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(54) **METHOD FOR CALIBRATING DIFFUSION TENSOR IMAGING PULSE SEQUENCES USED IN MRI USING AN ANISOTROPIC DIFFUSION PHANTOM**

VERFAHREN ZUR KALIBRIERUNG VON IMPULSSEQUENZEN IN DER DIFFUSIONSTENSOR-MRT MIT VERWENDUNG EINES ANISOTROPEN DIFFUSIONSPHANTOM

PROCÉDÉ D'ÉTALONNAGE DE SÉQUENCES D'IRM D'IMAGERIE DU TENSEUR DE DIFFUSION À L'AIDE D'UN FANTÔME DE DIFFUSION ANISOTROPIQUE

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(73) Proprietor: **Akademia Gorniczo-Hutnicza im. Stanislawa Staszica w Krakowie**
30-059 Krakow (PL)

(72) Inventor: **KRZYZAK, Artur**
30-505 Kraków (PL)

(74) Representative: **Kancelaria Eupatent.pl Sp. z.o.o**
Ul. Kilinskiego 185
90-348 Lodz (PL)

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Description

[0001] The description below 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.

[0002] 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. An article "Restricted self-diffusion of protons in colloidal systems by the pulsed-gradient, spin-echo method" by Tanner J E et al (JOURNAL OF CHEMICAL PHYSICS, vol. 49, no. 4, pp. 1768-1777, XP009121879, ISSN: 0021-9606) discloses a pulsed-gradient, spin-echo technique which has been used to study self-diffusion of protons in several colloidal systems in order to examine the usefulness of that technique in determining the extent to which the free movement of molecules in these systems is restricted by the colloidal structures present. One system studied was constructed of thin sheets of mica separated by narrow strips of aluminum foil and bound together with dental floss.

[0003] An article "Nuclear-Magnetic-Resonance Study of Self-Diffusion in a Bounded Medium" by R C Wayne et al (Phys. Rev., vol. 151,4 November 1966, pp. 264-272, XP055115693) discloses a diffusion phantom made from a gas separated into thin layers by Teflon separators, which is suitable for the calibration of a MR-DTI imaging sequence. The following acronyms will be used throughout the document:

MR - Magnetic Resonance
DTI - Diffusion Tensor Imaging
LC - Liquid Crystal

[0004] 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.

[0005] 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.

[0006] The anisotropic diffusion phantom for the calibration of any MR imaging sequence description below is any anisotropic diffusion model of any shape for the hydrogen contained in H_2O or in LC, for example. The diffusion model 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 example, 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 ^2H, ^3He, ^{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.

[0007] 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.

[0008] In the case in question: $D_1 = D_2$ and $D_2 \neq D_3$.

[0009] In the present example, the anisotropic diffusion model is determined as follows:

- typical one-dimensional 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.

[0010] 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.

[0011] 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.

[0012] 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,.

[0013] For the calibration of any MR imaging sequence by using the anisotropic diffusion phantom, 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.

[0014] 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]:

$$L = b\ D_M, \quad [3]$$

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.

[0015] 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.

[0016] 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.

[0017] 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:

[0018] 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.

[0019] The anisotropic diffusion phantom described above and the 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.

[0020] 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:

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

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.

[0021] 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. A method for calibration of an MR-DTI sequence for an MRI scanner, comprising the steps of:

- providing an anisotropic diffusion model phantom having a diffusion tensor with known predetermined values in an interaction area of an RF coil in a volume of the MRI scanner to be examined,
- wherein the anisotropic diffusion model phantom comprises a substance (2) that contains hydrogen nuclei and is arranged such that diffusion of the substance (2) that contains hydrogen nuclei is significantly restricted along an alignment axis for a specified temperature with respect to a specified range of diffusion times,
- rotating the anisotropic diffusion model phantom by at least six sets of Euler angles (α_L,β_L.γ_L) resulting in at least six distinct rotated positions, so that after each rotation the determinant det(D_M) for a matrix having columns corresponding to the components of the diffusion tensor D for the distinct set of Euler angles, is different from zero, wherein the matrix is defined as:

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

wherein for D_{ij}:

- *i* determines successive components of the diffusion tensor: xx, yy, zz, xy, xz, yz;
- *j* is in the range from 1 to 6 and determines successive sets of Euler angles;

- and measuring, for each rotated position of the anisotropic diffusion phantom, for each voxel of the volume of the MRI scanner to be examined, an MR image intensity for no diffusion gradient applied and an MR image intensity for each of at least six distinct non-collinear directions of diffusion gradient,
- on the basis of the measured MR image intensities and the known values of the diffusion tensor, determining a symmetrical "b" matrix for each of at least six distinct non-collinear directions of diffusion gradient for each voxel of the volume of the MRI scanner using the equation

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

wherein:

- A(b) represents the MR image intensity for a given direction of diffusion gradient,
- A(0) represents the MR image intensity for no diffusion gradient applied,
- b represents the symmetrical "b" matrix,
- D represents the diffusion tensor,
- i, j represent directions of diffusion gradients,

- for each voxel of a subject to be studied, providing the set of at least six symmetrical "b" matrices to be used for determining diffusion tensor in subsequent MR-DTI experiments using the calibrated MR-DTI sequence for the MRI scanner.

Patentansprüche

1. Verfahren zur Kalibrierung einer MR-DTI-Sequenz für einen MRT-Scanner, umfassend die folgenden Schritte:

- Bereitstellen eines anisotropen Diffusionsmodellphantoms, das einen Diffusionstensor mit bekannten vorbestimmten Werten in einem zu untersuchenden Interaktionsbereich einer HF-Spule in einem Volumen des MRT-Scanners aufweist,
- wobei das anisotrope Diffusionsmodellphantom eine Substanz (2) umfasst, die Wasserstoffkeme enthält und so angeordnet ist, dass eine Diffusion der Substanz (2), die Wasserstoffkeme enthält, entlang einer Ausrichtungsachse für eine spezifizierte Temperatur in Bezug auf einen spezifizierten Bereich von Diffusionszeiten deutlich eingeschränkt ist,
- Drehen des anisotropen Diffusionsmodellphantoms um mindestens sechs Sätze von Eulerwinkeln (α_L,β_L,γ_L), woraus sich mindestens sechs unterschiedliche gedrehte Positionen ergeben, sodass nach jeder Drehung die Determinante det(D_M) für eine Matrix, die Spalten aufweist, die den Komponenten des Diffusionstensors D für den verschiedenartigen Satz von Eulerwinkeln entspricht, von null verschieden ist, wobei die Matrix wie folgt definiert ist:

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

wobei für D_{ij}:

- *i* aufeinanderfolgende Komponenten des Diffusionstensors bestimmt: xx, yy, zz, xy, xz, yz;
- *j* in dem Bereich von 1 bis 6 liegt und aufeinanderfolgende Sätze von Eulerwinkeln bestimmt;
- und Messen, für jede gedrehte Position des anisotropen Diffusionsphantoms, für jedes zu untersuchende Voxel des Volumens des MRT-Scanners, einer MR-Bildintensität, wenn kein Diffusionsgradient angewendet wird und einer MR-Bildintensität für jede von mindestens sechs unterschiedlichen nicht kollinearen Richtungen eines Diffusionsgradienten,

- auf Grundlage der gemessenen MR-Bildintensitäten und der bekannten Werte des Diffusionstensors, Bestimmen einer symmetrischen "b"-Matrix für jede von mindestens sechs unterschiedlichen nicht kollinearen Richtungen eines Diffusionsgradienten für jedes Voxel des Volumens des MRT-Scanners unter Verwendung der folgenden Gleichung:

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

wobei:

- A(b) die MR-Bildintensität für eine gegebene Richtung eines Diffusionsgradienten darstellt,
- A(0) die MR-Bildintensität für einen nicht angewendeten Diffusionsgradienten darstellt,
- b die symmetrische "b"-Matrix darstellt,
- D den Diffusionstensor darstellt,
- i, j Richtungen von Diffusionsgradienten darstellen,

- für jedes Voxel eines zu analysierenden Subjekts, Bereitstellen des Satzes von mindestens sechs symmetrischen "b"-Matrizen, die zur Bestimmung des Diffusionstensors in darauffolgenden MR-DTI-Experimenten unter Verwendung der kalibrierten MR-DTI-Sequenz für den MRT-Scanner verwendet werden sollen.

Revendications

1. Procédé d'étalonnage d'une séquence MR-DTI pour un scanner IRM, comprenant les étapes de :

- production d'un fantôme modèle de diffusion anisotropique présentant un tenseur de diffusion avec des valeurs prédéfinies connues dans une zone d'interaction d'une bobine RF dans un volume du scanner IRM à analyser ;
- ledit fantôme modèle de diffusion anisotropique comprenant une substance (2) qui contient des noyaux d'hydrogène et étant disposé de sorte que la diffusion de la substance (2) qui contient des noyaux d'hydrogène soit considérablement limitée le long d'un axe d'alignement pour une température spécifiée par rapport à une plage spécifiée de temps de diffusion,
- mise en rotation du fantôme modèle de diffusion anisotropique suivant au moins six séries d'angles d'Euler (α_L, β_L, γ_L) conduisant à au moins six positions tournées distinctes, de sorte qu'après chaque rotation le déterminant det(D_M) pour une matrice comportant des colonnes correspondant aux composantes du tenseur de diffusion D pour la série distincte d'angles d'Euler, soit différent de zéro, ladite matrice étant définie comme étant :

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

dans laquelle pour D_{ij} :

- *i* détermine des composantes successives du tenseur de diffusion : xx, yy, zz, xy, xz, yz ;
- *j* se trouve dans la plage allant de 1 à 6 et détermine des séries successives d'angles d'Euler ;
- et mesure pour chaque position tournée du fantôme de diffusion anisotropique, pour chaque voxel du volume du scanner IRM à analyser, d'une intensité d'image RM pour aucun gradient de diffusion appliqué et une intensité d'image RM pour chacune d'au moins six directions non colinéaires distinctes de gradient de diffusion,

- sur la base des intensités d'images RM mesurées et des valeurs connues du tenseur de diffusion, détermination d'une matrice « b » symétrique pour chacune des au moins six directions non colinéaires distinctes de gradient de diffusion pour chaque voxel du volume du scanner IRM à l'aide de l'équation

$$\ln(\frac{A(b)}{A(0)}) = -\sum_{i=1}^{3} \sum_{j=1}^{3} b_{ij} D_{ij} ,$$

dans laquelle :

- A(b) représente l'intensité d'image RM pour une direction donnée de gradient de diffusion,
- A(0) représente l'intensité d'image RM pour aucun gradient de diffusion appliqué,
- b représente la matrice « b » symétrique,
- D représente le tenseur de diffusion,
- i, j représentent des directions de gradients de diffusion,

- pour chaque voxel d'un sujet à étudier, production de la série d'au moins six matrices « b » symétriques à utiliser pour déterminer un tenseur de diffusion dans des expériences MR-DTI ultérieures à l'aide de la séquence MR-DTI étalonnée pour le scanner IRM.

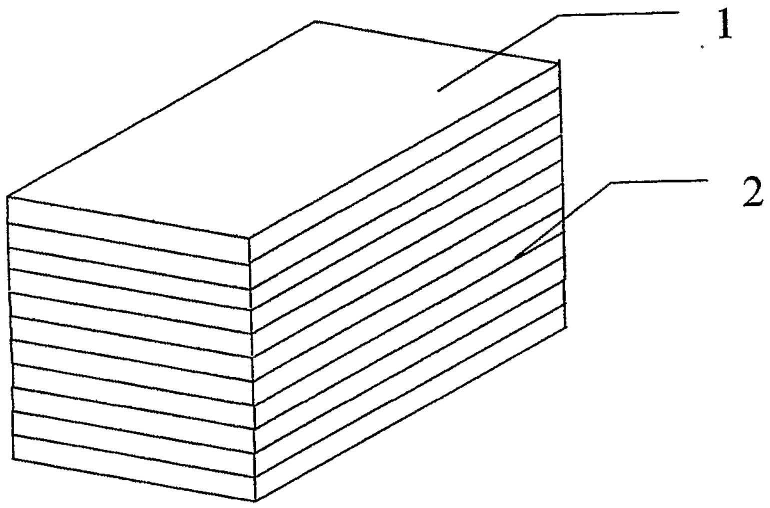

Fig.1.

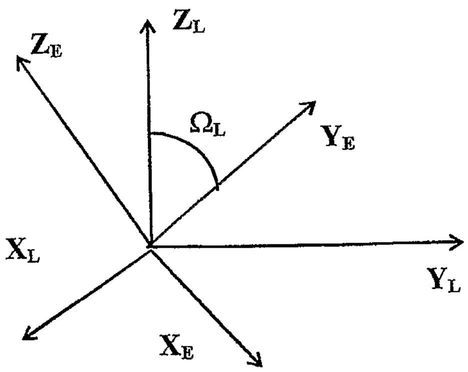

Fig.2.

REFERENCES CITED IN THE DESCRIPTION

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Non-patent literature cited in the description

- **TANNER J E et al.** Restricted self-diffusion of protons in colloidal systems by the pulsed-gradient, spin-echo method. *JOURNAL OF CHEMICAL PHYSICS,* vol. 49 (4), ISSN 0021-9606, 1768-1777 **[0002]**
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