(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
3 December 2009 (03.12.2009)

PCT

(10) International Publication Number
WO 2009/145648 A1

(51) International Patent Classification:
G01R 33/563 (2006.01) *G01R 33/58* (2006.01)

(21) International Application Number:
PCT/PL2009/000051

(22) International Filing Date:
19 May 2009 (19.05.2009)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
P.385276 26 May 2008 (26.05.2008) PL

(71) Applicant *(for all designated States except US)*: **INSTYTUT FIZYKI JADROWEJ PAN im. HENRYKA NIEWODNICZANSKIEGO** [PL/PL]; ul. Radzikowskiego 152, 31-342 Kraków (PL).

(72) Inventor; and

(75) Inventor/Applicant *(for US only)*: **KRZYZAK, Artur** [PL/PL]; kalwaryjska 96/26, 30-505 Kraków (PL).

(74) Agent: **DRELICHOWSKI, Henryk**; P.O. Box 24, 31-816 Kraków 39 (PL).

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

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

Published:

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

[Continued on next page]

(54) Title: ANISOTROPIC DIFFUSION PHANTOM FOR CALIBRATION OF DIFFUSION TENSOR IMAGING PULSE SEQUENCES USED IN MRI

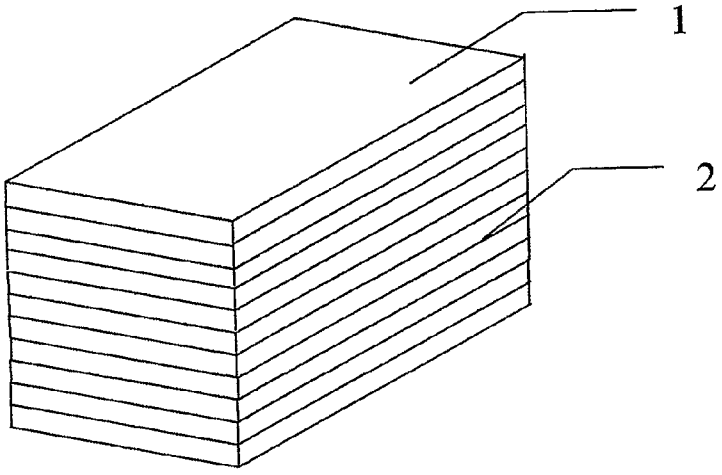

Fig.1.

(57) Abstract: The subject matter of the invention concerns the anisotropic diffusion phantom for the calibration of any diffusion MR-DTI imaging sequence and a method for the calibration of all the MRI scanners by using anisotropic diffusion models based on the "b" matrix, which is a quantity specific for every magnetic resonance (MR) imaging sequence and the MRI scanner used. It has application in the study of solids, amorphous materials, liquids and biological tissues. The anisotropic diffusion phantom for the calibration of any MR imaging sequence is any anisotropic diffusion model of any shape for the hydrogen H_2 contained in H_2O or LC, for example. The diffusion standard according to the invention is preferably a pipe with a bundle of capillaries filled with H_2O, hydrogel or any other substance that contains hydrogen nuclei or any volume, preferably cylindrical, filled with H_2O, hydrogel or any other substance that contains hydrogen nuclei or densely filled with non-magnetic cylindrical rods free of hydrogen nuclei. In another embodiment, the diffusion model is an array of thin glass plates (1) separated with layers of H_2O, hydrogel or any other substance that contains hydrogen nuclei (2). The model, being a pipe with a bundle of capillaries, has the capillaries selected so that the restriction of diffusion at a temperature in the direction perpendicular to the capillary axis is significant with respect to the range of diffusion times Δ in the diffusion MR imaging sequence. For the calibration of any MR imaging sequence using the anisotropic diffusion phantom of the invention, the anisotropic diffusion phantom is placed in the volume of the MRI scanner tested. Subsequently, the number of "b" matrices needed for the calculation of the diffusion tensor is determined based on the anisotropic diffusion model. This constitutes no less than six "b" matrices as defined spatially for each voxel and for the specific directions of the diffusion gradient vector. Therefore, in the simplest case, 36

[Continued on next page]

WO 2009/145648 A1

— *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))*

"b" matrices and one "b_o" matrix without diffusion gradients are determined. The anisotropic diffusion phantom is a diffusion model for which the diffusion tensor in the system of principal axes assumes known values. The diffusion model is rotated by various Euler angles, so that the determinant D_M of the matrix whose columns correspond to the components of the diffusion tensor D is different from zero after each rotation.

ANISOTROPIC DIFFUSION PHANTOM FOR CALIBRATION OF DIFFUSION TENSOR IMAGING PULSE SEQUENCES USED IN MRI

The subject matter of the invention concerns the anisotropic diffusion phantom for the calibration of any diffusion MR-DTI imaging sequence and a method for the calibration of any Magnetic Resonance Imaging (MRI) scanner by using anisotropic diffusion models based on the "b" matrix, which is a quantity specific for every magnetic resonance (MR) imaging sequence and MRI scanner that are used, employed in the examination of biological tissues, solids, amorphous materials and liquids.

In the prior art, the values of the "b" matrix that were needed to calculate the diffusion tensor were determined analytically and separately for every diffusion MR imaging sequence and MRI scanner; the results were approximate only due to the complex formulae used in the calculation. Alternatively, a single value of the "b" matrix that was assumed for the entire volume of the object in question was used for the calculation of the diffusion tensor.

A disadvantage of the diffusion tensor calculation methods known in the art is the large contribution of calculation errors as the approximate "b" matrix values are used and a lack of any spatial distribution of the "b" matrix is

assumed. Therefore, it is rather difficult to determine the water diffusion fluctuations in the object examined by using an MRI scanner properly, precisely and quantitatively, and the reproducibility of the results is non-existent. Distinct MR sequences occur for various MRI scanners; in consequence, the results are discrepant and hardly comparable. The results are fraught with errors as it is impossible to precisely determine the "b" matrix values.

The following acronyms will be used throughout the document:

MR - Magnetic Resonance

DTI - Diffusion Tensor Imaging

LC - Liquid Crystal

A calibration method of the invention for any MRI scanner eliminates these shortages and enables the precise and spatial determination of "b" matrix values for any MRI scanner and any imaging sequence, in particular DTI.

In the method of the invention, the "b" matrix is determined precisely based on the anisotropic diffusion model, for each voxel of the volume tested.

The anisotropic diffusion phantom for the calibration of any MR imaging sequence of the invention is any anisotropic diffusion model of any shape for the hydrogen contained in H_2O or in LC, for example. The diffusion model according to the invention is preferably a pipe with a bundle of capillaries filled with H_2O, hydrogel or any other substance that contains hydrogen. Other 3D shapes, preferably cylindrical, filled with densely non-magnetic cylindrical rods without hydrogen nuclei could be regarded as a reference diffusion model as well.. The rods are preferably made of glass, Teflon or any other material with similar properties. They are immersed in H_2O, hydrogel or

any other substance that contains hydrogen nuclei. In one embodiment, the diffusion model is an array of thin glass plates separated by the layers of H_2O, hydrogel or any other substance that contains hydrogen nuclei. The diffusion model can also be formed by anisotropic liquid crystals (LC) or others for other elements that may be used in imaging in future, such as for example ^{2}H, ^{3}He, ^{13}C, ^{14}N, ^{17}O, ^{19}F, ^{29}Si, ^{31}P, etc. The model, being a pipe with a bundle of capillaries, has the capillaries selected so that the restriction of diffusion at a temperature in the direction perpendicular to the capillary axis is significant with respect to the range of diffusion times Δ in the diffusion MR imaging sequence. For the diffusion model filled with water at ambient temperature, it is within a range of 0.1 μm to 100 μm. For hydrogel, the values are lower. The free diffusion of water molecules across the capillaries or across the cylindrical rods or perpendicularly to the plane of the thin glass plates is inhibited by the opposite capillary or rod wall or by the plane of the opposite thin glass plate and restricts the diffusion process. By adjusting the capillary diameters, cylindrical rod diameters or the thickness of the layers of H_2O, hydrogel or any other substance that contains hydrogen nuclei between thin glass plates, the diffusion limit is determined for specified diffusion times Δ and temperature T based on the fact that free diffusion is given by the Einstein-Smoluchowski equation:

$$\langle (\vec{r} - \vec{r}_o)(\vec{r} - \vec{r}_o) \rangle = 6Dt \quad [1]$$

where:

$\vec{r}$ - position vector of the diffusing molecule at time t,
$\vec{r}_o$ - initial position vector.

The equation determines the relation between the average square of the path and the diffusion coefficient D.

The anisotropic diffusion model in the system of principal axes has no less than two distinct diffusion tensor components, wherein for the phantom made of a bundle of capillaries it is a symmetrical diffusion tensor D:

$$\begin{pmatrix} D_{xx} & D_{xy} & D_{xz} \\ D_{yx} & D_{yy} & D_{yz} \\ D_{zx} & D_{zy} & D_{zz} \end{pmatrix}$$

which obtains the following form after diagonalisation in the system of the principal axes:

$$\begin{pmatrix} D_1 & 0 & 0 \\ 0 & D_2 & 0 \\ 0 & 0 & D_3 \end{pmatrix}$$

where:

D_{ij} - components of the symmetrical diffusion tensor in the laboratory system,

D_1, D_2 - diffusion coefficients determined in the transverse direction of the capillary,

D_3 - diffusion coefficient in the longitudinal direction of the capillary.

In the case in question: $D_1 = D_2$ and $D_2 \neq D_3$.

In the present invention, the anisotropic diffusion model is determined as follows:

- typical onedimensional experiments are carried out for the measurement of the diffusion coefficients for the anisotropy directions in order to determine e.g. D_1, D_2 and D_3 depending on the diffusion time and temperature. Thus, an anisotropic diffusion model is obtained, being a function of temperature T and diffusion time Δ.

Any MRI scanner can be calibrated by using the method of the invention in order to measure the "b" matrix precisely and spatially. It leads consequently into a precise measurement of the diffusion tensor assuming that in biological tissues it is primarily the water diffusion tensor.

The diffusion tensor is measured according to the known formula:

$$\ln\left(\frac{A(b)}{A(0)}\right) = -\sum_{i=1}^{3}\sum_{j=1}^{3} b_{ij} D_{ij} \qquad [2]$$

where:

A(b) – echo signal (MR image intensity), measured for each voxel,

A(0) – MR image intensity for b=0,

b_{ij} – element of the symmetrical "b" matrix,

D_{ij} – – element of the symmetrical diffusion tensor D.

It follows from formula [2] that for the DTI experiments, in order to calculate the water diffusion tensor, wherein the symmetrical tensor is a 3x3 matrix, no less than seven MR experiments need to be carried out, for which the MR sequences shall contain six distinct non-

collinear directions of diffusion gradients and one (the seventh) direction without diffusion gradients applied. Hence, for the simplest DTI experiment, no less than six symmetrical "b" matrices, each of which contains six distinct components, are determined for each diffusion gradient vector,.

For the calibration of any MR imaging sequence by using the anisotropic diffusion phantom of the invention, the anisotropic diffusion phantom is placed inside the volume of the MRI scanner tested. Subsequently, the number of "b" matrices needed for the calculation of the diffusion tensor is determined based on the anisotropic diffusion model. This constitutes no less than six "b" matrices to be defined spatially for each voxel and for the specific directions of the diffusion gradient vector. Therefore, in the simplest case, 36 "b" matrices and one "b_0" matrix - without diffusion gradients - are determined.

In order to determine the value of the "b" matrix for the direction of the diffusion gradient vector, a system of no less than six equations is solved for the distinct diffusion tensor D values. For a diffusion gradient vector direction, a diffusion tensor value is used based on the specified diffusion model for the diffusion time Δ and the temperature of the respective experiment. Various diffusion model tensor values are preferably obtained by rotating the anisotropic diffusion phantom inside the MRI scanner volume in question. The anisotropic diffusion phantom is a diffusion model for which the diffusion tensor in the system of the principal axes assumes known values. The diffusion model is rotated by various Euler angles, so that the determinant D_M of the matrix, whose columns correspond to the components of the diffusion tensor D is different from zero after each rotation.

$$\det(D_M) \neq 0$$

The following matrix is derived in the measurements:

$$D_M = \begin{pmatrix} D_{11} & D_{12} & D_{13} & D_{14} & D_{15} & D_{16} \\ D_{21} & D_{22} & D_{23} & D_{24} & D_{25} & D_{26} \\ D_{31} & D_{32} & D_{33} & D_{34} & D_{35} & D_{36} \\ D_{41} & D_{42} & D_{43} & D_{44} & D_{45} & D_{46} \\ D_{51} & D_{52} & D_{53} & D_{54} & D_{55} & D_{56} \\ D_{61} & D_{62} & D_{63} & D_{64} & D_{65} & D_{66} \end{pmatrix},$$

where for D_{ij}:

i - successive components of the diffusion tensor: xx, yy, zz, xy, xz, yz,

j = in the range of 1 to 6 - successive sets of Euler angles.

For the calculation of the "b" matrix values for a direction of the diffusion gradient vector, the following system of equations is solved, derived from equation [2]:

$$\mathbf{L = b\ D_M},\quad [3]$$

where:

b - six calculated components of the "b" matrix converted into the vector form ,

D_M - matrix whose columns are formed by the components of the model diffusion tensor after successive rotations by various Euler angles,

L - successive $\ln(\frac{A(b)}{A(0)})$ values from measurements (based on MR images) converted into the form of a transposed vector.

The system of equations [3] is solved for the remaining (no less than six non-collinear) directions of diffusion

gradients. Thus, 36 "b" matrices and a "b_0" matrix are derived. Therefore, the "b" matrix values are obtained for the specific directions of diffusion gradients and for each voxel of the volume in question.

Based on the calibration method of the invention, a diffusion model for the volume examined is formed and selected for an RF coil depending on its shape and parameters. The calibration is repeated every time before the change of the imaging sequence parameters, in particular when changing the diffusion gradients.

The advantage of the calibration method for any MRI scanner using anisotropic diffusion models based on the anisotropic diffusion phantom for the calibration of any diffusion MR-DTI imaging sequence is the precise and spatial determination of the "b" matrix value. As a result it is possible, contrary to the prior art, to precisely measure the diffusion tensor, first of all in biological systems, but also in other systems. Furthermore, the calibration method provides a real possibility to compare the diffusion tensor values for the objects tested, which are derived by using various MRI scanners and distinct MR imaging sequences.

Example:

The following operations were performed for the calibration of an MSED (Multislice Spin Echo Diffusion) sequence in an MRI scanner with a superconducting magnet (field intensity: 4.7 T) by using an anisotropic diffusion model at T = 21°C and diffusion time Δ = 50 ms:

1. An anisotropic diffusion phantom in the form of an array of thin glass plates separated with H_2O layers (thickness: 10 μm) was placed in an MRI scanner with

a superconducting magnet (field intensity: 4.7 T) in the influence area of a 3 cm birdcage RF coil. Tomographic measurements were carried out by using an MSED sequence.

2. MR tomographic measurements for the determination of the spatial "b" matrix for one direction of the diffusion gradient vector were carried out for six distinct positions defined by the rotation of the anisotropic diffusion phantom by Euler angles. The entire measurement volume tested in the MRI scanner in the interaction area of the RF coil was scanned to obtain the spatial distribution of the "b" matrix. The measurements were repeated for further diffusion gradient vector directions. A total of 36 MR measurements were carried out in six distinct diffusion gradient vector positions and an additional scan for the diffusion gradient vector = 0.
3. Subsequently, the operations in steps 1 and 2 were repeated for the other sequence parameters; as a result, a digital record of the spatial "b" matrix values was derived that corresponded to various imaging sequence parameters. The "b" matrix values, thus obtained, enabled the precise calculation of the diffusion tensor by using a DTI sequence in the parameter range for which the "b" matrix value was determined.

The anisotropic diffusion phantom and calibration method for any MR imaging sequence according to the embodiment is shown in the figure, wherein Fig. 1 shows the outline of the anisotropic diffusion phantom in the form of an array of thin glass plates separated with H_2O layers and Fig. 2 shows the phantom (diffusion model) rotation method by successive Euler angles.

The anisotropic diffusion phantom is made from thin glass plates 1, each of which is separated with a 10 μm H_2O

layer 2. The system of principal axes (E) shown in Fig. 2 is the laboratory reference system (L) related to the diffusion model after rotation and their mutual orientation as defined by the Euler angles

$$\Omega_L = (\alpha_L, \beta_L, \gamma_L).$$

Due to the symmetry, the diffusion tensor measured in the laboratory system (L) has 6 components different from zero. In the system of principal axes (E), the diffusion tensor is defined by three principal components and three Euler angles Ω_L. For a known tensor in the system of principal axes (E) and known Euler angles, the tensor values in the laboratory system (L) are determined by a rotation transformation $R(\alpha_L, \beta_L, \gamma_L)$ according to the formula:

$$D_L = R^{-1}(\Omega_L) D_E R(\Omega_L)$$

where:

$R(\Omega_L)$ – Wigner rotation matrix,

$\Omega_L = (\alpha_L, \beta_L, \gamma_L)$ – Euler angles that define the orientations of the system of principal axes (E) with respect to the laboratory system (L),

D_L, D_E – diffusion tensors in L and E systems, respectively.

The diffusion model is rotated by various Euler angles, so that the determinant D_M of the matrix, whose columns correspond to the components of the diffusion tensor D, is different from zero after each rotation.

$$\det(D_M) \neq 0$$

Claims

1. An anisotropic diffusion phantom for the calibration of any MR imaging sequence, characterised in that it is formed by any volume densely filled with non-magnetic capillary elements (1) free of hydrogen nuclei, filled with H_2O, hydrogel or another substance that contains hydrogen nuclei or it is formed by an array of thin glass plates (1) separated with layers of H_2O, hydrogel or another substance that contains hydrogen nuclei (2), wherein the diffusion phantom can also be formed by anisotropic liquid crystals (LC) or others for other elements, such as for example ^{2}H, ^{3}He, ^{13}C, ^{14}N, ^{17}O, ^{19}F, ^{29}Si, ^{31}P etc.

2. An anisotropic phantom according to Claim 1, characterised in that it is formed by a cylindrical volume densely filled with non-magnetic cylindrical rods free of hydrogen nuclei, separated with layers of H_2O, hydrogel or another substance that contains hydrogen nuclei.

3. An anisotropic phantom according to Claims 1 and 2, characterised in that by adjusting the capillary diameters, the cylindrical rod diameters or the thickness of the layers of H_2O, hydrogel or any other substance that contains hydrogen nuclei between thin glass plates, the diffusion limit is determined for specified diffusion times Δ and temperature.

4. An anisotropic phantom according to Claim 1, characterised in that the densely non-magnetic capillaries or other elements of the diffusion phantom are made of glass, Teflon or any other material with similar properties.

5. An anisotropic phantom according to Claim 1, characterised in that it is a pipe with a bundle of suitable capillaries filled with H_2O, hydrogel or any other substance that contains hydrogen nuclei so that the restriction of the diffusion at a given temperature in the direction perpendicular to the capillary axis is significant with respect to the range of diffusion times Δ in the diffusion MR imaging sequence.

6. A method for the calibration of any MRI scanner that consists in the spatial determination of the "b" matrix values, characterised in that for the calibration of any MRI scanner sequence by using the anisotropic diffusion phantom, the anisotropic diffusion phantom is placed in the interaction area of an RF coil in the volume of the MRI scanner tested, wherein subsequently, for the calculation of the diffusion tensor, the required number of "b" matrices are calculated based on the anisotropic diffusion model, which makes no less than six "b" matrices determined for each voxel and for each diffusion gradient vector direction required, and the "b" matrix values for the direction of the diffusion gradient vector are determined by solving a system of no less than six equations for the distinct diffusion tensor D values, wherein for the direction of the diffusion gradient vector various diffusion tensor values are obtained, preferably by rotating the

anisotropic diffusion phantom in the volume of the MRI scanner tested, being the diffusion model for which the diffusion tensor in the system of principal axes has known values, wherein the diffusion model is rotated by various Euler angles, so that the determinant D_M of the matrix whose columns correspond to the components of the diffusion tensor D after successive rotations of the diffusion model by specific Euler angles is defined by the matrix

$$D_M = \begin{pmatrix} D_{11} & D_{12} & D_{13} & D_{14} & D_{15} & D_{16} \\ D_{21} & D_{22} & D_{23} & D_{24} & D_{25} & D_{26} \\ D_{31} & D_{32} & D_{33} & D_{34} & D_{35} & D_{36} \\ D_{41} & D_{42} & D_{43} & D_{44} & D_{45} & D_{46} \\ D_{51} & D_{52} & D_{53} & D_{54} & D_{55} & D_{56} \\ D_{61} & D_{62} & D_{63} & D_{64} & D_{65} & D_{66} \end{pmatrix},$$

whose determinant $\det(D_M) \neq 0$ is different from zero; subsequently, for the calculation of "b" matrix values for the direction of the diffusion gradient vector, the following system of equations is solved:

$$L = b\ D_M,$$

and this operation is repeated for the required number of diffusion gradient vector directions, i.e. for no less than six non-collinear directions of diffusion gradients and no less than one for the direction without a diffusion gradient.

7. A method according to Claim 6, characterised in that for the anisotropic diffusion phantom, the diffusion tensor values in the system of principal axes D_1, D_2, D_3 as a function of temperature T and diffusion time Δ are determined in the typical unidimensional measurements of the diffusion coefficients for anisotropy directions.

8. A method according to Claim 6, characterised in that for the calibrated MRI scanner volume a diffusion model is formed and selected for an RF coil depending on its shape and parameters.

9. A method according to Claim 6, characterised in that the calibration of any MRI scanner is repeated every time before a change of imaging sequence parameters, in particular when changing diffusion gradients.

1/1

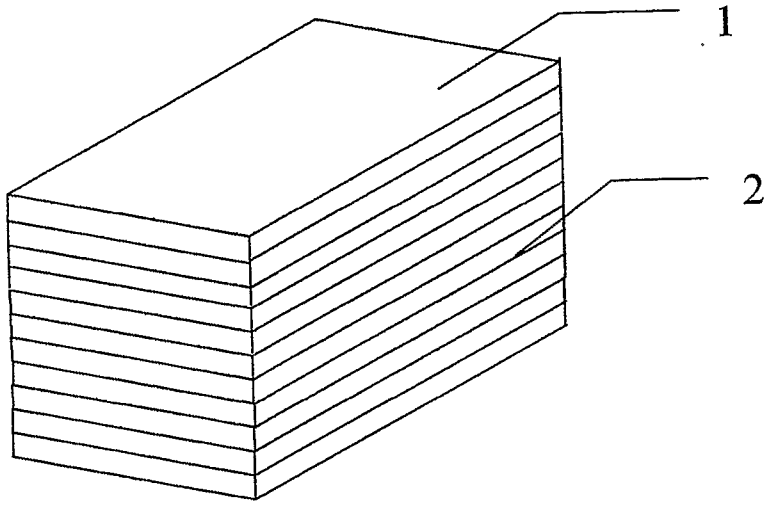

Fig.1.

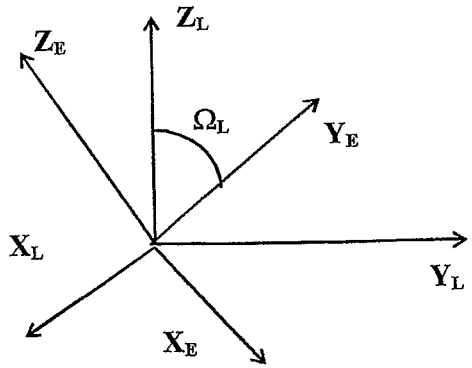

Fig.2.

INTERNATIONAL SEARCH REPORT

International application No
PCT/PL2009/000051

A. CLASSIFICATION OF SUBJECT MATTER
INV. G01R33/563 G01R33/58

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

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 practical, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	RAGUIN L G ET AL: "Quantitative Analysis of q-Space MRI Data" IFMBE PROCEEDINGS, INTERNATIONAL FEDERATION FOR MEDICAL AND BIOLOGICAL ENGINEERING, vol. 11, no. 1, 20 November 2005 (2005-11-20), page 6pp, XP007909573 ISSN: 1727-1983 page 1, column 2 - page 2, column 2 page 4; figures 2(A),3(B) ----- -/--	1,3,4

[X] 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 document 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
17 September 2009	24/09/2009

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Raguin, Guy

Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	TANNER J E ET AL: "Restricted self-diffusion of protons in colloidal systems by the pulsed-gradient, spin-echo method" JOURNAL OF CHEMICAL PHYSICS, AMERICAN INSTITUTE OF PHYSICS, NEW YORK, NY, US, vol. 49, no. 4, 15 August 1968 (1968-08-15), pages 1768-1777, XP009121879 ISSN: 0021-9606 page 1773 - page 1774	1,3,4
X	YANASAK N ET AL: "Use of capillaries in the construction of an MRI phantom for the assessment of diffusion tensor imaging: demonstration of performance" MAGNETIC RESONANCE IMAGING, ELSEVIER SCIENCE, TARRYTOWN, NY, US, vol. 24, no. 10, 1 December 2006 (2006-12-01), pages 1349-1361, XP025145525 ISSN: 0730-725X [retrieved on 2006-12-01] page 1350, column 2 - page 1351, column 2; figures 1,2	1,3,4
X	TOURNIER J D ET AL: "Resolving crossing fibres using constrained spherical deconvolution: Validation using diffusion-weighted imaging phantom data" NEUROIMAGE, ACADEMIC PRESS, ORLANDO, FL, US, vol. 42, no. 2, 9 May 2008 (2008-05-09), pages 617-625, XP023903351 ISSN: 1053-8119 [retrieved on 2008-05-09] page 618, column 2 - page 619, column 3	1,3,4
X	FIEREMANS ET AL: "Simulation and experimental verification of the diffusion in an anisotropic fiber phantom" JOURNAL OF MAGNETIC RESONANCE, ACADEMIC PRESS, ORLANDO, FL, US, vol. 190, no. 2, 1 November 2007 (2007-11-01), pages 189-199, XP022427559 ISSN: 1090-7807 page 191 - page 193; figures 1,2	2-5

-/--

INTERNATIONAL SEARCH REPORT

International application No
PCT/PL2009/000051

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CALLAGHAN ET AL: "Pulsed-Gradient Spin-Echo NMR for Planar, Cylindrical, and Spherical Pores under Conditions of Wall Relaxation" JOURNAL OF MAGNETIC RESONANCE. SERIES A, ACADEMIC PRESS, ORLANDO, FL, US, vol. 113, no. 1, 1 March 1995 (1995-03-01), pages 53-59, XP005118912 ISSN: 1064-1858 the whole document	1-5

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.2

Claims Nos.: 6-9

The non-compliance with the substantive provisions of Art. 5 and 6 PCT (see below and section "Re Item VIII" of the WO-ISA) is to such an extent that no meaningful search of claims 6-9 could be carried out at all (Art. 17(2) PCT).

Claim 6 does not comply with the requirements of Art. 5 and 6 PCT for the following reasons.

1. The passage "the calibration of any MRI scanner sequence by using the anisotropic diffusion phantom" lacks support by the description in that the description (page 1, first paragraph) merely supports that said "phantom" is "for the calibration of any diffusion MR-DTI imaging sequence" and no other possibility was disclosed. c

Additionally, claim 6 defines "a method for the calibration of any MRI scanner" and in this very broad context, the terms "the ''b'' matrix values" and "the diffusion tensor" lack an antecedent definition.

2. Moreover, the expression

"a method for the calibration of any MRI scanner that consists in the spatial determination of the ''b'' matrix values"

lacks clarity in that it is completely obscure in what way "the spatial determination of the ''b'' matrix values" results in the "calibration of any MRI scanner". This point should be clarified.

3. The terms "the anisotropic diffusion phantom", "the interaction area", "the volume of the MRI scanner", "the calculation of the diffusion tensor", "the required number of ''b'' matrices", "the anisotropic diffusion model", "each voxel" (since no imaging step has been defined), "each diffusion gradient vector direction required" (since no pulse sequence has been defined), "the distinct diffusion tensor values" each lack a proper antecedent definition.

4. Moreover, it is noted that it is completely unclear to what kind of "model" the term "the anisotropic diffusion model" refers (a phantom or a mathematical model linking experimental parameters to diffusion parameters). This should be clarified.

5. The term "specific Euler angles" lacks clarity in that it is completely obscure to which Euler angles reference is made.

6. Claim 6 lacks clarity in that it is unclear what the variable "L" represents (said variable lacks an antecedent definition).

7. In the context of the preceding objection, it is completely unclear what method step is defined by the passage "this operation is repeated...". and for what purpose said "operation is repeated". Therefore, claim 6 should be clarified.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

8. The expression "and no less than one for the direction without a diffusion gradient" lacks clarity in that it is completely obscure to which specific direction the expression "direction without a diffusion gradient" refers.

9. The passage

"the diffusion model for which the diffusion tensor in the system of principal axes has known values"

appears to refer to a method step for which an essential feature is missing (Rule 6.3(a) PCT and PCT/GL/ISPE 5.29, 5.33) in order to achieve the desired technical effect recited above. More specifically, the description (page 5, lines 1-9) suggests that one-dimensional experiments are required to determine said "diffusion tensor in the system of principal axes". Therefore, claim 6 should be included the features of claim 7.

10. In the context of the preceding objection, the application as a whole lacks sufficient disclosure (Art. 5 PCT) with regards to the method of claim 6 for the following reasons. Said method hinges on having an anisotropic diffusion phantom (presumably according to any one of claims 1-5, although none has been defined in claim 6), for which the diffusion tensor must first be determined according to the passage on page 5, lines 1-9 of the description.

(i) However, in order to do so, said one-dimensional experiments are insufficiently disclosed and would presumably require the knowledge of a reduced form of a ''b'' matrix. Since the end goal of the method of claim 6 is to obtain said ''b'' matrix, one ends up in a circular argument:

(1) determine the diffusion parameters of the diffusion method using uncalibrated ''b'' values, thereby resulting in inaccurate diffusion parameters; then

(2) determine the ''b'' matrix for different diffusion gradient vector directions using said inaccurate diffusion parameters.

Clearly, this method is flawed, does not appear to be able to work, and cannot deliver the result to be achieved, i.e. "the calibration of any diffusion MR-DTI imaging sequence" (page 8, 2nd full paragraph), nor the disclosed advantage of providing "the precise and spatial determination of the ''b'' matrix value" (page 8, 2nd full paragraph).

(ii) Moreover, the one and only embodiment of the description (page 8, last paragraph - page 10) fails to disclose the performance of said one-dimensional experiments and how the diffusion parameters of the diffusion phantom of figure 1 are determined, such that the skilled person is not provided with sufficient information to carry out the method of claim 6.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has

not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.2), should the problems which led to the Article 17(2)PCT declaration be overcome.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/PL2009/000051

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.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 6-9
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:
see FURTHER INFORMATION sheet PCT/ISA/210

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 additional search fees were timely paid by the applicant, this international search report covers allsearchable claims.

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

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search reportcovers 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.