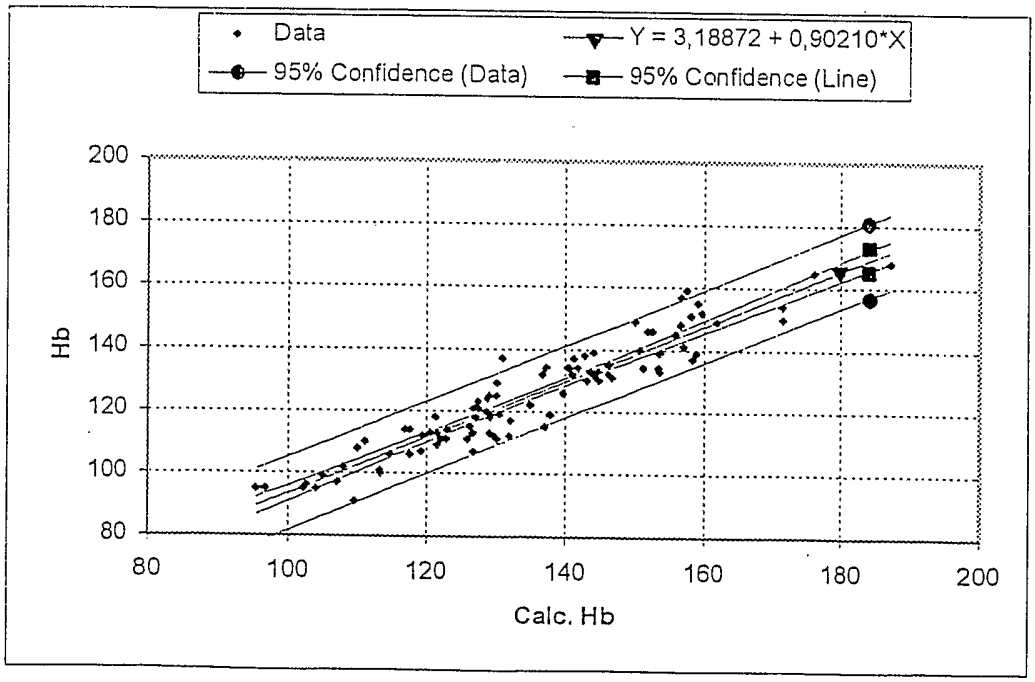
Data
Y = 3,18872 + 0,90210*X
95% Confidence (Data)
95% Confidence (Line)
Hb
200
180
160
140
120
100
80
80
100
120
140
160
180
200
Calc. Hb

Fig. 13

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 02/01530

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: G01N 27/02 // G01N 33/49, A61B 5/053
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)

IPC7: G01N

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

SE,DK,FI,NO classes as above

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

WPI DATA, EPO INTERNAL, PAJ, MEDLINE, CAPLUS, INSPEC, BIOSIS, EMBASE, SCISEARCH

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0417796 A2 (KABUSHIKI KAISHA TOYOTA CHUO KENKYUSHO), 20 March 1991 (20.03.91), abstract --	1-9
A	Med. Biol. Eng. Comput. vol. 37, 1999, M.Y. Jaffrin et al: "Comparison of optical, electrical, and centrifugation techniques for haematocrit monitoring of dialysed patients", pages 433-439, abstract -- --------	1-9

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

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"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)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"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
"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
"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
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
3 December 2002	04 -12- 2002
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Jens Waltin/Els Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

Information on patent family members

28/10/02

International application No.
PCT/SE 02/01530

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0417796 A2	20/03/91	SE 0417796 T3	
		DE 69014262 D,T	20/07/95
		JP 2665806 B	22/10/97
		JP 3099254 A	24/04/91