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— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

(54) Title: HARMONIC EXCITATION OF MR SIGNAL FOR INTERVENTIONAL MRI

(57) Abstract: The present invention is directed to a system and method for harmonic excitation of magnetic resonance (MR) signal for interventional MR imaging (MRI). The system includes an implantable RF coil that excites MR signals in the subject, when driven by lower frequency RF filed from an external coil. This approach permits detection of MR signal in close proximity of the inserted coil by a standard MRI receiver coil without background from the rest of the subject. The procedure allows precise determination of a position of the inserted coil, within the subject. The procedure also allows obtaining localized MR images and spectra.

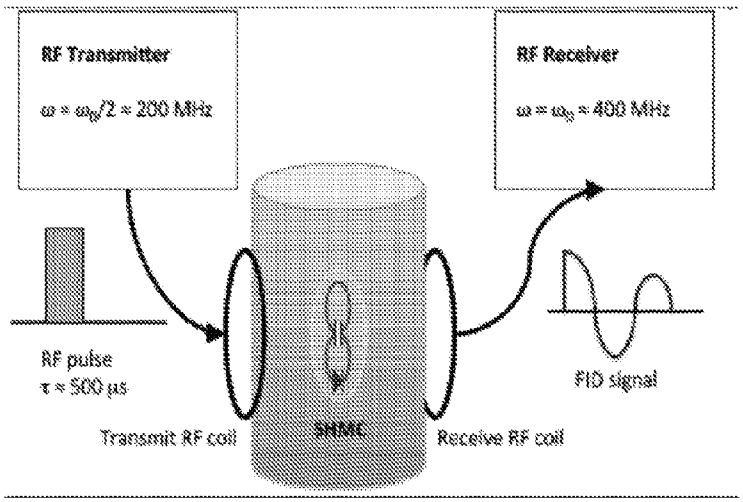


FIG. 1

WO 2015/187607 A1

HARMONIC EXCITATION OF MR SIGNAL FOR INTERVENTIONAL MRI

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Patent Application No. 62/006,296 filed June 2, 2014, which is incorporated by reference herein, in its entirety.

FIELD OF THE INVENTION

[0002] The present invention relates generally to imaging technologies. More particularly, the present invention relates to a system and method for generating harmonic excitation of magnetic resonance signal for interventional magnetic resonance imaging.

BACKGROUND OF THE INVENTION

[0003] Interventional magnetic resonance imaging (MRI) is used to guide minimally invasive procedures intra-operatively and interactively. In some instances interventional MRI can be used for interventional procedures such as radiation treatment and surgery. In some instances it would be beneficial to provide further MRI based guidance for these procedures.

[0004] Accordingly, there is a need in the art for a system and method to facilitate further guidance of interventional procedures using MRI.

SUMMARY OF THE INVENTION

[0005] The foregoing needs are met, to a great extent, by the present invention which provides a system for imaging including an implantable RF coil configured to excite magnetic resonance (MR) signals in a subject. The system includes an RF transmitter configured to generate an RF pulse field. Additionally, the system includes an RF receiver.

[0006] In accordance with an aspect of the present invention, the RF coil further includes a non-linear diode element. The non-linear diode element can take the form of a Schottky diode. The RF coil in the "ground state" with the open non-linear diode element is tuned to a fraction of the MR resonance frequency, ω_o/n. Alternately, the RF coil in the "activated state"

with the closed non-linear diode is tuned to the MR resonance frequency, ω_o. The RF transmitter produces the RF pulse field at a low frequency, ω_o/n. The RF receiver further comprises an MR receiver coil of a standard MR instrument, which is tuned to the MR resonance frequency, ω_o. The RF transmitter produces an RF filed at half-resonance frequency.

[0007] In accordance with another aspect of the present invention, a method for imaging includes implanting an RF coil configured to excite magnetic resonance (MR) signals in a subject. The method includes transmitting an RF pulse field with an RF transmitter configured to generate the RF pulse field. The method also includes receiving the RF pulse field with an RF receiver.

In accordance with yet another aspect of the present invention, the method includes using the RF coil having a non-linear diode element. The method includes using the RF coil having the non-linear diode element taking the form of a Schottky diode. The non-linear diode element is tuned to the MR resonance frequency, ω_o, or alternately, the non-linear diode is tuned to a fraction of the MR resonance frequency, ω_o/n. The RF pulse field is produced at a low frequency, ω_o/n. The method includes using the RF receiver having an MR receiver coil of a standard MR instrument. The method also includes producing a harmonic frequency $(\omega_o/n) \cdot m$ with the RF coil during the RF pulse field at a frequency, ω_o/n, due to nonlinearity of the diode element in the RF coil. The method includes producing an RF field at half-resonance frequency. Additionally, the method includes using two inductive parallel loops. The method can also include using a second harmonic generating microcoil.

BRIEF DESCRIPTION OF THE DRAWINGS

[0008] The accompanying drawings provide visual representations, which will be used to more fully describe the representative embodiments disclosed herein and can be used by those skilled in the art to better understand them and their inherent advantages. In these drawings, like reference numerals identify corresponding elements and:

[0009] FIG. 1 illustrates a schematic diagram of a second harmonic excitation MR experiment on a 9.4 T MR scanner, according to an embodiment of the present invention.

[0010] FIGS. 2A-2D illustrate a picture of and schematic diagrams of a second harmonic generating microcoil (SHMC) with a non-linear diode element, according to an embodiment of the present invention.

[0011] FIG. 3A illustrates a graphical view of a 1D spectra obtained with a standard external volume RF coil and those excited by SHMC and detected by the standard coil are shown using arbitrary scaling, according to an embodiment of the present invention.

[0012] FIG. 3B illustrates a 2D spin echo image of the sample with the embedded SHMC, TE/TR = 20/500 ms (left), a slice from a 3D gradient echo image of the sample generated by SHMC and detected by the standard coil, TE/TR=0.9/50 ms (center), a 3D reconstruction of gradient echo images obtained with the standard coil and SHMC (right).

[0013] FIG. 4A illustrates a side view of an RF coil attached to a subject.

[0014] FIGS. 4B-4C illustrate images related to an *in vivo* second harmonic excitation MR experiment, according to an embodiment of the present invention.

DETAILED DESCRIPTION

[0015] The presently disclosed subject matter now will be described more fully hereinafter with reference to the accompanying Drawings, in which some, but not all embodiments of the inventions are shown. Like numbers refer to like elements throughout. The presently disclosed subject matter may be embodied in many different forms and should not be construed as limited to the embodiments set forth herein; rather, these embodiments are provided so that this disclosure will satisfy applicable legal requirements. Indeed, many modifications and other embodiments of the presently disclosed subject matter set forth herein will come to mind to one skilled in the art to which the presently disclosed subject matter pertains having the benefit of the teachings presented in the foregoing descriptions and the associated Drawings. Therefore, it is to be understood that the presently disclosed subject matter is not to be limited to the specific embodiments disclosed and that modifications and other embodiments are intended to be included within the scope of the appended claims.

[0016] The present invention is directed to a system and method for harmonic excitation of magnetic resonance (MR) signal for interventional MR imaging (MRI). The system includes an implantable RF coil or a coil attached to an interventional device that excites MR signals in the subject, when driven by lower frequency RF filed from an external coil, due to nonlinearity of the diode element. This approach permits detection of MR signal in close proximity of the inserted coil by a standard MRI receiver coil without background from the rest of the subject and thus provides precise position of the coil and/or location of the device on MR images. In addition, the procedure allows obtaining localized MR images and spectra. MR-detectable devices are important for interventional procedures, and should provide a clear imaging signature while not degrading diagnostic imaging quality. The MR-detectable

probe design is based on excitation of MR signals by high-frequency RF harmonics generated by the probe with a non-linear element.

[0017] A system according to an embodiment of the present invention includes an implantable RF coil with a non-linear element such as a low barrier Schottky diode, tuned to the fractions of the MR resonance frequency (ω_0 /n, n=2, 3, …) and to the resonance frequency ω_0 once the nonlinear device (diode) is activated by the electric current generated by the low frequency RF field.. The implantable RF coil is irradiated by the pulsed RF field at a low frequency (ω_0 /n). The harmonic resonance frequency ω_0, generated during the RF pulse due to nonlinearity of the diode element, excites MR signals in a sample that can be detected by a standard MR receiver coil of a standard MR instrument. Standard imaging and spectroscopy pulse sequences can be used to (i) produce highly localized spectra and/or images of the structures in the close proximity to the implantable RF coil and (ii) to determine spatial position of the implantable RF coil with high precision that is essential for interventional procedures. Important for clinical application, as the circuit in its "ground state" is not tuned to the ω_0 resonance frequency there is no heat generation during a standard MRI performed at the resonance frequency ω_0 on the subject with the inserted coil.

[0018] The present invention is directed to an implantable RF coil with a non-linear diode element designed to excite MR signals in the subject when radiated by RF filed from an external coil at low frequency equal to one-half of the magnetic resonance frequency. Second harmonic generated in the coil by the nonlinear element is at the resonance frequency and produces MR signals in the subject in close proximity of the inserted coil that can be detected by a standard MRI receiver coil. The method allows obtaining localized MR images and spectra and determining a precise position of the inserted coil within the subject that can be important for the design of MR guided probes for interventional procedures.

[0019] All studies were performed on a Bruker 9.4T Biospec preclinical MR imaging and spectroscopy system that has a proton resonance frequency close to 400 MHz. Overall design of the experiment is shown in FIGS. 1 and 2A-2D. A single turn coil tuned to 200 MHz was driven by a broadband transmitter of the instrument generating RF pulses with the duration of ~500 μs and maximal power of ~ 200 W. The sample with the inserted second harmonic generating microcoil (SHMC) and the 200 MHz transmit coil were positioned within a standard 400 MHz volume resonator used as a receive RF coil. To maintain precise phase coherence between the two RF channels, the transmitter frequency was set at exactly half of the resonance frequency, ω_0. An implantable probe was designed to excite MR signals when driven by an external RF filed at half-resonance frequency. A standard multislice spin-echo imaging with TE/TR=6/1000 ms and 3D FLASH imaging with TE/TR=1.1/50 ms and flip angle of 10 degrees, was initially performed.

[0020] 3D SHMC FLASH images were acquired using square 500 μs RF pulses at 200 MHz and an RF power level of 35 dBm applied to the transmit coil. MR harmonic imaging experiments were performed with an agarose phantom and with an experimental animal model with implanted SHMC. The design and principle of operation of a second harmonic generating microcoil (SHMC) are shown in FIGS. 1 and 2A-2D.

[0021] The SHMC was constructed using two inductive parallel loops with diameters of 4 mm, connected by a 15 pF nonmagnetic capacitor, as shown in Fig. 2A. A low barrier (<250 mV) and low capacity (< 0.3 pF), Schottky diode (HSMS-2852, Avago Technologies) was inserted in the middle point of one of the loops. In the absence of RF excitation, the diode is open and the circuit is tuned at a resonance frequency of 200 MHz. During the 200 MHz RF pulse, the diode is transiently closed by the direct voltage in the circuit, and the resonance

frequency is shifted to 400 MHz, as shown in FIGS. 2B-2D. A single-turn loop 200 MHz transmit coil was constructed with an LC trap filter blocking the 400 MHz frequency.

[0022] As illustrated in FIG. 1, free induction decay (FID) at 400 MHz is produced by proton spins of the sample excited by the second harmonic generated by a microcoil with a non-linear diode element. An ellipse surrounds a region of the sample where the MR signal is generated. An important requirement is to position the transmitting RF coil parallel to the plane of SHMC to ensure good magnetic coupling between the coils.

[0023] The design and principle of operation of SHMC are shown in FIGS. 2A-2D. The coil consists of two inductive loops with diameters of approximately 4 mm connected by a 15 pF non-magnetic ceramic chip capacitor. One of the loops has a low barrier (<250 mV) and low capacity (< 0.3 pF) high-frequency Schottky diode (such as HSMS-2852, Avago Technologies). In the absence of RF excitation the diode is open and the circuit is tuned at a resonance frequency of 200 MHz. During the 200 MHz RF pulse the diode is transiently closed by the direct voltage generated in the circuit and the resonance frequency of the circuit with two parallel loops is shifted to 400 MHz. A 400 MHz second harmonic of the applied 200 MHz RF field excites nuclear magnetization of the protons in the sample to generate a free induction decay (FID) detected by the receiver system of the instrument.

[0024] FIGS. 2A-2D illustrate a picture and schematics of the SHMC and two different modes of operation. FIG. 2A illustrates an image of the SHMC, according to an embodiment of the present invention. FIG. 2B illustrates a schematic diagram of the image shown in FIG. 2A. FIGS. 2C and 2D illustrate two different modes of operation of the SHMC illustrated in FIG. 2B. FIG. 2C illustrates the SHMC without an applied RF field at a resonance frequency

of 200 MHz. FIG. 2D illustrates an SHMC with an applied RF field at a resonance frequency of 400 MHz.

[0025] A robust excitation of protons and generation of FID was detected in a 1D spectroscopy experiment performed using the experimental setup. The signal generated by the SHMC and detected by the standard volume coil of the instrument has significantly reduced line width due to smaller excitation volume of the SHMC (FIG. 3A). A T2 MR image of the sample with embedded SHMC is shown in FIG. 3B, left. Magnetic susceptibility artifacts generated by the capacitor and the diode (slightly magnetic) are visible in the image. A slice from a 3D gradient echo image generated by SHMC is shown in FIG. 3B center. Only sample areas next to the two loops of SHMC contribute to the detected MR signal. For comparison, a 3D reconstruction of gradient echo images obtained using a standard RF coil and SHMC with second harmonic excitation are shown in FIG. 3B, right. A T2 MR image of a 3% agarose phantom prepared in a standard 10 mm NMR tube with the embedded SHMC (FIG. 2A) is shown in FIG. 3B. Magnetic susceptibility artifacts from the capacitor and the diode are visible in the image. A matching slice from the 3D gradient echo SHMC image is shown in FIG. 3B. Only sample areas next to the SHMC contributed to the detected MR signal. A 3D reconstruction of fused gradient echo images obtained using a standard RF coil and the SHMC excitation are shown in FIG. 3A.

[0026] FIG. 4A illustrates a side view of an RF coil attached to a subject. FIGS. 4B-4C illustrate images related to an *in vivo* second harmonic excitation MR experiment, according to an embodiment of the present invention. *In vivo* MR experiments were performed after implanting SHMC in the mouse back and positioning animal in a 30 mm RF resonator, with the transmit RF coil attached to the animal, illustrated in FIG. 4A. Coronal and axial fused images obtained with a standard FLASH (gray-scale) and SHMC generated harmonics are shown in FIGS. 4

B and 4C. Coronal images were generated by maximum intensity projections of 6-8 slices extracted from 3D data matrices for the FLASH and SHMC imaging, respectively.

[0027] The present invention includes a novel technique to excite MR signals using a second harmonic generated by an RF coil with a nonlinear diode element driven at a half resonance frequency of the spectrometer. The method can be used to detect spatially localized spectra and images generated by spins in close proximity to the coil. One of the potential applications of the method includes using the coil for MR traceable probes to precisely measure the probe position and to overlay the probe location with a standard anatomical MR image during interventional procedures.

[0028] The many features and advantages of the invention are apparent from the detailed specification, and thus, it is intended by the appended claims to cover all such features and advantages of the invention, which fall within the true spirit and scope of the invention. Further, since numerous modifications and variations will readily occur to those skilled in the art, it is not desired to limit the invention to the exact construction and operation illustrated and described, and accordingly, all suitable modifications and equivalents may be resorted to, falling within the scope of the invention.

What is claimed is:

1. A system for imaging comprising:

an implantable RF coil configured to excite magnetic resonance (MR) signals in a subject;

an RF transmitter configured to generate an RF pulse field; and

an RF receiver.

2. The system of claim 1 wherein the RF coil further comprises a non-linear diode element.

3. The system of claim 2 wherein the non-linear diode element comprises a Schottky diode.

4. The system of claim 2 wherein the non-linear diode element is tuned to the MR resonance frequency, ω_o.

5. The system of claim 4 wherein the non-linear diode is tuned to a fraction of the MR resonance frequency, ω_o/n.

6. The system of claim 1 wherein the RF transmitter produces the RF pulse field at a low frequency, ω_o/n.

7. The system of claim 1 wherein the RF receiver further comprises an MR receiver coil of a standard MR instrument.

8. The system of claim 1 wherein the harmonic frequency $(\omega_o/n) \cdot m$ is produced by the RF coil during the RF pulse field at a frequency, ω_o/n, due to nonlinearity of the diode element in the RF coil.

9. The system of claim 1 wherein the RF transmitter produces an RF filed at half-resonance frequency.

10. A method for imaging comprising:

implanting an RF coil configured to excite magnetic resonance (MR) signals in a subject;

transmitting an RF pulse field with an RF transmitter configured to generate the RF pulse field; and

receiving the RF pulse field with an RF receiver.

11. The method of claim 10 further comprising using the RF coil having a non-linear diode element.

12. The method of claim 11 further comprising using the RF coil having the non-linear diode element comprising a Schottky diode.

13. The method of claim 11 further comprising tuning the non-linear diode element to the MR resonance frequency, ω_o.

14. The method of claim 13 further comprising tuning the non-linear diode to a fraction of the MR resonance frequency, ω_o/n.

15. The method of claim 10 further comprising producing the RF pulse field at a low frequency, ω_o/n.

16. The method of claim 10 further comprising using the RF receiver having an MR receiver coil of a standard MR instrument.

17. The method of claim 10 further comprising producing a harmonic frequency $(\omega_o/n)\bullet m$ with the RF coil during the RF pulse field at a frequency, ω_o/n, due to nonlinearity of the diode element in the RF coil.

18. The method of claim 10 further comprising producing an RF field at half-resonance frequency.

19. The method of claim 10 further comprising using two inductive parallel loops.

20. The method of claim 10 further comprising using a second harmonic generating microcoil.

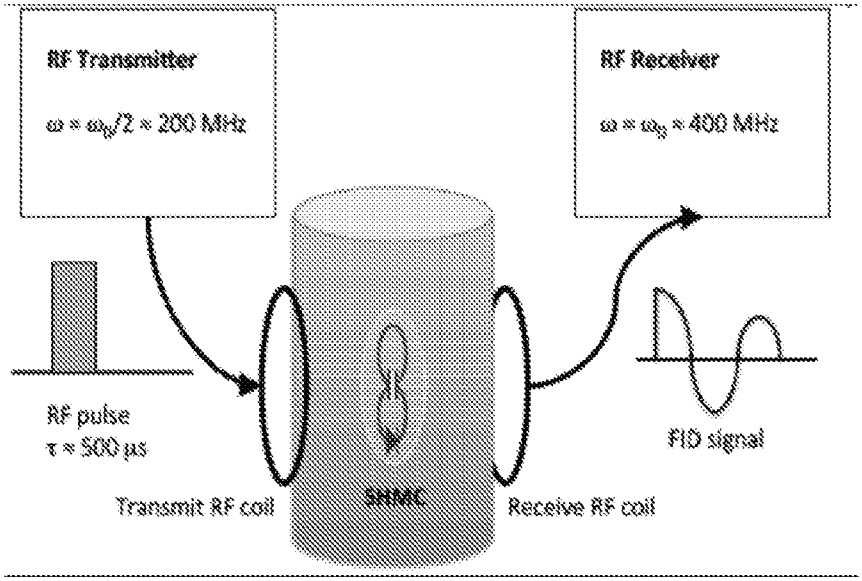

RF Transmitter
$\omega \approx \omega_0/2 \approx 200$ MHz
RF Receiver
$\omega \approx \omega_0 \approx 400$ MHz
RF pulse
$\tau \approx 500$ μs
FID signal
Transmit RF coil
SHMC
Receive RF coil

FIG. 1

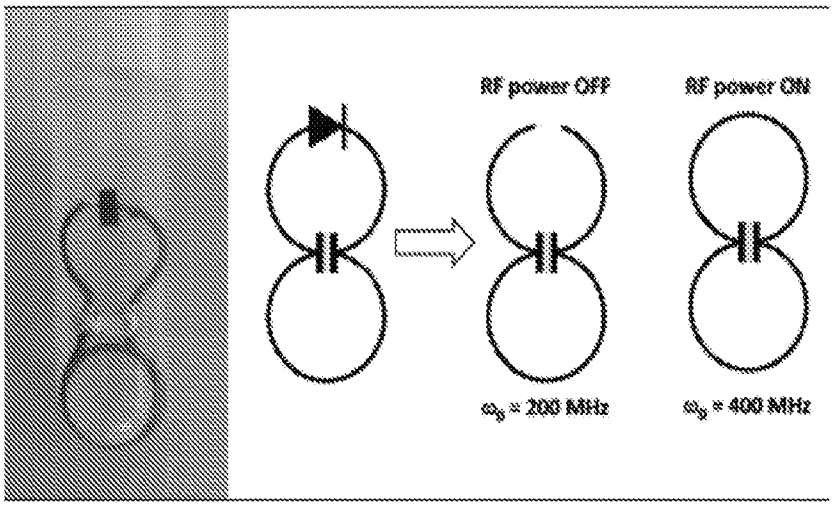


FIG. 2A FIG. 2B FIG. 2C FIG. 2D

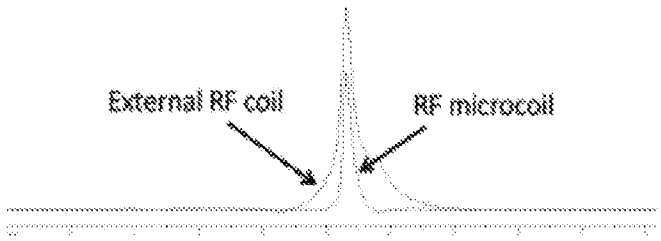


FIG. 3A

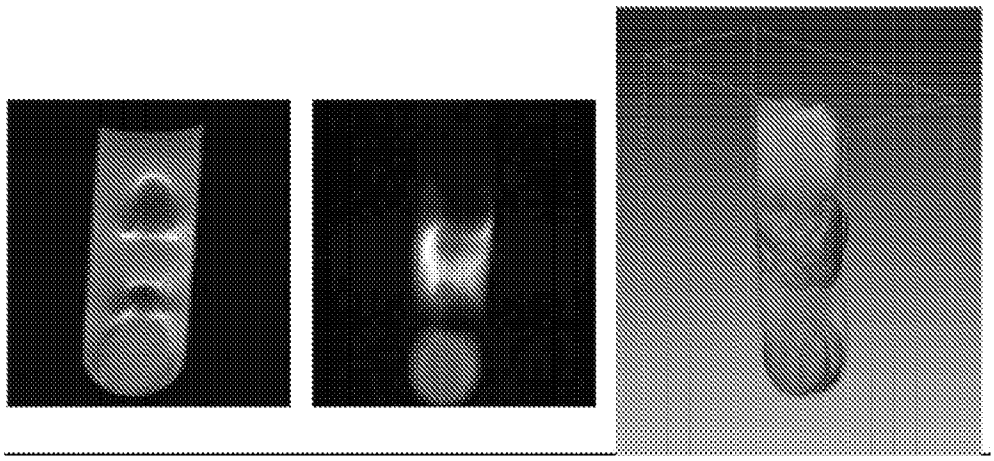


FIG. 3B

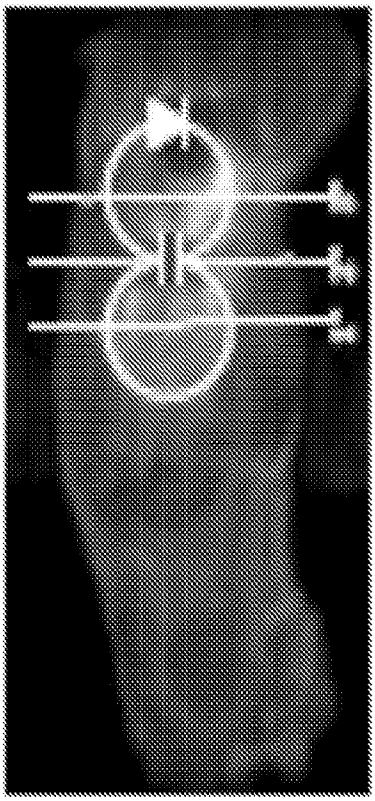


FIG. 4B

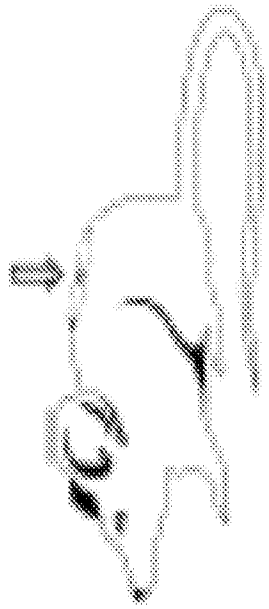
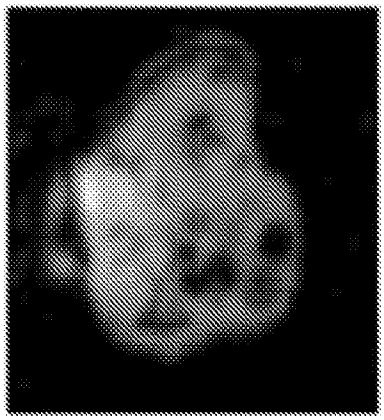
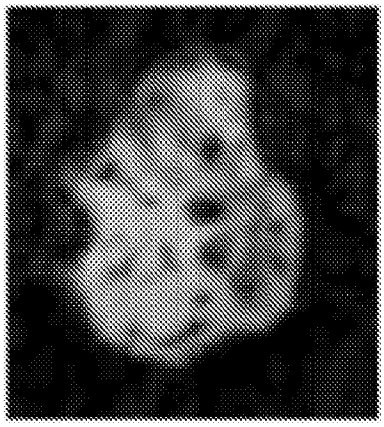


FIG. 4A





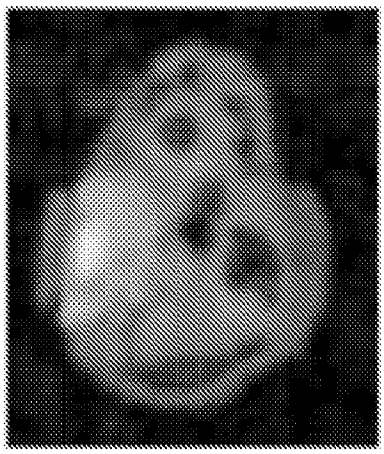


FIG. 4C

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2015/033652

A. CLASSIFICATION OF SUBJECT MATTER

A61B 5/055(2006.01)i, G01R 33/20(2006.01)i

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)
A61B 5/055; A61N 001/18; G01R 33/44; A61N 1/00; G01R 33/20

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
Korean utility models and applications for utility models
Japanese utility models and applications for utility models

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
eKOMPASS(KIPO internal) & keywords: implantable RF coil, magnetic resonance, RF transmitter, RF receiver, RF pulse field

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2012-0223705 A1 (THOMAS J. LOWERY et al.) 06 September 2012 See abstract, paragraphs [0004]-[0032] and figures 1A-4B.	1,6,7,9
Y		2,3
A		4,5,8
Y	US 2004-0068298 A1 (JORDI PARRAMON et al.) 08 April 2004 See abstract, claims 1-3 and figures 1-7.	2,3
A	US 2010-0256481 A1 (THOMAS H. MARECI et al.) 07 October 2010 See abstract, paragraphs [0031]-[0050] and figures 1-4.	1-9
A	US 5699801 A (ERGIN ATALAR et al.) 23 December 1997 See abstract, claims 1-29 and figures 1-5C.	1-9
A	US 2003-0171787 A1 (DAVID MONEY et al.) 11 September 2003 See abstract, paragraphs [0049]-[0059] and figures 1-5.	1-9

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

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

Date of the actual completion of the international search	Date of mailing of the international search report
29 October 2015 (29.10.2015)	**29 October 2015 (29.10.2015)**

Name and mailing address of the ISA/KR
International Application Division
Korean Intellectual Property Office
189 Cheongsa-ro, Seo-gu, Daejeon Metropolitan City, 35208,
Republic of Korea
Facsimile No. +82-42-472-7140

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Telephone No. +82-42-481-8131

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2015/033652

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 10-20
because they relate to subject matter not required to be searched by this Authority, namely:
Claims 10-20 pertain to a method for treatment of human body by surgery, and thus relate to a subject matter which this International Searching Authority is not required to search under PCT Article 17(2)(a)(i) and PCT Rule 39.1(iv).

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required addtional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of any additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/US2015/033652

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2012-0223705 A1	06/09/2012	AU 2008-343871 A1	09/07/2009
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