



(51) International Patent Classification:

G01R 33/46 (2006.01) G01R 33/28 (2006.01)  
A61B 5/00 (2006.01) G01V 3/00 (2006.01)

(21) International Application Number:

PCT/IL2013/050104

(22) International Filing Date:

5 February 2013 (05.02.2013)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

61/596, 569 8 February 2012 (08.02.2012) US

(71) Applicant: ANATECH ADVANCED NMR ALGORITHM TECHNOLOGIES LTD [IL/IL]; HaTavor 160, 44805 Nirit (IL).

(72) Inventors: SHAMES, Alexander; 14/8 Rahel Emeinu, 8459634 Beer-Sheva (IL). ROZENFELD, Yuri; 228/2 Ha-Keshet St. Neve Nof, 8050000 Yeruham (IL). KEINI, David; 3A Hardof St., 3474703 Haifa (IL).

(74) Agent: REINHOLD COHN AND PARTNERS; P.O.B. 13239, 61131 Tel-Aviv (IL).

(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, BN, BR, BW, BY, BZ, CA, CH, CL, 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, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, 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, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— of inventorship (Rule 4.17(iv))

Published:

— with international search report (Art. 21(3))

(54) Title: APPARATUS AND METHOD FOR NON-INVASIVE MEASUREMENT OF BLOOD PARAMETERS

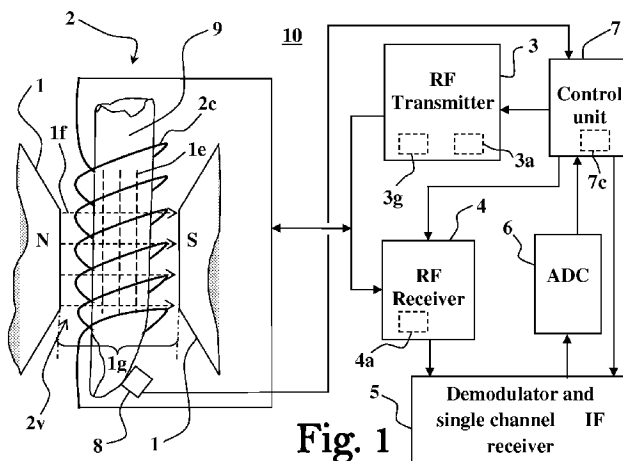


Fig. 1

(57) Abstract: The present invention provides techniques for non-invasive measurement of blood related parameters based on NMR (nuclei) relaxation techniques carried out using a relatively low constant magnetic field in the range of 0.15 to 0.5 Tesla. A plurality of electromagnetic excitation pulse sequences having relatively low radiofrequencies are applied over a living tissue placed in the magnetic field and blood related parameters of the examined subject are determined using a plurality of nuclear spin echo signals received from the tissue in response to the applied excitation sequences, thereby allowing to improve the accuracy of the obtained signals and substantially reducing the time duration of the process.

WO 2013/118115 A1

- 1 -

## APPARATUS AND METHOD FOR NON-INVASIVE MEASUREMENT OF BLOOD PARAMETERS

### TECHNOLOGICAL FIELD

The present invention is generally in the field of medical applications and relates to an apparatus and method for non-invasive assessment of living blood parameters, such as, for example, blood glucose content, blood viscosity, haematocrit, oxygen  
5 saturation and pH, using pulsed nuclear magnetic resonance (NMR) relaxometry techniques.

### BACKGROUND

There is an ongoing effort to develop non-invasive techniques for determining body fluid constituents, such as parameters of living blood. These non-invasive  
10 measurement techniques aim to simplify the test and constituents determination procedures, and substantially alleviate the discomfort associated with conventional invasive tests commonly used nowadays.

In case of diabetes, for example, diabetic patients must measure blood glucose by themselves on a daily basis by an *ex vivo* blood test. Self-monitoring of blood  
15 glucose is an important component of modern therapy for diabetic patients and offers information about blood glucose levels, and in many time points to enable stabilization of glucose levels in everyday life. The self-monitoring of blood glucose is suggested to be undertaken at least three or four times a day. However, it is reported that only 18% of diabetic patients periodically measure blood glucose levels, even in good social welfare  
20 sectors such as in the USA. Blood glucose measurement negligence is mainly due to invasive-type glucose meters that are used nowadays, that require in each test that blood samples be directly taken from the body of the patient *e.g.*, by piercing a finger of the patient. Such periodical blood tests employing the invasive method not only cause pain and discomfort during the blood taking process, but also impose mental and economic  
25 burdens with considerable costs of consumable accessories necessary for the blood taking operation.

Various devices for non-invasive measurement of blood glucose have been developed aiming to prevent the pain and displeasure associated with the conventional

- 2 -

blood taking process, to reduce use of diagnostic strips and the costs associated therewith, and to allow smoothly performing self-measurement of blood glucose levels. Such non-invasive blood glucose measurement techniques include, for example, analysis of a absorption spectrum in an infrared zone, impedance spectroscopy in a band  
5 of tens to hundreds MHz, and non-invasive blood glucose measurement based on NMR spectroscopy.

Some NMR based blood test techniques known from the patent literature will be briefly discussed below.

U.S. Patents Nos. 4,875,486, 5,685,300, 6,163,154, 6,404,197 and US patent  
10 publication No. 2010/030062A1, disclose NMR based techniques that are basically based on correlation between resonance peaks (or areas) appearing in NMR spectrum of blood (or of tissue) of the human body due to water and glucose components, or on a degree of chemical shift by the glucose component on the measured NMR caused by variations in a blood glucose concentration.

15 In the publication by Protasov *et al.*, (E. A. Protasov, O. C. Esikov and E. C. Karpova, "*Measurement of concentration of glucose in human blood by NMR method*," Scientific session MEPhI Conference, Vol. 5, pp. 3, 2003) a glucose concentration measurement method is described wherein an electromagnetic field is used and blood glucose levels are determined based on correlation between blood glucose levels  
20 measured in healthy subjects and a NMR spin-lattice relaxation time measured by a NMR absorption method.

US Patent No. 7,635,331 discloses a blood glucose sensor using permanent magnets to non-invasively measure blood glucose by means of the NMR absorption method applied to a human finger. In this non-invasive blood glucose sensor, a pair of  
25 permanent magnets is used to apply a constant magnetic field so as to remove variations in the magnetic field caused by an unstable power supply. A triangular waveform low frequency modulation magnetic field having uniform strength is used together with a weak acoustic wave modulation magnetic field to determine nuclear spin-lattice relaxation time of the finger's protons from changes of the NMR absorption signal as a  
30 function of low frequency modulation sequence. Blood glucose concentration is then determined by correlating between pre-determined blood glucose levels in healthy subjects and the determined proton spin-lattice relaxation time.

- 3 -

International patent publication No. WO 2012/118442 discloses techniques for *ex vivo* determining infection level of blood cells using magnetic resonance relaxometry. In this publication, a magnetic resonance relaxometry system is used to examine a sample of concentrated red blood cells taken from an examined subject by  
5 placing the red blood cells sample within a detection coil of the apparatus and determining an infection level based on transverse relaxation rates.

A non invasive blood fluidity measurement technique is described in EP 2,292,142, which suggests measuring the passage of light in a test site in a finger area of a patient, where pressure is applied over the test site in order to squeeze and  
10 flow out blood therefrom to the periphery of the test site.

#### GENERAL DESCRIPTION

There is need in the art for a novel measurement technique for non invasively measuring various blood related parameters which would provide accurate measurements within a short measurement time (no more than a few minutes) and  
15 moreover enable a measurement device to be miniature/portable, *e.g.*, of a hand held configuration.

The inventors of the present invention have surprisingly found that blood parameters of a subject may be non-invasively determined with improved accuracy, and within a relatively short time duration of measurement session, when employing  
20 magnetic resonance relaxometry techniques utilizing proper parameters of the magnetic field excitation stage. The apparatus of the present invention operates with a constant magnetic field which is a relatively low field, *i.e.*, in the range of 0.15 to 0.5 Tesla, and electromagnetic excitation signals of relatively low radiofrequencies, *i.e.*, in the range of 1 to 20 MHz. These parameters of the excitation stage enable use of smaller and simpler  
25 magnetic elements, thus significantly reducing the size, weight, and complexity of mechanical and electronic circuits of the measurement apparatus.

Decrease in the above parameters of the excitation stage might result in reduction of the signal-to-noise ratio of the detection stage. The present invention solves this problem by providing a certain time pattern for the excitation session and detection  
30 session based on relaxation curves associated with blood constituents.

The present invention thus provides a method and apparatus for *in vivo* non-invasive measurement of blood parameters based on NMR (nuclei) relaxation

- 4 -

techniques carried out on an organ (body part of the examined subject, such as a finger phalange, also referred to as a tissue or test organ) over which a relatively low constant magnetic field in the range of 0.15 to 0.5 Tesla is applied. Blood parameters of the examined subject are determined using nuclear spin echo signals received from the test  
5 organ in response to specific (*e.g.*, short hard off-resonance) electromagnetic pulse sequences having relatively low radiofrequencies (RF). As will be understood from the following disclosure the techniques described herein allow determining nuclear spin echo signals received from living body tissue and/or fluids of an examined subject in response to electromagnetic excitation signals, with improved selectivity with regard to  
10 different blood/tissue components and within relatively short durations of time (*e.g.*, within 1 to 5 minutes).

In general, techniques of the present invention employ a pulsed NMR apparatus to acquire nuclear spin echo signals. The NMR apparatus comprises a probehead configured and operable to accommodate the test organ of the examined subject in a test  
15 volume defined therein. The probehead is configured and operable to apply the constant magnetic field inside the test volume, apply electromagnetic excitation signals over the test organ located inside the test volume, and acquire electromagnetic signals from the test organ responsive to the applied excitation signals. The excitation signals are applied in some embodiments in a direction substantially perpendicular to the  
20 direction of the constant magnetic field.

The NMR apparatus further comprises a receiver configured and operable to process the electromagnetic signals received by the probehead and extract therefrom nuclear spin echo signals. In some possible embodiments the receiver is a single channel receiver. For example, the receiver may comprise a single channel IF receiver  
25 configured and operable to down convert the electromagnetic signals received by the probehead from the test organ. The receiver may further comprise a demodulator configured and operable to extract the nuclear spin echo signals from the signals received from the probehead unit. The nuclear spin echo signals are then processed by a processor to determine one or more blood parameters of the tested subject.

30 The probehead may include a magnetostatic field applying unit comprising a permanent magnet assembly or Helmholtz coils for applying the constant magnetic field. For example, in some embodiments the constant magnetic field is obtained between magnetic poles of a permanent magnet assembly, thereby defining the test

- 5 -

volume between the magnetic poles of the permanent magnet assembly. The test volume may be configured in the form of a gap or, alternatively, an elongated chamber adapted to accommodate a finger of the examined subject, or a portion thereof (*e.g.*, one or more finger phalanges).

5           The probehead further comprises at least one inductive coil located along a length of the test volume under which the constant magnetic field is applied by the magnetostatic field applying unit. The coil is configured and operable to receive a portion of the test organ within its coil turns, to apply the electromagnetic excitation signals along a length of the test organ portion disposed in it, and acquire  
10 electromagnetic signals from the test organ responsive to the applied excitation signals. The coil may thus apply the electromagnetic excitation signals in a direction substantially perpendicular to the direction of the constant magnetic field applied inside the test volume.

          The blood parameters of the examined subject are determined in some  
15 embodiments based on relaxation time / relaxation rates extracted from the decaying / uprising nuclear spin echo signals (nuclear magnetization relaxation curves), said nuclear relaxation times / rates associated with different blood constituents of the examined subject. In some embodiments the relaxation times / rates are determined using a multifunctional analysis technique employing multi-dimensional (*e.g.*, two-  
20 dimensional, or three-dimensional) data, acquired as sets of one-dimensional spin echo signals obtained with at least one variable delay time, to thereby achieve sensitive, selective and reliable correlations of the measured relaxation times / rates with predetermined relaxation times / rates associated with blood parameters of healthy and deceased subjects.

25           In some embodiments the excitation signals comprise a plurality of radiofrequency pulse sequences, each pulse sequence comprising two or more radiofrequency pulses having predetermined time durations and predetermined delay times separating between successive pulses in the pulse sequence. Accordingly, responsive to the plurality of pulse sequences, a plurality of decaying spin echo signals  
30 are obtained, the plurality of decaying spin echoes may be processed to obtain spin echo signals with improved signal to noise ratios. The delay times used to separate between successive pulses on the time axis may vary from one pulse sequence to another. For

- 6 -

example, the delay times used in successively applied pulse sequences may be gradually increased (or decreased).

There is thus provided an apparatus for use in non-invasive assessment of blood related parameters (*e.g.*, blood glucose content, blood viscosity, blood haematocrit, 5 blood oxygen saturation, and blood pH) of an examined subject. According to some embodiments the apparatus comprises a signal generator configured and operable to generate excitation signals (*e.g.*, off-resonance excitation pulses) in a radiofrequency range of 1 to 20 MHz and a probehead unit (*e.g.*, having an electromagnetic shield to substantially attenuate external electromagnetic interferences) defining a test site for a 10 living tissue of the subject being examined and comprising a magnetic field source unit configured and operable to generate a substantially uniform magnetic field of about 0.15 to 0.5 Tesla in a magnetic field region in which the test site is located, to thereby magnetize blood in said living tissue, at least one inductive coil (*e.g.*, having a cylindrical or a saddle shape) placed in the test site so as to be in the magnetic field 15 region and to be exposed to the excitation signals, the inductive coil being configured to surround at least a part of the living tissue when placed in said test site, the at least one inductive coil thereby responding to said magnetic field and said RF excitation signals by generation of electromagnetic excitation signals in a direction substantially perpendicular to a direction of the magnetic field to thereby affect the blood 20 magnetization in the living tissue, and generating an electromagnetic response to nuclear spin echo signals from the living tissue.

The apparatus comprises a receiver unit (*e.g.*, a single channel IF receiver) configured and operable to receive the electromagnetic response of the at least one inductive coil and generate measured data indicative thereof, and a control unit 25 connected to the probehead unit for operating the signal generator and to the receiver to provide predetermined time patterns of the generation of the excitation RF signals and of the receipt of the electromagnetic response, the control unit being configured and operable to process the measured data and extract data indicative of the nuclear spin echo signals from the living tissue, to determine relaxation magnetization curves (*e.g.*, 30  $T_{1i}$  spin-lattice relaxation magnetization curves,  $T_{1pi}$  spin-lattice relaxation magnetization in rotating frame curves, and/or  $T_{2i}$  spin-spin relaxation magnetization decays) of blood constituents associated with the blood related parameters, and determine at least one blood related parameter.

- 7 -

The receiver unit may comprise a demodulator configured and operable for demodulating signals associated with the nuclear spin echo signals from the electromagnetic response. The receiver unit may further comprise a signal amplifier for amplifying the electromagnetic response from the coil.

5 In some applications the control unit comprises a pulse controller module configured and operable to switch the apparatus operation between its excitation and acquisition cycles.

According to some embodiments the apparatus also comprises a pulsed RF generator and pulsed RF power amplifier configured and operable to generate the  
10 excitation signals.

In some applications the magnetic field source unit comprises a thermostabilized permanent magnet assembly (e.g., made from rare-earth hard magnetic materials such as, but not limited to,  $\text{Sm}_x\text{Co}_y$  and/or NdFeB alloys.) and/or a set of Helmholtz coils. For example, the Helmholtz coils may be configured and operable to correct  
15 temperature field drift and/or homogeneity.

In some embodiments the probehead further comprises a temperature sensor configured and operable to measure temperature of the tissue and generate temperature data indicative thereof, and the control unit is configured and operable to determine the at least one blood related parameter based on said temperature data.

20 According to another aspect, there is provided a method for use in non-invasive assessment of blood related parameters, the method comprising creating a substantially uniform magnetic field of about 0.15 to 0.5 Tesla within a magnetic field region at least partially overlapping with a test site where living tissue of an examined subject is to be located, to thereby magnetize blood in said living tissue, applying electromagnetic  
25 excitation signals of a range of 1 to 20 MHz in said test site to thereby affect the blood magnetization in the living tissue to cause nuclear spin echo signals from the living tissue, the electromagnetic excitation signals being applied with a predetermined time pattern, receiving, with a predetermined time pattern, electromagnetic radiation responsive to the nuclear spin echo signals from the living tissue, processing data  
30 corresponding to the received electromagnetic radiation, extracting therefrom data indicative of the nuclear spin echo signals from the living tissue, and determining relaxation time curves (e.g., using a multifunctional approximation) of blood

- 8 -

constituents associated with the blood related parameters, to thereby determine at least one blood related parameter.

In some embodiments the determining of the blood related parameters comprises correlating the obtained relaxation time curves with a pre-determined matrix of relaxation time curves associated with the blood related parameters. In some applications the pre-determined matrix of relaxation times is calibrated to comply with a set of blood related parameters measured for the examined subject using conventional *ex vivo* blood test. In this way sensitivity of the blood assessment to a predetermined blood related parameter may substantially improved.

10 The excitation signals may comprise an overturning excitation signal having a predetermined time duration  $\tau_1$  to overturn magnetization of blood constituents' nuclei towards a plane substantially perpendicular to direction of electromagnetic field of said signal, and a consecutive refocusing signal having a time duration  $\tau_2 \geq \tau_1$  to turn magnetization of the blood constituents' nuclei towards a plane substantially perpendicular to the direction of electromagnetic field of said signal to form nuclear spin echo, said overturning and refocusing signals being separated by a predetermined time delay.

In some applications the excitation sequence comprises at least one additional excitation pulse applied before the overturning excitation signal and having a predetermined time duration  $\tau_{pj}$  and predetermined time delay  $\tau_{dk}$ , to thereby form specific excitation sequence of electromagnetic field pulses suitable for exciting time dependent magnetizations of the blood constituents' nuclei.

Optionally, the time delay between the overturning and refocusing signals is adjusted to obtain the electromagnetic radiation responsive to the nuclear spin echo signals within a predefined time duration after the refocusing signal, said predefined time duration being greater than a predetermined dead time associated with the receiving of the electromagnetic radiation.

In some embodiments the method comprises applying the excitation signals a predetermined number of times, the time delay between the overturning signal and the refocusing signal being different in at least some of the excitation sequences, and determining the blood related parameters based on magnetization relaxation time curves determined for electromagnetic radiation received in response to the applied excitation signals.

- 9 -

In some applications the radio frequency of the excitation signals is set for carrying out NMR relaxometry for one or more of the following protons:  $^1\text{H}$ ,  $^{13}\text{C}$ ,  $^{19}\text{F}$ , and  $^{31}\text{P}$ .

The magnetization relaxation curve may be built from nuclear spin echoes  
5 obtained using the Hahn technique or solid echo technique. In possible applications, the electromagnetic excitation signals are carried out according to one or more of the following techniques: inversion recovery technique, progressive saturation technique, spin-lock technique, Hahn technique, and Carr-Purcell-Meiboom-Gill (CPMG) technique.

## 10 BRIEF DESCRIPTION OF THE DRAWINGS

In order to understand the invention and to see how it may be carried out in practice, embodiments will now be described, by way of non-limiting example only, with reference to the accompanying drawings, in which like reference numerals are used to indicate corresponding parts, and in which:

15 **Fig. 1** is a block diagram of a non-invasive blood parameters measurement apparatus according to some possible embodiments;

**Fig. 2** schematically illustrate a possible Hahn spin echo excitation pulse sequence, and acquisition having a variable delay usable for measurements of  $T_{2i}$  spin-spin relaxation times in living blood according to some possible embodiments;

20 **Fig. 3** shows graphical plots of experimental spin echo values, best least-square fit carried out using a single exponential model, and best least-square fit carried out using a double exponential model, obtained with the setup used in **Example 1**;

**Fig. 4** schematically illustrates a saturation comb excitation sequence combined with phase cycled Hahn spin echo detection, and having a variable delay time  $\tau_{dRi}$ , as  
25 used in **Example 2** to measure  $T_{1i}$  spin-lattice relaxation times in living blood;

**Fig. 5** shows graphical plots of experimental spin echo values, best least-square fit carried out using a single exponential model, and best least-square fit carried out using a double exponential model, obtained with the setup used in **Example 2**;

**Fig. 6** is a graphical illustration showing the dependence of the  $^1\text{H}$  spin-lattice  
30 relaxation time  $T_{1i}$  measured in **Example 3** on a series of forefinger phalanges as a function of blood glucose content;

- 10 -

**Fig. 7** is a graphical illustration showing dependence of the  $^1\text{H}$  spin-lattice relaxation time  $T_1$  measured in **Example 4** on a series of fresh blood samples as a function of blood viscosity; and

**Fig. 8** is a flowchart demonstrating a process for assessing blood parameters of a  
5 subject according to some possible embodiments.

### DETAILED DESCRIPTION OF EMBODIMENTS

The present invention is directed to techniques of *in vivo* non-invasive assessment of living blood parameters (such as glucose concentration, whole blood  
10 viscosity, haematocrit, oxygen saturation, pH) based on pulsed nuclear magnetic resonance (NMR) relaxometry applied to a finger of a subject.

According to some possible embodiments NMR signals are obtained from a finger phalange of an examined subject using a NMR probehead designed to accommodate at least a portion of the examined finger inside an inductive coil located  
15 between poles of a constant magnet assembly. Accordingly, the probehead may be configured to define an elongated test volume having geometrical dimensions suitable to accommodate the examined finger, and apply a magnetostatic field in a first direction inside the test volume. In this way, the magnetostatic field is applied over the examined finger once it is introduced into the test volume of the NMR probehead. The inductive  
20 coil of the probehead is preferably configured to apply electromagnetic excitation signals in a second direction being substantially perpendicular to the direction of the magnetostatic field applied by the constant magnet assembly, and acquire responsive electromagnetic relaxation signals from the examined organ.

In some possible embodiments the magnetostatic field applied by the constant  
25 magnet assembly is substantially perpendicular to a longitudinal axis of the examined finger *i.e.*, perpendicular to the length of the examined finger. Accordingly, the electromagnetic excitation signals in such embodiments are applied in a direction being substantially perpendicular to the direction of the applied magnetostatic field such that it is substantially aligned with the longitudinal axis of the examined finger *i.e.*, along the  
30 length of the examined finger.

The permanent magnet assembly may be adapted to apply a magnetostatic field having sufficient homogeneity (*e.g.*, smaller than 10 ppm) over the test volume.

- 11 -

For example, in some embodiments an *in vivo* blood test is carried out by placing a finger phalange in the test volume of the probehead (*i.e.*, where the magnetostatic field is generated), applying electromagnetic energy pulses (also referred to herein as excitation signals) by a coil of the probehead to excite nuclear spin echoes  
5 from protons (or other nuclei) in the living liquids, tissues and bones of the finger, and using the probehead coil to acquire electromagnetic relaxation signals from the finger phalange in response to the applied excitation signals. The acquired relaxation signals are then analyzed and processed to obtain NMR signals (*e.g.*, spin-lattice and/or spin-spin relaxation signals) of the excited nuclei, and the blood parameters of the examined  
10 organ are determined based on the NMR signals obtained.

For instance, the nuclear spin-lattice and/or the spin-spin relaxation times of various kinds of protons (or other nuclei) in the fluids, tissues and bones, of the examined finger may be determined employing comprehensive multifunctional analysis of the nuclear spin echo decay measured after specific sequences of the excitation radio  
15 frequency pulses have been applied. In this way, assessment of various blood parameters may be carried out by correlating between a pre-determined matrix of various spin-lattice and spin-spin relaxation times / rates associated with blood parameters obtained from healthy subjects and nuclear spin-lattice and spin-spin relaxation times / rates obtained from the examined finger.

20 In some possible embodiments the magnetostatic field applied by the constant magnet assembly in the test volume is in the range of 0.15 to 0.5 Tesla, preferably about 0.3 Tesla. In some embodiments the frequency of the applied electromagnetic energy (also referred to herein as radio frequency pulses) is in the range of 1 MHz to 20 MHz, preferably about 10 to 20 MHz. For example, the frequency of the electromagnetic  
25 excitation signals applied by the probehead may be within a radio frequency band chosen to satisfy off-resonance excitation conditions *e.g.*, by controllably shifting the frequency of the excitation signal pulses from the exact resonance frequency associated with nuclei of a particular material being examined.

In some possible embodiments, a pulsed radio frequency generator is used for  
30 generating the electromagnetic (radio frequency) excitation pulses applied over the examined finger through the inductive coil of the probehead.

With reference to **Fig. 1**, there is shown a compact (*e.g.*, desktop size *i.e.*, that may be placed on a desk, for example is size of a desktop printer) light weight (*e.g.*, up

- 12 -

to 5 kg) apparatus **10** for non-invasive assessment of blood parameters according to some possible embodiments. The apparatus **10** comprises an inductive NMR probehead **2** comprising an inductive coil **2c** arranged along a test volume **2v** defined inside the probehead **2**. As shown in **Fig. 1**, the coil **2c** is adapted to receive the finger **9** of the tested subject within its windings. The coil **2c** may be made from wound electrical conducting wire made from silver, or silver plated copper, and having a wire cross sectional area of about 0.2 to 3 mm<sup>2</sup>. For example, in some embodiments the internal diameter of the coil **2c** should be sufficient to accommodate a phalange of a forefinger *e.g.*, in the range of 20 to 35 mm, preferably about 30 mm. The number of coil turns in coil **2c** may generally be about 20 to 50.

In the apparatus exemplified in **Fig. 1** the finger **9** is introduced into the test volume **2v** such that the magnetic field **1f** from the magnet assembly **1** is applied over a portion of the finger **9** placed between the "N" and "S" poles of the magnet assembly **1**. In this example, the permanent magnet assembly **1** is configured to apply a magnetostatic field **1f** being substantially perpendicular to the length of the finger **9** and the coil **2c** is adapted to apply the electromagnetic excitation signals **1e** substantially along the length of the examined finger, such that the direction of the magnetic field **1f** is substantially perpendicular to the direction of the excitation signals **1e**.

For example, the permanent magnet assembly **1** may be constructed from two or more permanent magnets (*e.g.*, made from samarium cobalt or neodymium-iron-boron alloys) arranged to define the test volume **2v** between at least one pair of "N" and "P" poles of the permanent magnet arrangement. In some embodiments the volume in gap **1g**, between the "N" and "P" poles of the magnet arrangement **1** defining the test volume **2v**, is about 500 to 700 mm<sup>3</sup>. With this configuration the magnetic field **1f** in the test volume **2v** may generally be in the range of 0.15 to 0.5 Tesla.

In preferred embodiments the apparatus **10** is configured to apply a relatively low (*e.g.*, 0.15 to 0.5 Tesla) and uniform constant magnetic field **1f** over the examined finger, and off-resonance low radio frequency excitation signal pulses **1e** (*e.g.*, in the range of 1 MHz to 20 MHz) in a direction substantially perpendicular to the direction of the magnetic field **1f**.

The magnet arrangement **1** may further include a pair of Helmholtz coils (not shown) configured and operable to correct temperature field drift and/or linear homogeneity of the constant magnetic field **1f** generated by the permanent magnets. It is

- 13 -

known that permanent magnets have significant temperature drift of their main field. This drift may be compensated by precise thermal stabilization of the magnet, or by applying correction current to the Helmholtz coils. The same coils may be used for improvement of the field's linear homogeneity.

5           It is however noted that other probehead arrangements may be employed to apply the magnetic field **1f** and the excitation signals **1e** in directions that are different from those demonstrated in **Fig. 1**, while guaranteeing that the direction of the magnetic field **1f** is substantially perpendicular to the direction of the excitation signals **1e**.

          In some embodiments the probehead **2** further comprises circuitry for automatic  
10 switching between working resonant frequencies, and/or circuitry for automatic tuning and matching. The operation and design of such circuitries is known to those skilled in the art and thus will not be described herein for the sake of brevity.

          It is noted that the magnetic field obtained using such small sized permanent magnet assembly **1** (*e.g.*, about 80×60×40 mm<sup>3</sup>) cannot be homogeneous enough within  
15 the test volume **2v** configured to accommodate a phalange of the finger **9**. Therefore, the NMR tests carried out with apparatus **10** are performed using a magnetic field having quite modest (less than 20 ppm) homogeneity. This means that the NMR signals obtained using apparatus **10** have quite broad lines (in frequency domain) or short free induction decay (FID) (in time domain).

20           The registration of short FIDs is a complicated task (due to receiver dead time and circuit ringing artifacts), and therefore, according to some possible embodiments, measurements of the relaxation signals are carried out using nuclear spin echo signals in a time domain. In this way, the received NMR signals may be shifted from the "dangerous" dead time region of the circuitry. Moreover, the intensity of echoes in  
25 slightly inhomogeneous fields is typically quite strong, such that working with spin echo signals allow precise measurements of even short T<sub>1</sub> (*i.e.*, spin-lattice relaxation times) and T<sub>2</sub> (*i.e.*, spin-spin relaxation times) values (*e.g.*, in the range of 20 – 100 microseconds).

          The NMR apparatus **10** further comprises a pulsed RF transmitter **3** electrically  
30 connected to the probehead **2** and configured and operable to apply radio frequency excitation signals through the inductive coil **2c** of the probehead. The probehead **2** is further connected to an RF receiver **4** configured and operable to receive through the coil **2c** radio frequency electromagnetic relaxation signals from the examined finger **9**

- 14 -

responsive to the radio frequency excitation signals applied by the RF transmitter **3**. A single channel IF (intermediate frequency) receiver and demodulator unit **5** may be used to down convert the RF relaxation signals received from the receiver **4** and demodulate the down-converted signals. As exemplified in **Fig.1**, the control unit **7** may be  
5 configured and operable to provide the demodulator unit **5** control signal for adjusting the gain of the IF receiver. For example, when operating with different materials (changing the nuclei under examination *e.g.*, from  $^1\text{H}$  to  $^{19}\text{F}$ ) unit **5** adjusts the frequency of signals generated by its local oscillator **5a**, to obtain the same intermediate frequency (IF), and also adjusts the gain of the IF receiver.

10 In some embodiments the transmitter **3** comprises a pulsed RF generator **3g** and pulsed RF power amplifier **3a** configured and operable to generate high power RF excitation pulses to be applied to the examined finger **9** through the coil **2c** of the probehead **2**. In addition, in some possible embodiments the receiver **4** comprises a signal amplifier **4a** configured and operable to amplify electromagnetic signals received  
15 from the coil **2c**.

According to some possible embodiments, a pulse controller module **7c** may be used in the control unit **7** to switch the apparatus operation **10** between its excitation and acquisition cycles. For example, the pulse controller module **7c** may be configured to switch the generation of signals between frequencies usable for generation of excitation  
20 signals and frequencies usable for the demodulation carried out by the demodulator **5**, to open pulse gate (not shown) and/or receiver protection gates (not shown), and suchlike.

It is worth noting that in the case of off-resonance detection, the signal received via the single channel IF receiver **5** cannot disappear altogether due to improper signal phase in this channel, whereas at on-resonance detection this may occur. The NMR  
25 signal detected by the single channel IF receiver and demodulator unit **5** is digitized by the analog to digital converter (ADC) **6**, and the digitized NMR signal from the ADC **6** is then received and processed by the control unit **7** to determine one or more blood parameters therefrom.

In some possible embodiments the probehead **2** further comprises a temperature  
30 sensor **8** configured and operable to measure the temperature of the examined finger **9**, and generate data indicative thereof. The measurement data generated by the temperature sensor **8** is received and processed by the control unit **7**, and used thereafter to adjust reference data used in the determination of the blood related parameters. Since

- 15 -

most nuclear relaxation rates in liquids are highly sensitive to temperature, it is very important to measure the temperature of examined organ and adjust the reference data used in the blood related parameters determination stage accordingly. Thus, in some embodiments employing a correlation matrix to determine the blood related parameters, the measured temperature of the examined finger is one of the main parameters in the database of reference data used for the constructions of the correlation matrix, *e.g.*, the relaxation time  $T_1$  corresponding to the blood viscosity at some fixed temperature, or a relaxation curve obtained for glucose at a certain temperature, and suchlike.

In operation, a sequence of at least two relatively short (hard, *e.g.*, having 0.5 to 3  $\mu$ sec pulse lengths)  $\pi/2$  and  $\pi$  phase shifted (*e.g.*,  $\pi/2$  phase shifted inversion pulse followed by  $\pi$  phase shifted refocusing pulse) RF pulses at off-resonance low frequency are applied to the examined finger **9** (or any other designated body part) inserted into the NMR probehead **2**. Short hard (also known as non-selective) off-resonance pulses provide enhanced nuclear spin echo signals from all corresponding nuclei of the examined finger **9** (or other body portion) including not only nuclei of the living liquids characterized by narrow NMR lines, but also of nuclei in semi-immobilized and immobilized tissues and bones characterized by broad NMR lines, and consequently, shorter relaxation times. The same excitation technique allows registration of NMR signals from nuclei located in areas where the polarizing magnetic field of the permanent magnet is inhomogeneous. Compared with the continuous wave (CW) method disclosed in US 7,635,331, the technique disclosed herein increases total nuclear magnetization observed and makes the blood parameters measurement apparatus **10** more sensitive and reliable.

The advantages of using low field/low frequency NMR apparatus originate from two principal practical aspects. First, relatively small weight and low-cost permanent magnets of up to 0.5 Tesla are commercially available nowadays (*e.g.*, PM 1055 from Metrolab, Switzerland or magnets of S-25 – S-30 series from Supermagnete, Switzerland). Second, at low RF frequencies (*e.g.*, 1 – 20 MHz) characteristic relaxation times of the most abandoned blood nuclei – protons drop from seconds to fraction of seconds (R. A. Brooks, J. H. Battocletti, A. Sanges Jr., S. J. Larson, R. L. Bowman and V. Kudravcev, Nuclear Magnetic Relaxation in Blood, IEEE Transactions on Biomedical Engineering, V. 22(1) 1975, p.12), that allows shortening the total examination time from tens of minutes to a few minutes. Hard off-resonance pulse

- 16 -

excitation and detection of the nuclear spin echo signals allows also using a single-channel data acquisition that makes the tester simpler and allows reducing its final cost.

Multifunctional analysis of nuclear magnetization decays, such as “longitudinal” spin-lattice relaxation times  $T_{1i}$  (where  $i$  is a positive integer used for indexing spin-lattice relaxation times associated with different materials), “longitudinal” spin-lattice relaxation time in rotating frame  $T_{1\rho i}$  and “transverse” spin-spin relaxation time  $T_{2i}$ , for each  $i$ -constituent of  $N$  distinguishable blood constituents, allows more precise selective determination of the living blood parameters (*e.g.*, blood glucose level, blood viscosity, haematocrit, oxygen saturation, pH, and suchlike) by correlating between a pre-determined matrix of relaxation times /rates associated with various blood parameters measured in healthy subjects and the nuclear spin-lattice relaxation times obtained from the finger of the examined subject.

The proposed NMR apparatus **10** allows individual calibration of the pre-determined matrix of various blood parameters to a set of blood parameters measured for the same individual by conventional invasive blood tests aiming to improve sensitivity of the blood assessment to the most critical (for this individual) blood parameters. This calibration assumes exchanging relaxation times and blood parameters from the pre-determined (by clinical trials) correlation matrix by real relaxation times / rates and blood parameters obtained by precise measurements done on the individual. Thus, for individuals suffering from diabetes, for example, the general pre-determined correlation matrix may be adjusted according to personal blood glucose levels of the specific individual as obtained using conventional invasive blood tests, whereas for individuals suffering from hyperviscosity syndrome the adjustment of the correlation matrix may take into account personal variations of the blood viscosity obtained through use of conventional invasive blood tests.

**Fig. 8** is a flowchart demonstrating a process **80** for assessing blood parameters of a subject according to some possible embodiments. The process **80** commences in step **81** by introducing the test organ (*e.g.*, finger phalange) into a test volume (**2v**) in which the organ is under constant magnetic field (**1f**) conditions. Next, in step **82**, one or more electromagnetic (EM) excitation pulse sequences are applied over the test organ, in step **83** responsive relaxation signals are received from the test organ, and in step **84** magnetization relaxation curves are constructed from the received spin echo signals. Optionally, in step **81a**, one or more delay times between successive excitation

- 17 -

pulse signals in each excitation pulse sequence are adjusted before they are applied to the test organ in step **82**. The applying of excitation signals and acquiring responsive relaxation signals of steps **81** and **82**, and optional step **81a** of adjusting the delay times, may be repeated a plurality ( $M_k$ ) of times to improve the overall signal to noise ratio and improve the detection of spin echo signals in step **84**.

In step **85** nuclear relaxation times are determined from the magnetization relaxation curves for one or more blood constituents. The relaxation times obtained are then correlated in step **86** with respective relaxation times associated with blood parameters collected from multiple subjects, both healthy and deceased. The correlation results are then used in step **87** to determine blood parameters of the examined subject. Optionally, a calibration step **85a** may be performed before carrying out the correlation step **86**. The calibration step **85a** allows adjusting the process for the assessment of blood parameter of a specific subject, for example, by adjusting the one or more relaxation times to comply with blood parameters of the examined subject preliminarily obtained through the invasive blood taking procedure.

## EXAMPLES

20

### Example 1

The first phalange of a forefinger of a living subject was placed in a specially designed NMR probe comprising a copper coil (**2c**) having an internal diameter of about 15 mm and length of about 20 mm. The copper coil in this example is part of a tuned tank circuit (*i.e.*, resonant circuit *e.g.*, LC circuit), placed between the poles of an electromagnet of a commercial Varian E-12 EPR spectrometer. *In vivo* measurements were carried out in a fixed magnetic field  $B_0 = 0.273$  Tesla at radiofrequency  $f_0 = 11.62$  MHz. The thermal stabilization of the examined finger was kept by internal body temperature at normal physiological conditions ( $36.6 \pm 0.5$  °C). Measurements of spin-spin relaxation times  $T_{2i}$  (where  $i$  is a positive integer used for the indexing of excitation/SE acquisition cycles) of  $^1\text{H}$  nuclei in the examined forefinger phalange were conducted using a single RF channel of a commercial Tecmag Libra-NMRkitII pulsed solid state NMR spectrometer by applying off-resonance ( $\Delta f = 5$  kHz) excitation in the form of phase cycled Hahn spin-echo sequence with a variable delay  $\tau_{SEi}$  defining a

- 18 -

time duration between the end of the excitation pulses (**21** and **22** in **Fig. 2**) and a peak (**23p**) of their respective relaxation signals (**23**). The homogeneity of the EPR spectrometer's magnet is modest enough to provide quite short  $T_2^*$  values that allow observation of strong Hahn spin echo (SE) signals.

5 **Fig. 2** graphically illustrates the excitation sequence used in this example. As seen in **Fig. 2** the first electromagnetic exciting pulse **21** ( $\pi/2$  phase shifted) having  $\tau_{\pi/2}$  duration and phase  $\phi_1$  is separated from the second (refocusing) electromagnetic exciting pulse **22** ( $\pi$  phase shifted) having  $\tau_{\pi}$  duration and phase  $\phi_2$  by a variable delay  $\tau_{dSEi}$ . SE signal acquisition with the received phase  $\phi_3$  starts after a time duration  $\tau_{SEi}$  -  
 10  $\tau_{Acq}/2$  has passed since the end of the second electromagnetic exciting pulse **22**, where  $\tau_{SEi} = (\tau_{\pi/2} + \tau_{\pi})/2 + \tau_{dSEi}$ . The time delays  $\tau_{dSEi}$  between each pair of consecutive excitation RF pulses **21** and **22** are chosen such that  $\tau_{SEi} > \tau_{DT}$ , where  $\tau_{DT}$  is the receiver dead time. Upon completion of the acquisition of the relaxation signals, the system is changed into a wait state during the recycle delay time  $\tau_{LD} \sim 1.3T_1$  ( $T_1$  being the spin-  
 15 lattice relaxation time for  $^1H$ ), during which no excitation pulses are applied before the next excitation/SE acquisition cycle. While consecutive excitation/SE acquisition cycles have the same delay  $\tau_{dSEi}$  times between their respective excitation RF pulses **21** and **22**, their phases  $\phi_1$ ,  $\phi_2$  and  $\phi_3$ , are different, as chosen according to the phase cycling scheme being used (*e.g.*, two, four or sixteen phases). The use of some phase cycling  
 20 techniques effectively quenches all powerful RF pulse passage artifacts (like tank circuit ringing etc.), which allows precise measurements of the SE signals at long delays  $\tau_{dSEi}$ .

In order to improve the SE signal to noise ratio at each delay  $\tau_{dSEi}$  the pulse excitation/SE acquisition cycle is repeated  $N_{Acq}$  times where, according to the corresponding phase cycle scheme,  $N_{Acq}$  is a number divisible by two, four or sixteen.  
 25 The peak values of the SE magnitude, obtained by the digital quadrature detection technique, as a function of the delay  $\tau_{dSE}$  between the  $\pi/2$  and  $\pi$  pulses are plotted in **Fig. 3**. **Fig. 3** shows a typical  $^1H$  nuclei spin echo decay curve obtained on the forefinger phalange by NMR at  $f_0 = 11.62$  MHz. The open circles in **Fig. 3** represent experimental spin echo values, the dashed line curve in **Fig. 3** is a plot of best least-

- 19 -

square fit carried out using a single exponential model, and the dotted line is a plot of best least-square fit carried out using a double exponential model.

The best least-square fitting supposing the model of only one type of  $^1\text{H}$  nuclei  $SE = SE_0 \cdot e^{-2\tau_{dSE}/T_2}$  provides  $T_2 = 94 \pm 4$  ms and  $R^2=0.9933$ , whereas the best least-square fitting supposing the model of two types of  $^1\text{H}$  nuclei  $SE = SE_{01} \cdot e^{-2\tau_{dSE}/T_{21}} + SE_{02} \cdot e^{-2\tau_{dSE}/T_{22}}$  provides  $T_{21} = 196 \pm 9$  ms,  $T_{22} = 52 \pm 2$  ms,  $R^2=0.9999$ , and the weighting ratio between two types of nuclei is  $SE_{01}/SE_{02} = 20 : 46$ . This example clearly demonstrates that the relaxation measurements of the  $^1\text{H}$  nuclei in the living forefinger phalange reveals at least double component structure of this  $^1\text{H}$  nuclear system.

### Example 2

*In vivo*  $^1\text{H}$  spin-lattice relaxation times measurements were done on a living forefinger phalange of an individual using the instrumental setup used in **Example 1** ( $f_0 = 11.62$  MHz). The thermal stabilization of the examined finger was kept by internal body temperature at normal physiological conditions ( $36.6 \pm 0.5$  °C). Off-resonance ( $\Delta f=5$  kHz) excitation of  $^1\text{H}$  nuclei and SE acquisition was carried out using the saturation comb excitation sequence combined with phase cycled spin echo detection, as demonstrated in **Fig. 4**.

This excitation sequence allows shortening of the test time duration needed for precise measurements of long spin-lattice relaxation times  $T_1$ . The excitation sequence exemplified in **Fig. 4** begins with of a train (comb) of  $m$  ( $m = 8 \div 20$ ) saturating ( $\pi/2$  phase shifted) pulses **41**, each having  $\tau_{\pi/2}$  time duration and phase  $\varphi_1$ , and separated by delay times  $\tau_{\text{Sat}}$ , where  $T_2^* < \tau_{\text{Sat}} < T_1$ . Following the  $m$  saturating pulse train (comb) of  $m$  ( $m = 8 \div 20$ ) saturating pulses **41** there is a variable delay time  $\tau_{\text{dRi}}$ . Thereafter the excitation sequence proceeds with the reading ( $\pi/2$  phase shifted) pulse **42** having a  $\tau_{\pi/2}$  time duration and phase  $\varphi_1$ , followed by a fixed delay having a  $\tau_{\text{dSE}}$  time duration, and the ( $i^{\text{th}}$ ) excitation sequence is then concluded with the refocusing ( $\pi$  phase shifted) pulse **43** having a  $\tau_{\pi}$  time duration and phase  $\varphi_2$ . The acquisition of the SE signal is

- 20 -

then performed with the receiver phase  $\phi_3$  starting at a  $\tau_{SE} - \tau_{Acq}/2$  time duration after the end of the refocusing pulse **43**, where  $\tau_{SE} = (\tau_{\pi/2} + \tau_{\pi})/2 + \tau_{dSE}$ .

The time delay  $\tau_{dSE}$  between the reading pulse **42** and the refocusing pulse **43** is chosen such that  $\tau_{SE} > \tau_{DT}$ , where  $\tau_{DT}$  is the receiver dead time. Upon completion of the acquisition event, the system enters a wait state having a time duration  $\tau_{LD} \ll T_1$ , during which no excitation pulses are applied. After the time duration  $\tau_{LD}$  a new ( $i+1$ ) excitation/SE acquisition cycle is commenced. While the same delay time  $\tau_{dRi}$  is used in consecutive excitation/SE acquisition cycles, a set of different phases  $\phi_1$ ,  $\phi_2$  and  $\phi_3$  are chosen according to a predetermined phase cycling scheme that is being used (*e.g.*, two, four or sixteen phases). The use of some phase cycling techniques effectively quenches all powerful RF pulse passage artifacts (like tank circuit ringing etc.), which allows precise measurements of the weak SE signals at short delays  $\tau_{dRi}$ .

In order to improve the SE signal to noise ratio at each delay  $\tau_{dRi}$  the saturation comb excitation/SE acquisition cycle is repeated  $N_{Acq}$  times, where, according to the corresponding phase cycle scheme being used,  $N_{Acq}$  is a number divisible by two, four or sixteen. The peak values (**44p**) of the SE magnitude (magnetization  $M$ ) obtained by the digital quadrature detection technique, as a function of the delay  $\tau_{dRi}$  between the saturating pulses (**41**) train (comb) and reading pulse **42** are plotted in **Fig. 5**.

**Fig. 5** shows graphical plots of a typical  $^1H$  nuclei magnetization curve obtained from the forefinger phalange by NMR excitation at  $f_0 = 11.62$  MHz. The open circles in **Fig. 5** represent experimental magnetization values, the dashed line is a plot of best least-square fit carried out using a single exponential model, and the dotted line is a plot of best least-square fit carried out using a double exponential model.

Best least-square fit supposing the model of only one type of  $^1H$  nuclei  
 $M = M_0 \cdot (1 - e^{-\tau_{dR}/T_1})$  provides  $T_1 = 636 \pm 98$  ms and  $R^2 = 0.9281$ , whereas best least-square fit supposing the model of two types of  $^1H$  nuclei  
 $M = M_{01} \cdot (1 - e^{-\tau_{dR}/T_{11}}) + M_{02} \cdot (1 - e^{-\tau_{dR}/T_{12}})$  provides  $T_{11} = 1250 \pm 43$  ms,  $T_{12} = 46 \pm 5$  ms,  $R^2 = 0.9994$ , and the weighting ratio between the two types of nuclei is  $M_{01}/M_{02} = 22:13$ . This example clearly demonstrates that the relaxation measurements of the  $^1H$

- 21 -

nuclei in the living forefinger phalange reveals at least double component structure of this  $^1\text{H}$  nuclear system.

### Example 3

5  $^1\text{H}$  spin-lattice relaxation times measurements were carried out *in vivo* on a series of living forefinger phalanges of individuals having different blood glucose levels using the instrumental setup used in **Example 1** ( $f_0 = 11.62$  MHz) and saturation comb sequence combined with phase cycled spin-echo detection as used in **Example 2** (see **Fig. 4**). Thermal stabilization of the examined finger phalanges was maintained by  
10 internal body temperature at normal physiological conditions ( $36.6 \pm 0.5$  °C). All individuals under the tests did not suffer from diseases affecting blood viscosity (like polycythemia, hydraemia etc.). Parallel assessment of the blood glucose level was done using a commercial Abbot FreeStyle Lite invasive strip-type glucose meter. Results of the series of tests are shown in **Fig. 6**, showing dependence of the  $^1\text{H}$  spin-lattice  
15 relaxation time  $T_{11}$  measured on the series of forefinger phalanges as a function of the blood glucose content.

**Fig. 6** demonstrates clear dependence of the  $^1\text{H}$  spin-lattice relaxation time  $T_{11}$  on the blood glucose content. Within the normal physiological range of blood glucose levels, and above the normal level the relaxation time  $T_{11}$  shows a tendency to increase.

20

### Example 4

$^1\text{H}$  spin-lattice relaxation times measurements were carried out *ex vivo* on a series of fresh blood samples collected from individuals having different blood viscosity parameters. The collected time samples were placed inside NMR tubes having a 5 mm  
25 external diameter and a 20 mm length, and entered into the NMR probe coil, using the instrumental setup used in **Example 1** ( $f_0 = 11.62$  MHz) and saturation comb sequence combined with phase cycled spin-echo detection as used in **Example 2** (see **Fig. 4**). For these samples the best least square fit was obtained by using a single spin-lattice relaxation time  $T_1$ . The thermal stabilization of the samples under the tests was carried  
30 out at the temperature  $36.6 \pm 0.5$  °C by external nitrogen flow temperature accessories. All individuals under these tests had approximately the same blood glucose content (within the range of 6 - 8 mmol/L estimated by a commercial invasive strip-type

- 22 -

glucometer). Parallel assessment of the fresh blood viscosity was carried out using a commercial Brookfield rotational viscometer.

Results of the series of tests are shown in **Fig. 7**. The results shown in **Fig. 7** demonstrate clear dependence of the  $^1\text{H}$  spin-lattice relaxation time  $T_1$  on the blood viscosity. Notably, deviations of the blood viscosity from its normal physiological range (4 – 5 mPa·s) at constant blood glucose level cause measurable shortening of the relaxation time  $T_1$ .

The above examples and description have of course been provided only for the purpose of illustration, and are not intended to limit the invention in any way. As will be appreciated by the skilled person, the invention can be carried out in a great variety of ways, employing more than one technique from those described above, all without exceeding the scope of the invention.

**CLAIMS:**

1. An apparatus for use in non-invasive assessment of blood related parameters of an examined subject, the apparatus comprising:
  - a signal generator configured and operable to generate excitation signals in a radiofrequency range of 1 to 20 MHz;
  - a probehead unit defining a test site for a living tissue of the subject being examined, the probehead unit comprising:
    - a magnetic field source unit configured and operable to generate a substantially uniform magnetic field of about 0.15 to 0.5 Tesla in a magnetic field region in which said test site is located, to thereby magnetize blood in said living tissue;
    - at least one inductive coil placed in said test site so as to be in the magnetic field region and to be exposed to the excitation signals, the inductive coil being configured to surround at least a part of the living tissue when placed in said test site, said at least one inductive coil thereby responding to said magnetic field and said RF excitation signals by generation of electromagnetic excitation signals in a direction substantially perpendicular to a direction of said magnetic field to thereby affect the blood magnetization in the living tissue, and generating an electromagnetic response to nuclear spin echo signals from the living tissue;
    - a receiver unit configured and operable to receive said electromagnetic response of the at least one inductive coil and generate measured data indicative thereof; and
    - a control unit connected to the probehead unit for operating the signal generator and to the receiver to provide predetermined time patterns of the generation of the excitation RF signals and of the receipt of the electromagnetic response, said control unit being configured and operable to process the measured data and extract data indicative of the nuclear spin echo signals from the living tissue, to determine relaxation times or rates of blood constituents associated with the blood related parameters, and determine at least one blood related parameter.
2. The apparatus according to claim 1 wherein the receiver is a single channel IF receiver.

- 24 -

3. The apparatus according to claim 1 or 2 wherein the receiver unit comprises a demodulator configured and operable for demodulating signals associated with the nuclear spin echo signals from the electromagnetic response.
4. The apparatus according to any one of the preceding claims wherein the receiver  
5 unit comprises a signal amplifier for amplifying the electromagnetic response from the coil.
5. The apparatus according to any one of the preceding claims wherein the control unit comprises a pulse controller module configured and operable to switch the apparatus operation between its excitation and acquisition cycles.
- 10 6. The apparatus according to any one of the preceding claims comprising a pulsed RF generator and pulsed RF power amplifier configured and operable to generate the excitation signals.
7. The apparatus according to any one of the preceding claims wherein the magnetic field source unit comprises a thermostabilized permanent magnet assembly  
15 and/or a set of Helmholtz coils.
8. The apparatus according to claim 7 wherein the permanent magnet assembly is made from rare-earth hard magnetic materials.
9. The apparatus according to claim 8 wherein the rare-earth hard magnetic materials comprise  $\text{Sm}_x\text{Co}_y$  and/or NdFeB alloys.
- 20 10. The apparatus according to claim 7 wherein the Helmholtz coils are configured and operable to correct temperature field drift and/or homogeneity.
11. The apparatus according to any one of the preceding claims wherein the probehead further comprises a temperature sensor configured and operable to measure temperature of the living tissue and generate temperature data indicative thereof, the  
25 control unit being configured and operable to determine the at least one blood related parameter based on said temperature data.
12. The apparatus according to any one of the preceding claims wherein the probehead further comprises an electromagnetic shield to substantially attenuate external electromagnetic interferences.

- 25 -

13. The apparatus according to any one of the preceding claims wherein the coil has a cylindrical shape or a saddle shape.
14. A method for use in non-invasive assessment of blood related parameters, the method comprising:
- 5 creating a substantially uniform magnetic field of about 0.15 to 0.5 Tesla within a magnetic field region at least partially overlapping with a test site where living tissue of an examined subject is to be located, to thereby magnetize blood in said living tissue;
- applying electromagnetic excitation signals of a range of 1 to 20 MHz in said test site to thereby affect the blood magnetization in the living tissue to cause nuclear
- 10 spin echo signals from the living tissue, said electromagnetic excitation signals being applied with a predetermined time pattern;
- receiving, with a predetermined time pattern, electromagnetic radiation responsive to the nuclear spin echo signals from the living tissue;
- processing data corresponding to said received electromagnetic radiation,
- 15 extracting therefrom data indicative of the nuclear spin echo signals from the living tissue, and determining relaxation times or rates of blood constituents associated with the blood related parameters, to thereby determine at least one blood related parameter.
15. The method according to claim 14 wherein the determining of the relaxation times or rates is carried out using a multifunctional approximation.
- 20 16. The method according to claim 14 or 15 wherein the determining of the blood related parameters comprises correlating the obtained relaxation times or rates with a pre-determined matrix of relaxation times or rates associated with the blood related parameters.
17. The method according to claim 16 comprising calibrating the pre-determined
- 25 matrix of relaxation times to comply with a set of blood related parameters measured for the examined subject using a conventional *ex vivo* blood test.
18. The method according to claim 17 wherein the calibrating is carried out so as to improve sensitivity of the blood assessment to a predetermined blood related parameter.
19. The method according to any one of claims 14 to 18 wherein the blood related
- 30 parameters comprise one or more of the following: blood glucose content, blood viscosity, blood haematocrit, blood oxygen saturation, and blood pH.

- 26 -

20. The method according to any one of claims 14 to 19 wherein the excitation signals are off-resonance excitation pulses.
21. The method according to any one of claims 14 to 20 wherein the excitation signals comprise an overturning excitation signal having a predetermined time duration  $\tau_1$  to overturn magnetization of blood constituents' nuclei towards a plane substantially perpendicular to direction of electromagnetic field of said signal, and a consecutive refocusing signal having a time duration  $\tau_2 \geq \tau_1$  to turn magnetization of the blood constituents' nuclei towards a plane substantially perpendicular to the direction of electromagnetic field of said signal to form nuclear spin echo, said overturning and refocusing signals being separated by a predetermined time delay.
22. The method according to claim 21 wherein the excitation sequence comprises at least one additional excitation pulse applied before the overturning excitation signal and having a predetermined time duration  $\tau_{pj}$  and predetermined time delay  $\tau_{dk}$ , to thereby form specific excitation sequence of electromagnetic field pulses suitable for exciting time dependent magnetizations of the blood constituents' nuclei.
23. The method according to claim 21 or 22 wherein the time delay between the overturning and refocusing signals is adjusted to obtain the electromagnetic radiation responsive to the nuclear spin echo signals within a predefined time duration after the refocusing signal, said predefined time duration being greater than a predetermined dead time associated with the receiving of the electromagnetic radiation.
24. The method according to any one of claims 21 to 23 comprising:  
applying the excitation signals a predetermined number of times, the time delay between the overturning signal and the refocusing signal being different in at least some of the excitation sequences; and  
determining the blood related parameters based on magnetization relaxation curves determined for electromagnetic radiation received in response to the applied excitation signals.
25. The method according to any one of claims 14 to 24 wherein the radio frequency of the excitation signals is set for carrying out NMR relaxometry for one or more of the following protons:  $^1\text{H}$ ,  $^{13}\text{C}$ ,  $^{19}\text{F}$ , and  $^{31}\text{P}$ .

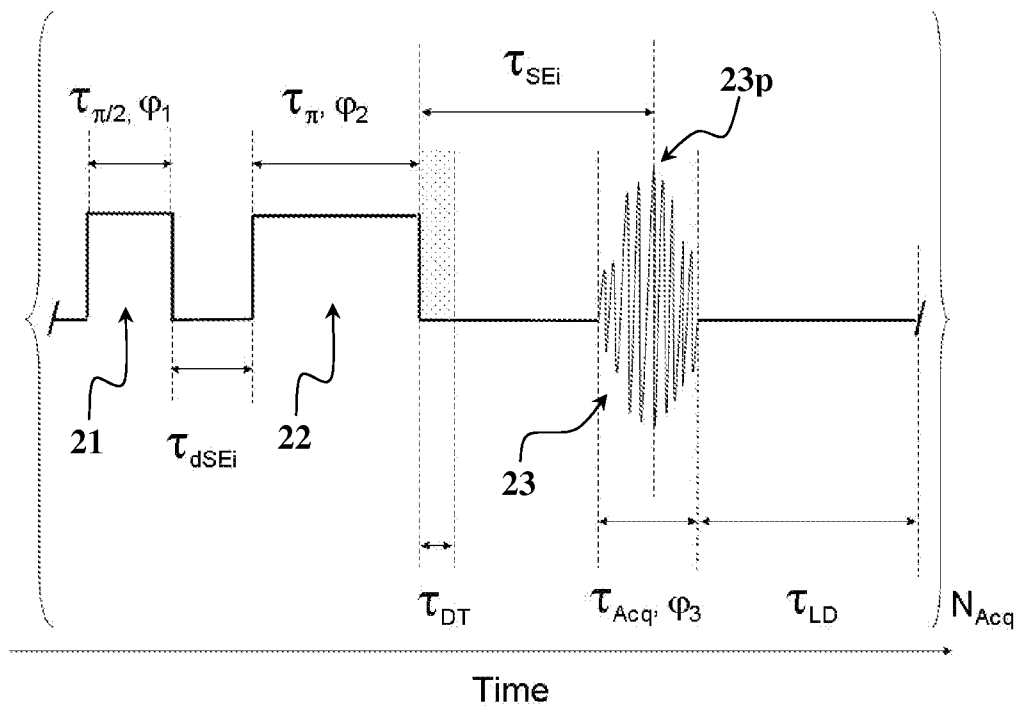
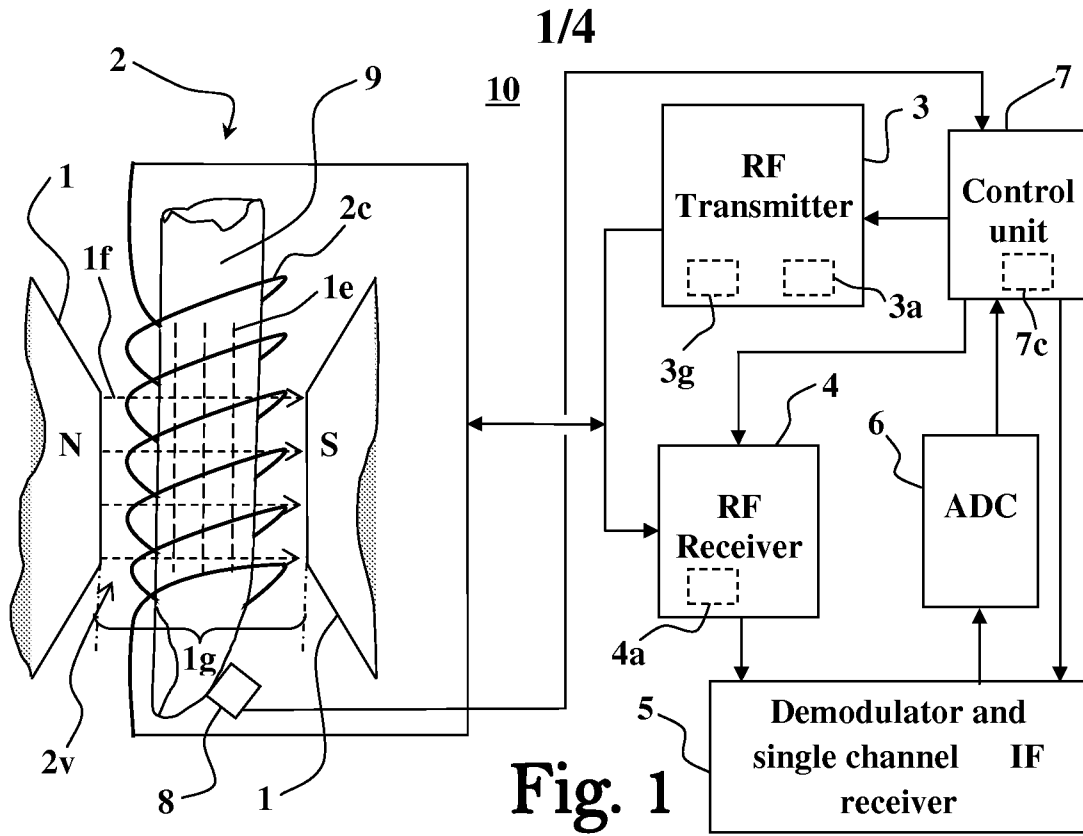
- 27 -

26. The method according to any one of claims 14 to 25 wherein the magnetization relaxation curves are built from nuclear spin echoes obtained using the Hahn technique or solid echo technique.

27. The method according to any one of claims 14 to 26 wherein applying of the  
5 electromagnetic excitation signals being carried out according to one or more of the following techniques: inversion recovery technique, progressive saturation technique, spin-lock technique, Hahn technique, and Carr-Purcell-Meiboom-Gill (CPMG) technique.

28. The method according to any one of claims 14 to 27 wherein the determined  
10 magnetization relaxation curves comprise:  $T_{1i}$  spin-lattice magnetization relaxation curves,  $T_{1\rho i}$  spin-lattice magnetization relaxation in rotating frame curves, and  $T_{2i}$  spin-spin magnetization relaxation curves.

15



2/4

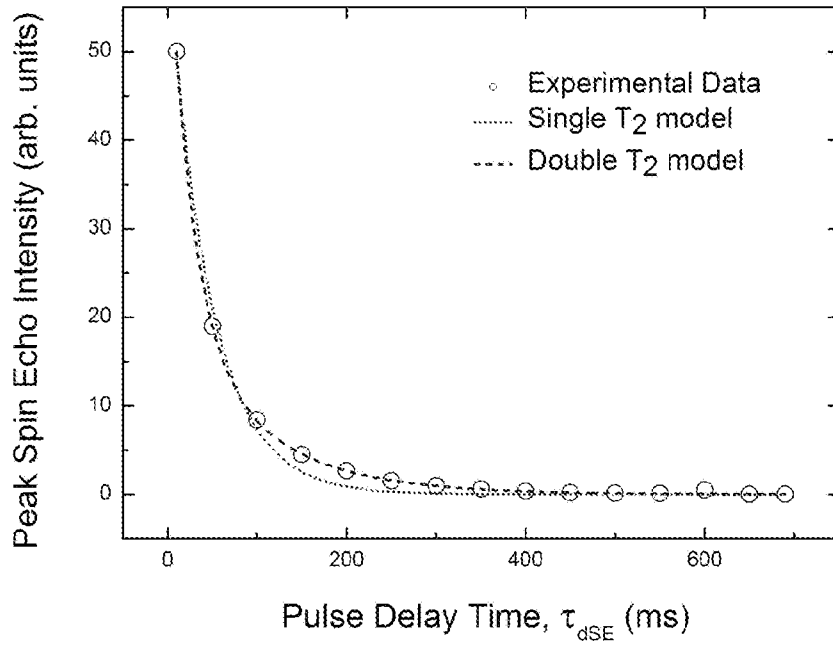


Fig. 3

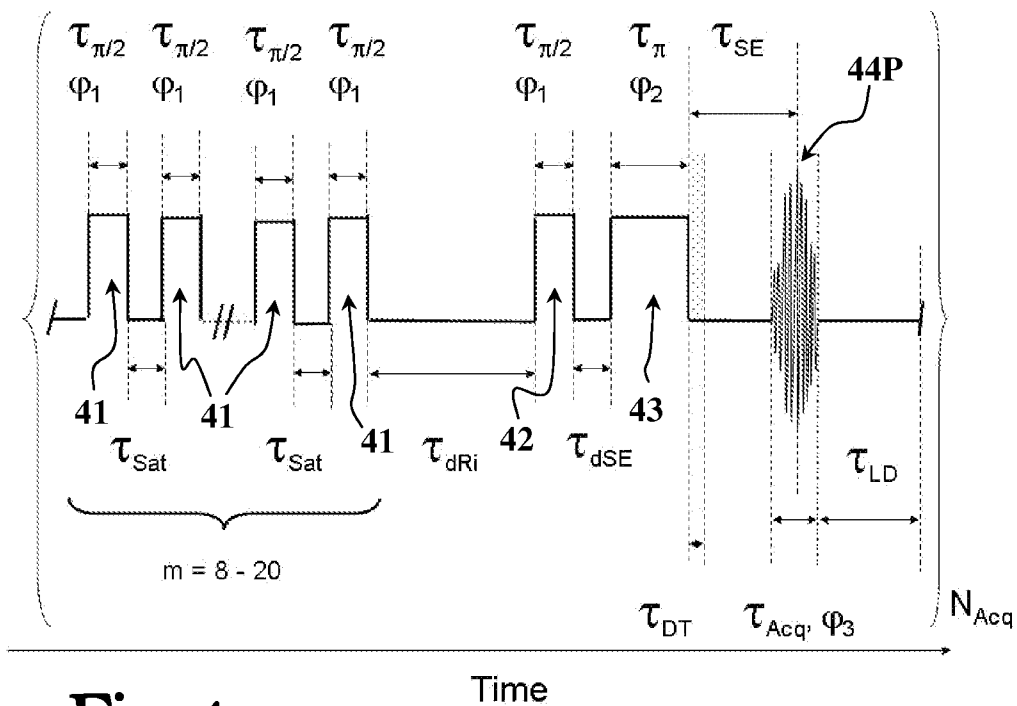
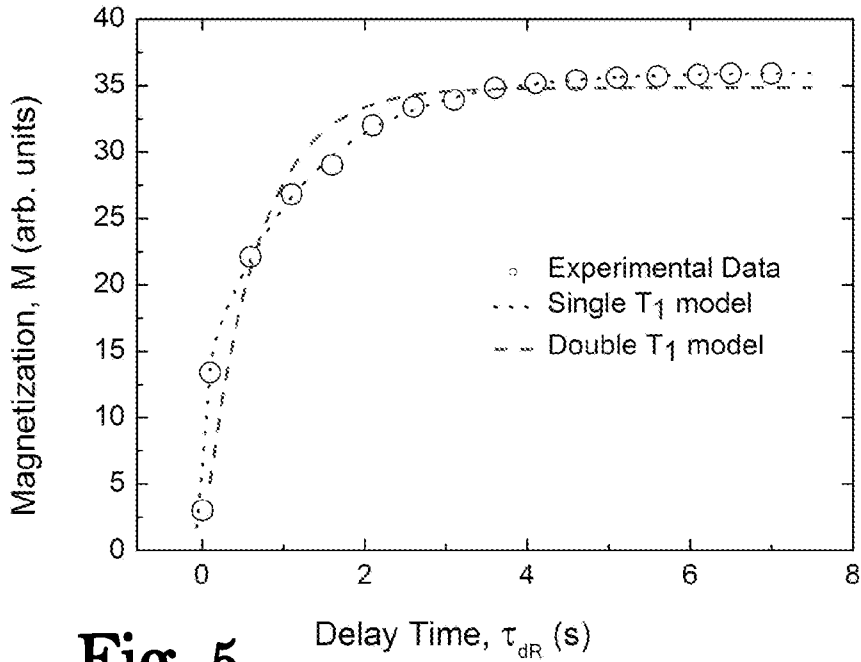
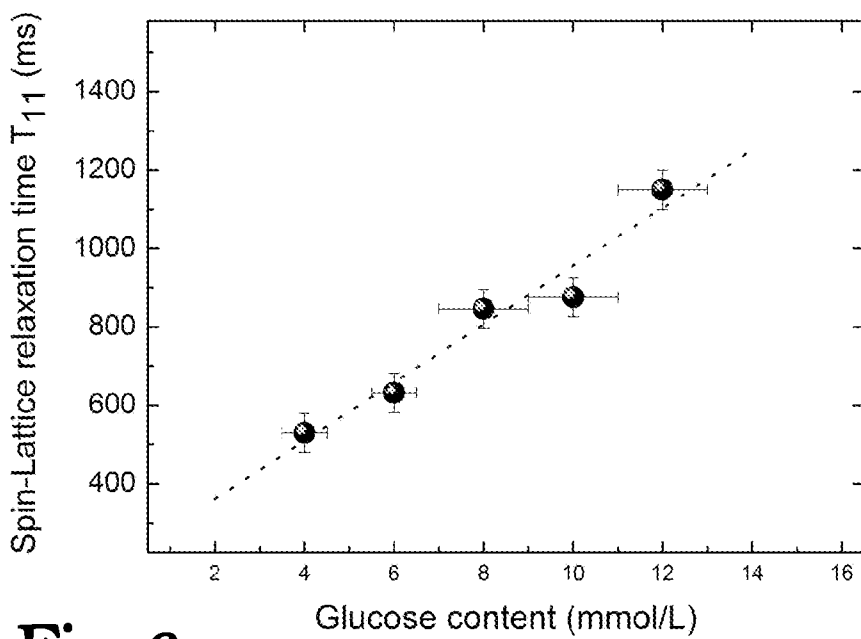


Fig. 4

3/4

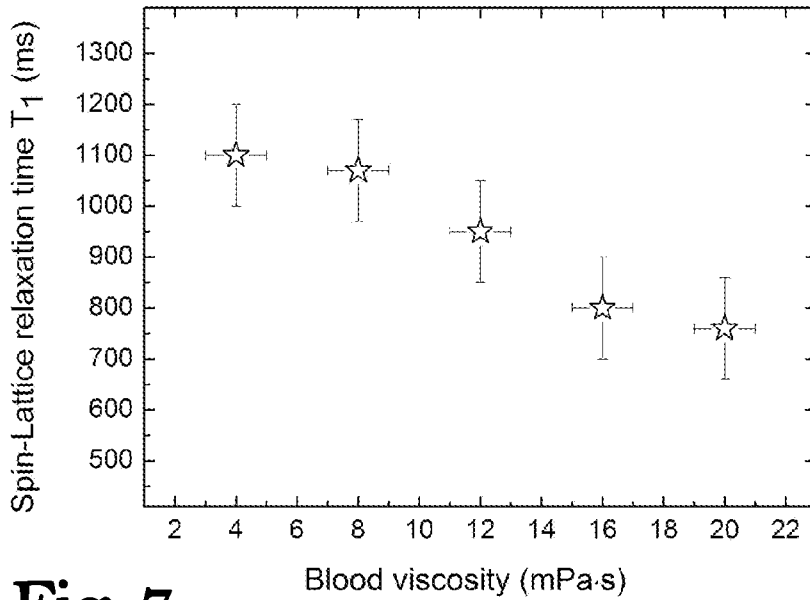


**Fig. 5**

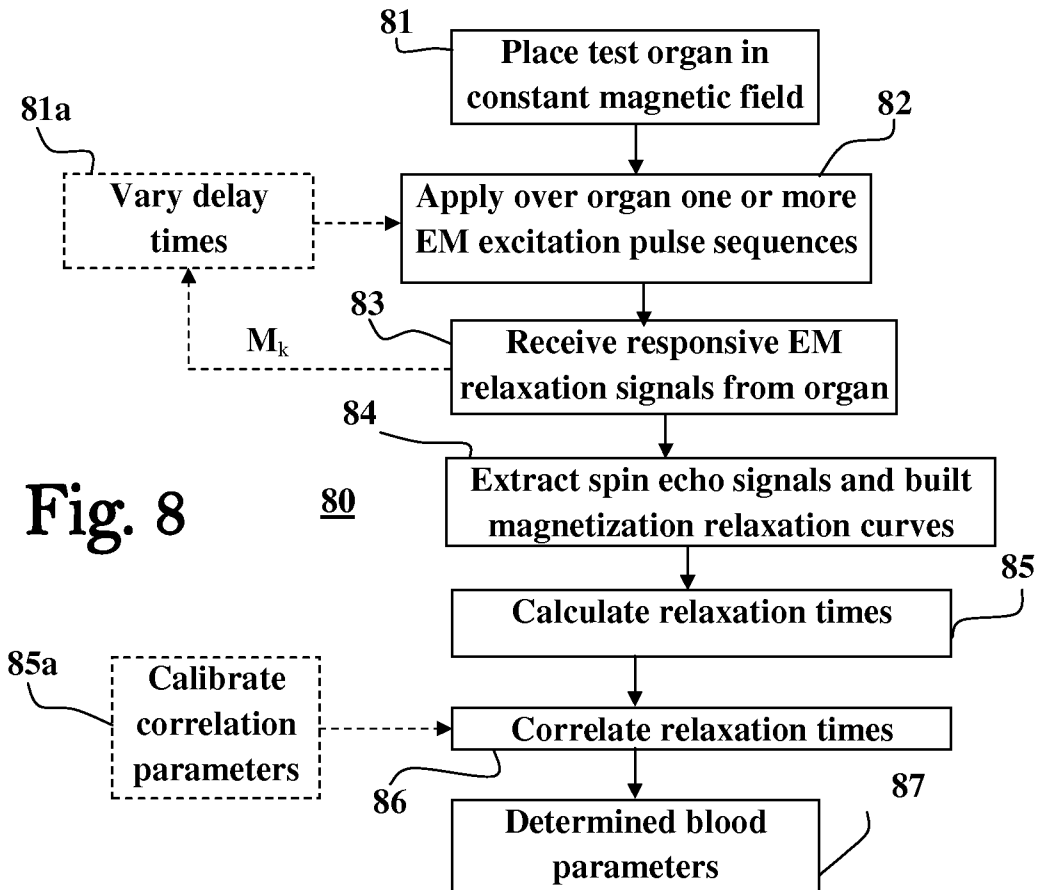


**Fig. 6**

4/4



**Fig. 7**



**Fig. 8**

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/IL2013/050104

<b>A. CLASSIFICATION OF SUBJECT MATTER</b> IPC (2013.01) G01R 33/46, A61B 5/00, G01R 33/28, G01V 3/00  According to International Patent Classification (IPC) or to both national classification and IPC		
<b>B. FIELDS SEARCHED</b>  Minimum documentation searched (classification system followed by classification symbols) IPC (2013.01) G01R 33/46, A61B 5/00, G01V 3/00  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) Databases consulted: THOMSON INNOVATION, Esp@cenet, Google Patents		
<b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 7940045 B2 Carpenter et al. 10 May 2011 (2011/05/10) The whole document	1,14-20
Y	The whole document	2-13,21-28
Y	US 2011109310 A1 Hornung. 12 May 2011 (2011/05/12) (Figs. 1-4, paragraphs: 5, 20, 22, 25, 26, 28, 31 ).	2-13,21-28
Y	US 2007178598 A1 Jeyarajah et al. 02 Aug 2007 (2007/08/02) (abstract, paragraphs: 58, 76, 79, 80).	11
Y	WO WO9216851 A1 Dechene et al. 01 Oct 1992 (1992/10/01) (abstract, p. 11 line 12, claims 2, 12, 13).	7,10,26-28
<input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C. <input checked="" type="checkbox"/> 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 26 May 2013		Date of mailing of the international search report 28 May 2013
Name and mailing address of the ISA: Israel Patent Office Technology Park, Bldg.5, Malcha, Jerusalem, 9695101, Israel Facsimile No. 972-2-5651616		Authorized officer NIMER Emad  Telephone No. 972-2-5657801

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/IL2013/050104

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2007116602 A1 Lee 24 May 2007 (2007/05/24) (abstract, Figs. 1, 5A, 7, 8, 9, 14).	1-28
Y	US 6163154 A Anderson et al. 19 Dec 2000 (2000/12/19) (abstract, Figs. 3, 14, 15-18).	1-28
Y	US 2011128000 A1 Harvey. 02 Jun 2011 (2011/06/02) (abstract, Fig. 1).	21-24
A	US 5592086 A Weinstock et al. 07 Jan 1997 (1997/01/07) The whole document.	1-28

INTERNATIONAL SEARCH REPORT  
Information on patent family members

International application No.  
PCT/IL2013/050104

Patent document cited search report	Publication date	Patent family member(s)	Publication Date
US 7940045 B2	10 May 2011	EP 1851561 A2	07 Nov 2007
		US 2008088308 A1	17 Apr 2008
		US 7550971 B2	23 Jun 2009
		US 2009219022 A1	03 Sep 2009
		US 7940045 B2	10 May 2011
		US 2011175614 A1	21 Jul 2011
		US 8134365 B2	13 Mar 2012
		WO 2006076631 A2	20 Jul 2006
		WO 2006076631 A3	31 Aug 2006
US 2011109310 A1	12 May 2011	EP 2325668 A1	25 May 2011
		JP 2011102804 A	26 May 2011
		US 2011109310 A1	12 May 2011
		US 8324897 B2	04 Dec 2012
US 2007178598 A1	02 Aug 2007	US 2007178598 A1	02 Aug 2007
		WO 2007081933 A2	19 Jul 2007
		WO 2007081933 A3	07 Sep 2007
WO WO9216851 A1	01 Oct 1992	NONE	
US 2007116602 A1	24 May 2007	AU 2006284832 A1	08 Mar 2007
		AU 2006284832 A8	01 May 2008
		AU 2006284832 B2	02 Jun 2011
		CA 2620861 A1	08 Mar 2007
		EP 1932009 A2	18 Jun 2008
		JP 2009506345 A	12 Feb 2009
		US 2007116602 A1	24 May 2007
		US 7564245 B2	21 Jul 2009
		US 2009134869 A1	28 May 2009
		US 8102176 B2	24 Jan 2012

INTERNATIONAL SEARCH REPORT  
Information on patent family members

International application No.  
PCT/IL2013/050104

Patent document cited search report	Publication date	Patent family member(s)	Publication Date
		US 2011020788 A1	27 Jan 2011
		US 8310231 B2	13 Nov 2012
		US 2011021374 A1	27 Jan 2011
		US 8310232 B2	13 Nov 2012
		US 2011020787 A1	27 Jan 2011
		US 8334693 B2	18 Dec 2012
		US 2011018538 A1	27 Jan 2011
		US 8344731 B2	01 Jan 2013
		US 2011020953 A1	27 Jan 2011
		US 2012107839 A1	03 May 2012
		US 2012313639 A1	13 Dec 2012
		WO 2007027843 A2	08 Mar 2007
		WO 2007027843 A3	02 Aug 2007
US 6163154 A	19 Dec 2000	AU 2093899 A	12 Jul 1999
		CA 2316365 A1	01 Jul 1999
		EP 1053483 A2	22 Nov 2000
		JP 2001526920 A	25 Dec 2001
		NZ 505419 A	31 May 2002
		US 6163154 A	19 Dec 2000
		US 6404197 B1	11 Jun 2002
		WO 9932897 A2	01 Jul 1999
		WO 9932897 A3	10 Sep 1999
US 2011128000 A1	02 Jun 2011	CN 101512371 A	19 Aug 2009
		CN 101512371 B	05 Sep 2012
		EP 2078210 A2	15 Jul 2009
		US 2011128000 A1	02 Jun 2011
		US 8072211 B2	06 Dec 2011
		WO 2008026174 A2	06 Mar 2008
		WO 2008026174 A3	12 Jun 2008

INTERNATIONAL SEARCH REPORT  
Information on patent family members

International application No.  
PCT/IL2013/050104

Patent document cited search report	Publication date	Patent family member(s)	Publication Date
US 5592086 A	07 Jan 1997	AU 680433 B2	31 Jul 1997
		AU 4924493 A	12 Apr 1994
		CA 2144879 A1	31 Mar 1994
		EP 0663074 A1	19 Jul 1995
		EP 0663074 A4	05 Jun 1996
		GB 9222990 D0	16 Dec 1992
		GB 2270761 A	23 Mar 1994
		GB 2270761 B	12 Jun 1996
		JP H06130008 A	13 May 1994
		JP 2647786 B2	27 Aug 1997
		SG 70559 A1	22 Feb 2000
		US 5317265 A	31 May 1994
		US 5517119 A	14 May 1996
		US 5592086 A	07 Jan 1997
		WO 9407154 A1	31 Mar 1994

专利名称(译)	用于血液参数的非侵入式测量的设备和方法		
公开(公告)号	<a href="#">EP2812716A1</a>	公开(公告)日	2014-12-17
申请号	EP2013746441	申请日	2013-02-05
[标]申请(专利权)人(译)	ANATECH高级NMR算法TECH		
[标]发明人	SHAMES ALEXANDER ROZENFELD YURI KEINI DAVID		
发明人	SHAMES, ALEXANDER ROZENFELD, YURI KEINI, DAVID		
IPC分类号	G01R33/46 A61B5/00 G01R33/28 G01V3/00		
CPC分类号	A61B5/02055 A61B5/02035 A61B5/055 A61B5/14532 A61B5/14535 A61B5/14539 A61B5/14542 A61B5/6826 G01R33/383 G01R33/448 G01R33/4608		
代理机构(译)	斯特劳斯, 亚历山大		
优先权	61/596569 2012-02-08 US		
其他公开文献	EP2812716A4		
外部链接	<a href="#">Espacenet</a>		

#### 摘要(译)

本发明提供了基于使用0.15至0.5特斯拉范围内的相对低的恒定磁场进行的NMR (核) 弛豫技术来非侵入性地测量血液相关参数的技术。在放置在磁场中的活组织上施加具有相对低的射频的多个电磁激励脉冲序列, 并且使用响应于所施加的激励从组织接收的多个核自旋回波信号来确定被检查对象的血液相关参数。因此, 允许改善所获得信号的准确性并显著减少该过程的持续时间。