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(54) Title: MAGNETIC RESONANCE BASED MAGNETIC FIELD PROBES WITH CONTROLLABLE RELAXATION TIME

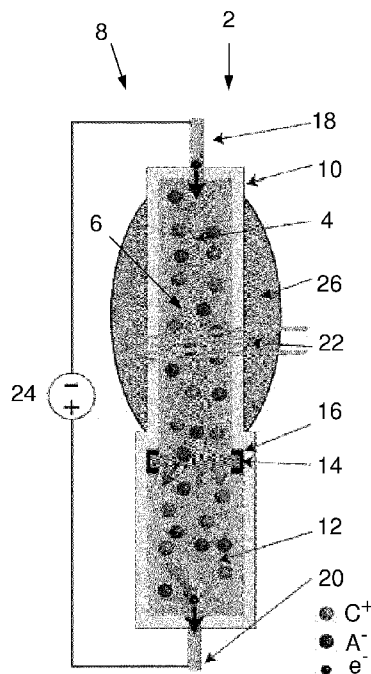


Fig. 1a

(57) Abstract: A magnetic field probe, particularly for magnetic resonance imaging and spectroscopy applications, comprises: - a probe medium that exhibits magnetic resonance (MR) at an operating frequency in the presence of a main magnetic field; - means for pulsed MR excitation of said probe medium within a resonator volume of said field probe and means for receiving an MR signal generated by said probe medium within said resonator volume. The magnetic field probe further comprises adjusting means for continuously adjusting a MR relaxation time to a preselected value within an operating range.



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Magnetic resonance based magnetic field probes with controllable relaxation time

Field of the Invention

- 5 The present invention generally relates to devices and methods of controlling the effective longitudinal and transverse relaxation time of the nuclear magnetic resonance (NMR) or electron spin resonance (ESR) of a probe medium in a magnetic resonance (MR) based magnetic field probe.

Background of the Invention

- MR based magnetic field probes offer high sensitivity and bandwidth at high magnetic fields [1]. Further the phase of the MR signal obtained therefrom represents the field integral with time which is of special interest in applications of such sensors in NMR and MRI applications. Therefore the directly measured
15 temporal field integrals do not suffer from error accumulation as it is the case when integrating the signal of other types of magnetic field sensors such as Hall devices.

- For this purpose, however, the coherence in the probe has to exhibit a life-time
20 which spans the time interval over which the magnetic field shall be integrated, which requires the relaxation times of the NMR active sample to be substantially of the order of magnitude of said time interval of interest or longer. Further, the obtained precision in the field measurement scales with the power of $3/2$ with the coherence life time. However, after the coherence has relaxed or dephased – by
25 internal field variations or externally induced field gradients – to a signal level that does not provide any more the required signal-to-noise ratio (SNR) the probe should not be directly re-excited since then occurring echoes would impinge on the field measurement. Therefore the probes exhibit a dead time which is directly related to the thermal relaxation times (T_1 , T_2) of the NMR active
30 sample and amounts typically – depending on application and required accuracy – to one to several times the thermal relaxation times.

Since many applications especially in the field of MRI field monitoring [2] require measurement intervals of very variable length - ranging from several 100 μ s to more than 100 ms - it has been known to adapt the relaxation times of the MR active probe medium to the repetition rate required by the application by means of relaxation agents. However, this means that a probe, once it has been manufactured, shall be dedicated to applications or acquisition methods with a certain maximum acquisition duration and repetition rate. This is particularly unfavorable when integrating probes into a system. Therefore, it would be highly desirable to have means for controlling the relaxation times of NMR or ESR based field probes in-situ and reversibly.

Summary of the Invention

It has now been recognized that the relaxation time of an MR based field sensor is a determinant parameter for its application.

15

Therefore, according to one aspect of the invention, there is provided a magnetic field probe, particularly for magnetic resonance imaging and spectroscopy applications, which comprises:

- a probe medium that exhibits magnetic resonance (MR) at an operating frequency in the presence of a main magnetic field;
- means for pulsed MR excitation of said probe medium within a resonator volume of said field probe and means for receiving an MR signal generated by said probe medium within said resonator volume.

The magnetic field probe further comprises adjusting means for continuously adjusting a MR relaxation time of the probe medium to a preselected value within an operating range.

The term "continuously adjusting" shall be understood as the ability to adjust a MR relaxation time *in situ*, i.e. within the resonator volume at arbitrary times and,

in particularly, not being limited to the time before assembly of the magnetic field probe.

Another aspect of the invention relates to the use of a magnetic field probe according to the invention for measuring dynamic magnetic field evolution in a magnetic resonance imaging or spectroscopy apparatus.

Another aspect of the invention relates to a method of controlling the signal life time and relaxation properties of a magnetic field probe in a magnetic imaging or spectroscopy apparatus.

Advantageous embodiments are defined in the dependent claims.

In the present context, an MR (NMR or ESR) type magnetic field probe generally comprises a magnetic resonance (MR) active substance, means for pulsed MR excitation of said substance and means for receiving an MR signal generated by said substance. It will be understood that in order to provide acceptable signal levels, the MR probes require the presence of a sufficiently intense main magnetic field. Such MR probes have been described e.g. in EP 1 582 886 A1 or in WO 2007/118715 A1.

In principle, the MR magnetic field probes could be operated on an electron spin resonance (ESR) transition. In an advantageous embodiment, the field probes operate on a nuclear magnetic resonance transition (claim 2). Examples of suitable nuclei comprise, but are not limited to, ^1H , ^2H or ^{19}F . Especially reactions and mechanisms so far disclosed for ^1H can be equally employed for ^2H based field sensors and in similar ways to ^{19}F and ionic liquids.

For some applications, especially for localization of interventional devices, it would be sufficient to use just one magnetic field probe. Clearly, however, with one magnetic field probe it will not be possible to distinguish magnetization dy-

namics in the object from field fluctuations of other origin such as magnet drifts, thermal effects, etc. It will thus be preferable to determine magnetic field intensity in a plurality of at least two magnetic field probes located at different distance from the object so as to distinguish sample magnetization from background field
5 fluctuations. In a particularly preferred embodiment the measurements are carried out with a plurality of four or even more numerous magnetic field probes so as to determine multiple patterns of background fields (such as e.g. spherical harmonics) to be subtracted from the acquired signals.

10 According to a favorable embodiment (claim 3), the relaxation time in each probe is controlled to some extent by the use of one or more relaxation agents, which preferably contain a paramagnetic constituent such as e.g. Ni, Mn, Cu, Fe, Gd and their ions, or other paramagnetic ions, molecules, radicals or particles. The relaxation time can therefore be controlled by altering the concentration of the
15 relaxation agent(s) or by altering the relaxation efficiency of the agent(s) by changing ambient factors such as local temperature, pressure, pH, effective diffusion rate, hydration, molecular conformation, radicalization or polarization (claim 4).

20 According to an advantageous embodiment, the probe medium is contained in a first half-cell of an electrochemical cell located within said resonator volume, the operation of said electrochemical cell causing a change in concentration of said relaxation agent (claim 5).

25 According to a further embodiment, the probe medium is also contained in a second half cell of said electrochemical cell, said second half cell being located outside of said resonator volume (claim 6).

According to yet another embodiment, the first and second half cells are in fluid
30 communication across an ion bridge or ion selective membrane (claim 7).

According to still another embodiment, the magnetic field probe is configured to be mountable within a magnetic resonance imaging or spectroscopy apparatus (claim 11). This includes but is not limited to the incorporation into so-called dynamic field cameras (see EP 2515132 A1).

5

In state-of-the-art embodiments the relaxation times of the involved materials and the NMR active sample employed for the field sensing in particular are chosen related to the targeted repetition time of the field measurement and can be adjusted by the choice of the materials, their treatment such as curing, hardening
10 tempering etc. and by agents added to the employed substances. Such relaxation agents are typically based or contain a paramagnetic constituent such as paramagnetic molecules, radicals, atoms or ions – in particular Gd, Fe, Mn, Cr, Cu, V, Co, Ni, Dy or complexes with such atoms/ions or effectively paramagnetic nano-particles. The resulting relaxation is dependent on the concentration of the
15 agent and other factors modulating the relaxivity of the agent by altering the coupling and the exchange efficiency between the nuclear spin and the relaxation agent or the motion of the molecules. These factors comprise in particular pH, temperature, aggregate phase, viscosity, diffusivity, gelling, hydration, polarization, ionization or radicalization of the agent in the solution and the conformation
20 state of the relaxation agent.

The relaxation of the probe materials and the NMR active substance in particular can therefore be controlled by altering one or several of these factors at least in the sensitive area of said NMR/ESR excitation and detection arrangement. In
25 particular, approaches as described in [3], which discloses methods based for altering the relaxivity of a relaxation agent in a general context, can be employed for the construction and application of field probes with tunable relaxation times. For this the probe has to be equipped with means to control the pH, apply high frequency radiation/light/UV/ionizing radiation or heat, add/remove or activate/deactivate metal ions or enzymes or control redox potentials in order to use
30 the activatable contrast agent to tune the relaxation time of at least the NMR ac-

tive sample in the probe. Further electrochemical and sonochemical/physical reactions (claim 8) can be employed to control the relaxation time of the NMR active sample.

5 Further the speed and the cycle life time of the employed reactions and its properties can be enhanced by mixing, stirring, induction or enhancement of convection, (ultra-)sound, (ultra-)sound cavitation, (ultra-)sound standing waves, (ultra-)sound modulation, vibration and other methods increasing or enhancing the mass transport properties or the relaxation agent and or the NMR active substance. This is in particular the case when employing electrochemical reactions
10 where the ion diffusion often represents the speed limiting factor. Further local concentration gradients can be decreased which would result in inhomogeneous signal evolution and often in a reduced cycle lifetime of the electrochemical device.

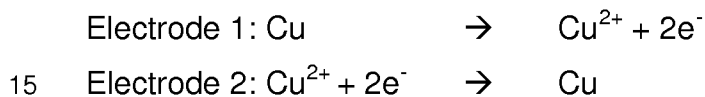
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In general, preferred reactions altering the relaxation properties are substantially performed in liquid or solid phase and substantially do not have reactants nor products in gas phase. If materials in gas phase are involved they are preferably kept or dissolved in a liquid, gel, foam, fabric or tissue. Further, the reactions are
20 preferably substantially isochoric.

In one preferred embodiment the concentration of the relaxation agent in the NMR active region of the probe is controlled by electrochemical reactions by which the relaxing ions are oxidized from one electrode and reduced on the other.
25 Such the concentration of relaxation agent can be controlled in the region in which the magnetic resonance is detected. Candidate reactions are typically found in electroplating and secondary cell embodiments. Further, many of the techniques and adjuvants such as charging current/voltage optimizations, adjuvants, brighteners, inhibitors, gellings, membranes, etc. known from these applications can be directly applied to enhance reaction speed, life cycle count and
30 reliability. Further the properties of the reaction can be enhanced by adding addi-

tional electrolytes such Na, Ca, K and other salts. In certain preferred embodiments, an ion selective membrane is employed to maintain concentration gradients between the MR sensitive volume or a volume containing it and other compartments. Further, membranes or gel layers suppressing dendrite growth and enhancing the abrasion and deposition properties at electrodes can be employed.

Example reactions demonstrated are based on dissolved CuSO_4 or CuNO_3 . A copper containing set of electrodes are in contact with the NMR/ESR active solution. Applying an electric potential to said electrodes oxidizes the copper in contact with said electrode while on the oppositely polarized electrode structure copper ions are reduced and deposited.



In this case, the employed reaction is typically applied for electroplating/electrolysis and is similarly feasible using other metallic ions such as Ni, Fe, Mn, Gd, Au, Ag, In, Dy, Cd, Ta, Ti, Pt, Pd, Rh, Ru and a variety of anions such as sulfates, nitrates, hydrates, complex forming chelates etc.

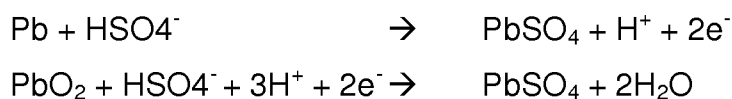
In another preferred embodiment the electrochemical reaction is used to control a metal-ion responsive relaxation agent as mentioned in [3]. The advantage of this embodiment is that the metal ion directly involved in the electrochemical reaction has not to be a viable relaxation agent; however it can modulate the relaxivity of another relaxation agent. This is of particular interest since often the paramagnetic ions form paramagnetic metal deposits which pose susceptibility matching problems degrading the NMR performance of the field probe.

Another preferred embodiment uses reactions of the type as manganese nitrate/sulfate electrolysis. In this case no ion selective membrane is required sep-

arating the two half cells since the dissolved manganese salt is plated as Mn metal on one electrode, and as manganese oxide on the other electrode. However the manganese ion concentration is reduced in the solution.

- 5 Another preferred embodiment controls the relaxation properties of the NMR/ESR active sample by controlling the pH of the medium. Since the pH is a key factor for the relaxivity of the contrast agent, a change in pH alters the resulting relaxation. This mechanism can also be employed in conjunction with altering the concentration of the relaxation agent enhancing the effectivity. Electrochemical processes as employed in alkaline batteries, lead acid accumulators, metal
10 hydrate cells, electrolyte-, tantalum- and super-capacitors can be employed. In one embodiment the pH change in the electrolyte of a lead acid battery system, which then forms the NMR active sample, can be employed to alter the relaxivity of GdCl dissolved in the same solution:

15



- increases the pH while the inverse reaction during charging decreases the pH
20 again. The relaxivity of the GdCl changes, which in turn alters the net relaxation properties in the NMR/ESR active region. Also manganese or aluminum hydroxide reactions can be used.

- In another embodiment (claim 9) photochemical reactions are used to either
25 substantially alter the pH at least in the NMR active region or to activate a photoactive relaxation agent as mentioned in [3].

- In a further embodiment (claim 10) the relaxation of one species of magnetic resonance is modulated by dynamic nuclear polarization transfers by Over-
30 houser effects [4] or dynamic nuclear polarization [5] by applying RF or optical pumping to another MR active species.

In another embodiment light or ionizing radiation is applied to modulate the relaxation at least in the NMR active region. The radiation thereby forms ions or radicals which then induce NMR relaxation. Altering the level of radiation exposure thereby alters the relaxation of the NMR active sample.

5

In the cases where the relaxation time of the MR active sample can be modulated significantly faster than the duration of either the obtained MR signal or the required repetition rate of the re-excitation, high relaxation rates can be switched on only in a part of the field probe signal acquisition, preferably after the required acquisition period in order to relax the coherence before the next excitation but also in order to enhance signal efficiency of the probe.

10

Brief description of the drawings

The above mentioned and other features and objects of this invention and the manner of achieving them will become more apparent and this invention itself will be better understood by reference to the following description of embodiments of this invention taken in conjunction with the accompanying drawings, wherein

15

Fig. 1 shows a magnetic field probe, (a) in a sectional view (left) and (b) in a photographic view (right);

20

Fig. 2 shows, from top to bottom: Bias voltage and current; resulting T1 relaxation times; T2* relaxation times, plotted on a common time axis; and FIDs obtained at conditions holding at the color coded times as indicated by the color bar;

25

Fig. 3 shows a comparison of FID acquisitions performed with a probe with tunable relaxation time adjusted for long (blue) and short lived (green) signals; top: single FIDs (in arbitrary units); middle: signals acquired in fast succession (every 20 ms) with identical scanner gradient pulses; bottom: difference in signal phase (rad)

30

of two echo signals for the two relaxation time adjustments shown in the top panel.

Detailed description of the invention

- 5 The magnetic field probe 2 shown in Figs. 1a and b for magnetic resonance imaging and spectroscopy applications comprises a probe medium 4 that exhibits magnetic resonance (MR) at an operating frequency in the presence of a main magnetic field. Further, the field probe comprises means for pulsed MR excitation of said probe medium within a resonator volume 6 of said field probe and
- 10 means for receiving an MR signal generated by said probe medium within said resonator volume. Still further, the field probe comprises adjusting means 8 for continuously adjusting a MR relaxation time of the probe medium to a preselected value within an operating range.
- 15 In the example shown in Figs. 1a and 1b, the field probe is configured as an electrochemical cell comprising a first electrochemical half cell 10 and a second electrochemical half cell 12 which are in fluid communication across an ion exchange membrane 14 peripherally surrounded by a gasket 16 forming a fluid seal against an inner wall region of the field probe housing. The first electro-
- 20 chemical half cell contains a first electrode 18 and the second electrochemical half cell contains a second electrode 20. The first electrochemical half cell contains the MR active medium 4 and has a resonator region 6 surrounded by a solenoid 22 used for transferring pulsed MR excitation to the probe medium and for receiving an MR signal generated by the probe medium. As shown schematically
- 25 in Fig. 1a for the purpose of illustrating the operating principle, the electrochemical system comprises cationic species C^+ and anionic species A^- and electrons e^- . The concentration of the MR active species in the resonator volume is controlled by applying a suitable voltage to the two electrodes by means of a voltage source 24. In the example shown, the resonator volume is surrounded by a sus-
- 30 ceptibility matching jacket 26.

Example 1: Field probes with in-situ controllable thermal relaxation times

Introduction

NMR based magnetic field sensors have been demonstrated to measure the dynamic magnetic field evolution inside an MRI scanner with extreme accuracy [1]. Based on these measurements system imperfections as well as externally induced field perturbations can be assessed and then corrected for in post-processing [2] or by real-time field feed-back [6]. However, once the FID of the probe relaxed or got dephased, the field and the k-space trajectory cannot be tracked anymore. The probe can only be re-excited after the coherences have thermally relaxed. Otherwise occurring spurious echoes would impinge the field measurement which is based on the signal evolution of an FID in the magnetic field. When manufacturing the probes, the relaxation times of the NMR active sample are therefore adjusted by relaxation agents to the targeted repetition time in the application. Alternatively, several fast relaxing probe sets are employed in interleaved fashion which allows acquiring the magnetic field evolution continuously [7], but inflicting a suboptimal random-walk error propagation when tracking k-space trajectories. In this work we present an approach to adapt the thermal relaxation times (T_1, T_2) of NMR based field probes in-situ by use of reversible electrochemical reactions inside the probe.

Methods

The thermal relaxation in the field probe is adjusted by paramagnetic metal ions (dopant) that offer very low T_1/T_2 ratio maximizing the signal yield. Thereby the relaxation time is dependent on the concentration $c(X)$ and the ambient conditions of the dopant x influencing its specific relaxivity ($r_{1,2}^X$) with respect to T_1 and T_2 :

$$R_{1,2} = 1/T_{1,2} \propto r_{1,2}^0 + r_{1,2}^X \cdot c(X)$$

The resulting relaxation time can hence be controlled by the concentration of the paramagnetic ions in the NMR active region. Secondary cells as employed in rechargeable batteries perform reactions in which the concentration of metal ions in the electrolyte or close to the electrode is dependent on the charging state.

5 Similarly, a probe with controllable relaxation time was based on a microfluidic copper sulphate secondary concentration cell. The electrolyte in both half cells is aqueous copper sulphate ($Cu_2(SO_4)_2$) where the Cu^{2+} ion acts as relaxation agent. The half cells are separated by an anion exchange membrane which lets the sulphate ions pass while hindering the copper ions from entering the other
10 half cell. Thereby a concentration gradient between the two half-cells can be maintained. Applying a voltage to the copper electrodes oxidizes the copper at the anode increasing the concentration of Cu^{2+} in the corresponding half-cell. In turn Cu^{2+} is reduced at the cathode and plated onto the electrode decreasing the concentration in that half-cell. Charge is equilibrated by the exchange of sulphate
15 ions through the membrane. By exciting and picking up the NMR signal in only one half-cell the NMR relaxation time of the probe is altering when charging/discharging the concentration cell.

The probe consists of a capillary (0.8 mm ID) initially filled with 14 g/L $Cu_2(SO_4)_2$
20 solution with sodium sulphate of equal molarity as passive electrolyte. The membrane was fitted into a PMMA housing that forms the second half-cell. Experiments were performed at 3T using the probe's tuned solenoid coil. The τ_1 relaxation time was measured by a saturation recovery experiment using a two pulse sequence with variable delay between the pulses. T_2^* was assessed by the exponential decay of the FID. The electrochemical potential was applied by a lab voltage supply and the corresponding ion current was measured by a Picoammeter
25 (Keythley, Cleveland, Oh.).

Results

30 Fig. 2 shows the obtained results. The top row plots the applied voltage across the electrodes and the resulting ion current in the 100 μA range. Two cycles of

enriching copper ions and depleting the half-cell were run over 180 *min* in total. The corresponding behavior of the relaxation times are plotted below showing that they could be controlled within a range of 4 to 45 *ms* in T_1 and 4 to 25 *ms* in T_2^* as limited by the static shim. The plot at the bottom shows FIDs acquired colored from blue to red dependent on the time of their acquisition.

Discussion

Electrochemical processes known from battery and electroplating applications offer MR compatible means to control relaxation times of fluids employed in NMR based field probes. By adapting the relaxation time of the probe, the field measurement can be optimized for the targeted application enabling a single probe to cover most of the applied sequences ranging from fast gradient echoes to single-shot read-outs with the same acquisition and signal processing chain. The proposed copper sulphate electrolysis is thereby only one potential candidate reaction. An alternative was also found based on manganese salts that can be electrolyzed into manganese and its oxide omitting the necessity of an ion selective membrane, however at the cost of enhanced susceptibility matching problems due to the strong paramagnetism of these substances. Also many similar photochemical reactions are potential candidates, some of them involving more complex chemical compounds in the system.

The reaction speed of the current approach is mainly limited by the speed of ion migration in the capillary. The speed of relaxation change can therefore be optimized by reducing the distance between the electrodes and the NMR active region or by enhancing the diffusive ion transport by convection or mixing as it could be induced by localized heating, stirring, rotation, vibrations or ultrasound induced pressure gradients

Rather than tuning the relaxation times other material parameters can be controlled by similar reactions e.g. the bulk susceptibility. Closely controlling relaxation time and/or susceptibility could also be applied for calibration, validation and

reference phantom setups in which they could not only alter a property but also induce stationary spatial gradients of that property.

In common with many other secondary cells the studied field probe exhibits limits
5 regarding cycle lifetime caused by electrode abrasion, dendrite formation or gas-
singing. Many of the known counter-measures however, such as optimizing charg-
ing currents and local potentials or chemical adjuvants are compatible with the
proposed NMR field probe.

10 Example 2

A further illustration of the effects of adjustable relaxation time are shown in Fig.
3. The top image shows the single FIDs acquired in the two states of adjustment
exhibiting a long and a short relaxation time in the same magnetic field probe.
The plots in the middle show signals acquired in fast succession (every 20 ms)
15 while the scanner played identical gradient pulses in every single acquisition.
Here four succeeding FIDs are plotted in color tones from light to dark. It can be
clearly seen that the long lived FIDs are due to the echo formation not being
identical. This accumulated echo history introduces a significant error in the sig-
nal phase of the probe as shown by the difference in signal phase of echo 2 and
20 3 shown in the plot on the bottom for the two relaxation time adjustments already
shown above. Since the gradient action in both acquisitions is identical, the dif-
ference of the accrued signal phase of an ideal NMR should ideally be constant,
but this is the case only for the short-lived adjustment (green).

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Claims

1. A magnetic field probe, particularly for magnetic resonance imaging and spectroscopy applications, comprising:
 - 5 - a probe medium that exhibits magnetic resonance (MR) at an operating frequency in the presence of a main magnetic field;
 - means for pulsed MR excitation of said probe medium within a resonator volume of said field probe and means for receiving an MR signal generated by said probe medium within said resonator volume;
- 10 characterized in comprising adjusting means for continuously adjusting a MR relaxation time of the probe medium to a preselected value within an operating range.
2. The magnetic field probe according to claim 1, wherein said magnetic resonance is nuclear magnetic resonance (NMR).
- 15 3. The magnetic field probe according to claim 1 or 2, wherein said adjusting means provide for a substantially reversible adjusting of said MR relaxation time.
- 20 4. The magnetic field probe according to one of claims 1 to 3, wherein said adjusting means are configured to adjust a concentration of a relaxation agent contained in said probe medium.
- 25 5. The magnetic field probe according to claim 4, wherein said probe medium is contained in a first half-cell of an electrochemical cell located within said resonator volume, the operation of said electrochemical cell causing a change in concentration of said relaxation agent.

6. The magnetic field probe according to claim 5, wherein said probe medium is also contained in a second half cell of said electrochemical cell, said second half cell being located outside of said resonator volume.
- 5 7. The magnetic field probe according to claim 6, wherein said first and second half cells are in fluid communication across an ion bridge or ion selective membrane.
8. The magnetic field probe according to one of claims 1 to 3, wherein said
10 adjusting means are based on a sonochemical process.
9. The magnetic field probe according to one of claims 1 to 3, wherein said adjusting means are based on a transfer of dynamic nuclear polarization.
- 15 10. The magnetic field probe according to one of claims 1 to 3, wherein said adjusting means are based on a photochemical process.
11. The magnetic field probe according to one of claims 1 to 10, which is configured to be mountable within a magnetic resonance imaging or spectroscopy
20 apparatus.
12. Use of the magnetic field probe according to one of claims 1 to 11 for measuring dynamic magnetic field evolution in a magnetic resonance imaging or spectroscopy apparatus.
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13. A method of controlling the signal life time and spin relaxation properties of a magnetic field probe according to one of claims 1 to 11 in a magnetic imaging or spectroscopy apparatus.

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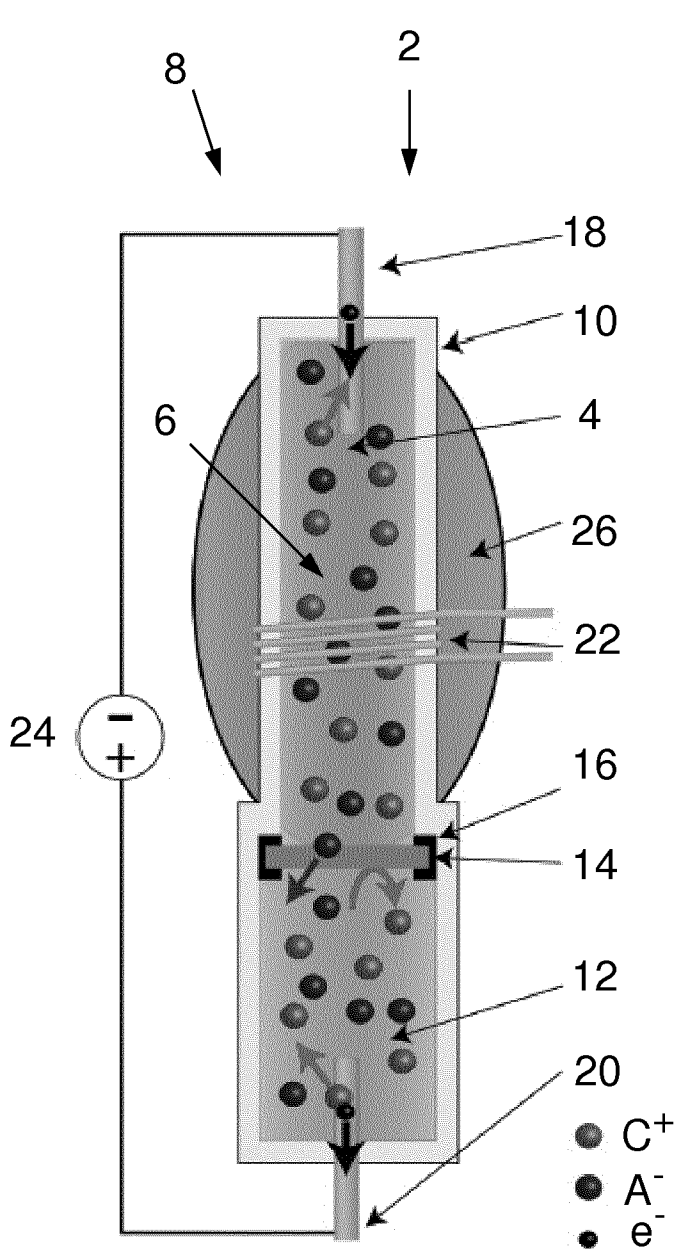


Fig. 1a

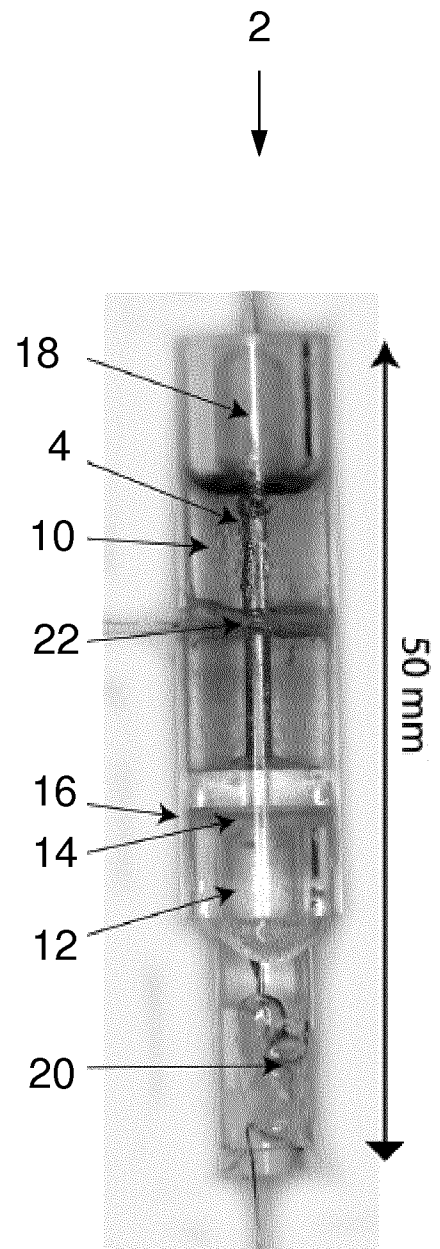


Fig. 1b

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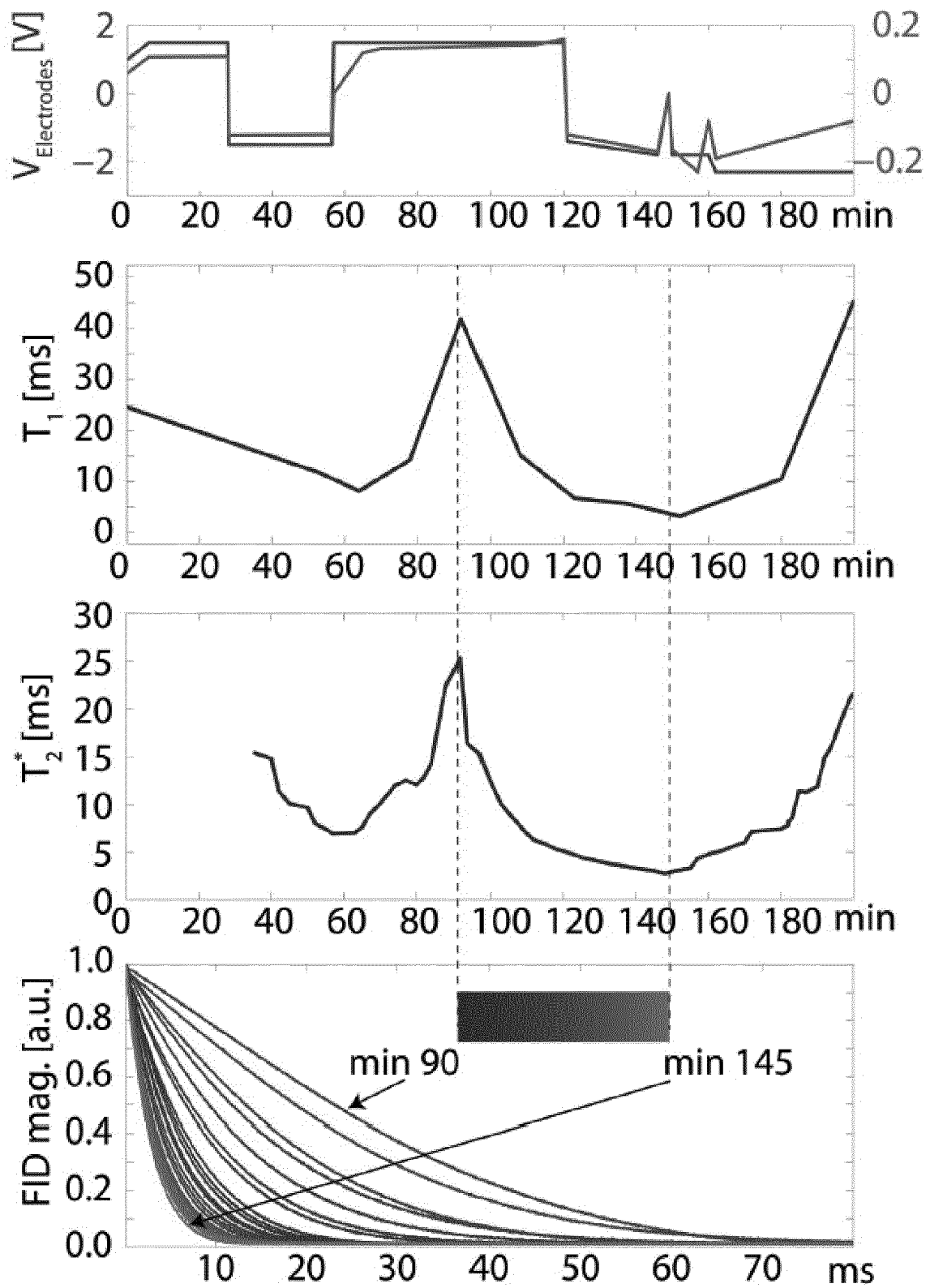


Fig. 2

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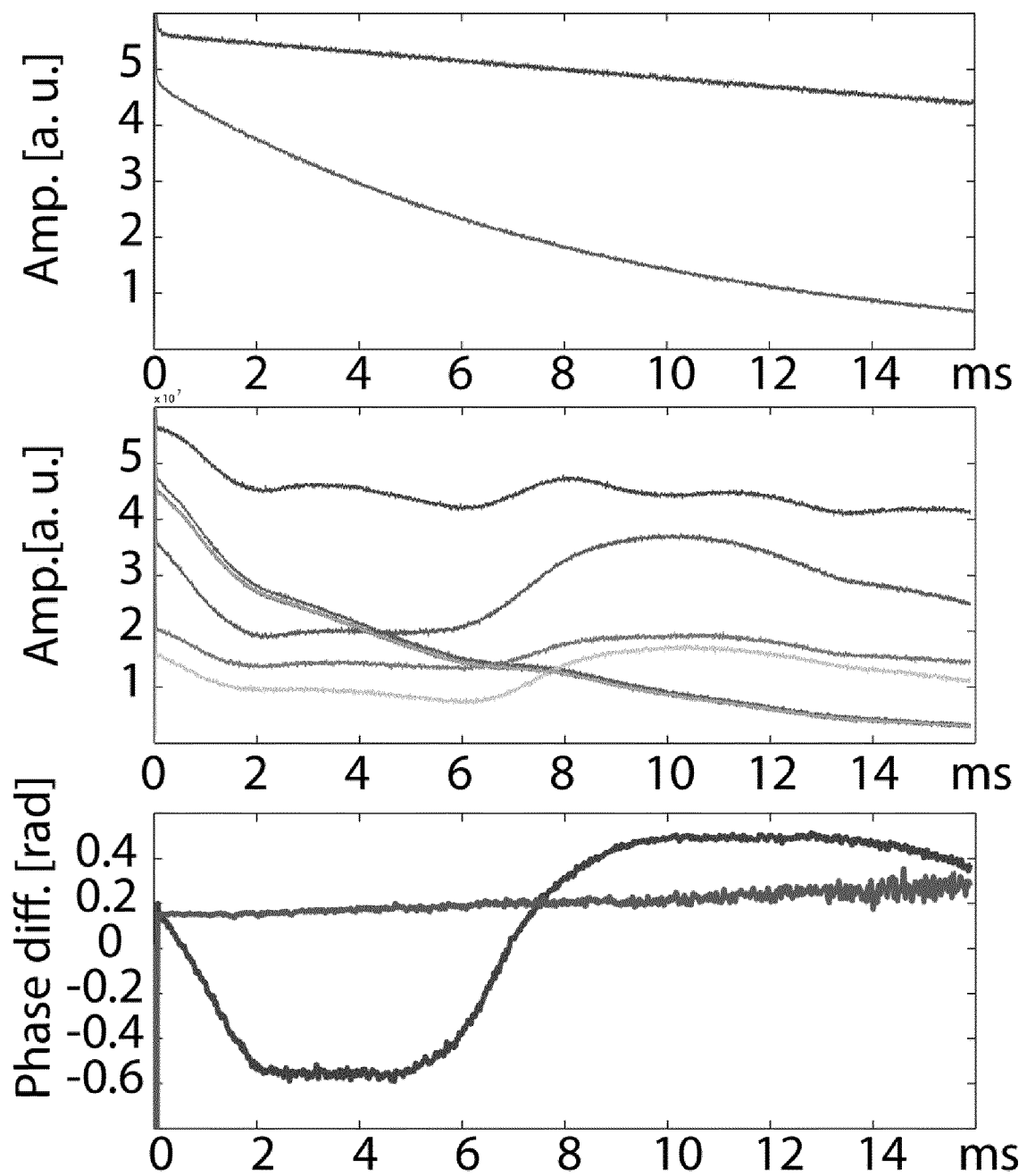


Fig. 3

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2016/061053

A. CLASSIFICATION OF SUBJECT MATTER

INV. G01R33/24 G01R33/56 G01R33/58
ADD. G01R33/565

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)

G01R G01N A61B G01V

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)

EPO-Internal, BIOSIS, COMPENDEX, EMBASE, INSPEC, IBM-TDB, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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Further documents are listed in the continuation of Box C.



See patent family annex.

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Date of the actual completion of the international search

7 October 2016

Date of mailing of the international search report

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INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2016/061053

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
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