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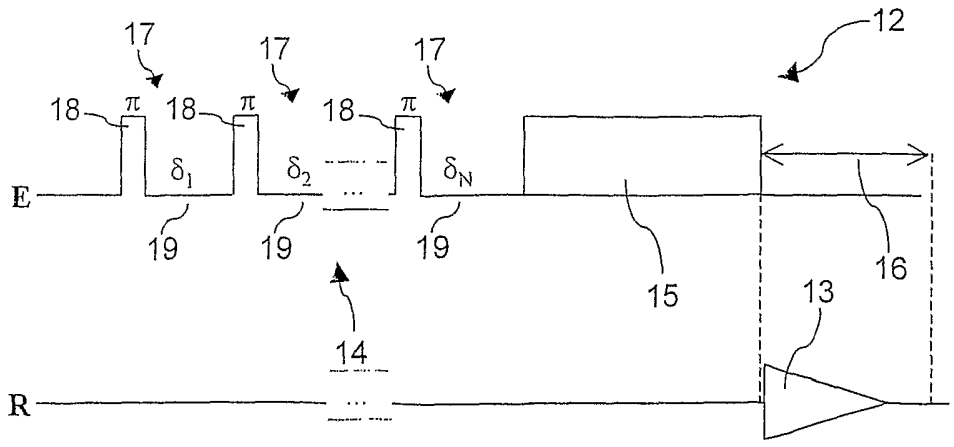
(54) **Title:** PULSE SEQUENCE FOR ACQUIRING NUCLEAR MAGNETIC RESONANCE DATA AS A FUNCTION OF THE LONGITUDINAL RELAXATION



(57) **Abstract:** A nuclear magnetic resonance apparatus (1) acquires nuclear magnetic resonance data from a sample (3) by emitting sequences of radiofrequency pulses (12) consisting, each, of a preparation pulse sequence (14) for bringing the nuclear magnetization of the sample (3) into a desired state, and a subsequent excitation pulse sequence (15) for exciting the nuclear magnetization of the sample (3) , and by accumulating, during accumulation periods (16) which follow the respective sequences of radiofrequency pulses (12) , the response signals (13) emitted by the sample (3) in response to the excitation pulse sequence (15) ; the preparation pulse sequence (14) is composed of a succession of at least two elementary sequences (17) arranged in succession and composed, in their own turn, of respective inversion pulses (18) for inverting longitudinally the nuclear magnetization of the sample (3), followed by respective idle delays (19), during which no radiofrequency pulses are emitted, having respective durations (Di) such as to impose a desired course on the longitudinal relaxation of the nuclear magnetization of the sample (3) .

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PULSE SEQUENCE FOR ACQUIRING NUCLEAR MAGNETIC RESONANCE DATA AS A FUNCTION OF THE LONGITUDINAL RELAXATION

TECHNICAL FIELD

The present invention concerns with a method for acquiring nuclear magnetic resonance data from a sample and, in particular, a sequence of radiofrequency pulses which permits to acquire nuclear magnetic resonance data as a function of longitudinal relaxation of the nuclear magnetization of various components of the sample. The method for acquiring nuclear magnetic resonance data presented in this invention finds advantageous, though not exclusive applications in measurements based on the techniques of nuclear magnetic resonance spectroscopy (NMR Spectroscopy), of nuclear magnetic resonance relaxometry (NMR Relaxometry), and of magnetic resonance imaging (MRI), which the following description will be referred to without, due to this, loosing in terms of generality.

BACKGROUND ART

As known, nuclear magnetic resonance techniques are widely used to measure chemical and physical characteristics of a sample of any kind of substance, biological or non-biological, by exploiting the interaction between external magnetic fields and the nuclear magnetization of appropriate nuclides present

in the sample which results from the linear combination of magnetic moments of the individual nuclides of the sample itself.

In general, to carry out a nuclear magnetic resonance measurement on a sample means to acquire data according to a procedure composed of the following phases:

- preparation of the nuclear magnetization of the sample, which sometimes entails the emission of at least one preparation sequence of radiofrequency pulses;
- excitation of the nuclear magnetization of the sample, which entails the emission of an excitation sequence of radiofrequency pulses for bringing the nuclear magnetizations of the nuclides into a plane transversal to the external magnetic field and thus permits their detection;
- accumulation of the transient response signals, which are known as free induction decays (FID's), emitted by the sample in response to the excitation; and
- evaluation of the accumulated response signals.

The oscillation frequency of the radiofrequency pulses must be substantially close to the so-called 'Larmor frequency' of the nuclides of the sample (resonance condition).

The evaluation of the accumulated response signals

depends upon the type of the employed preparation and excitation pulse sequences and upon the type of the employed magnetic resonance technique.

The nuclear magnetic resonance spectroscopy concerns with chemical investigation of a sample through the analysis of nuclear magnetic resonance spectra of the nuclides present therein and it is principally used for chemical and structural analysis of molecules in solutions. In particular, the transient response signals are analyzed by means of Fourier transform, obtaining one- or more-dimensional radiofrequency spectra which exhibit and correlate among themselves the nuclides present in various chemical groups of the molecules.

Nevertheless, in case of very complex samples such as protein solutions, biological fluids, blood plasma, urine, etc., the nuclear magnetic resonance spectra become nearly unmanageable due to the overlap of a multitude of components with comparable intensities. Indeed, there exist acquisition procedures which foresee sequences of radiofrequency pulses capable of selecting spectral components of the sample according to various chemical groups but which fail to discriminate such components, for example, according to the location of the chemical groups in specific molecules.

The nuclear magnetic resonance relaxometry concerns with chemical and/or physical investigation of

a sample by measurements of the relaxation times of the sample nuclear magnetization. In general, the nuclear magnetic resonance relaxometry is applied in samples with low molecular mobility such as solid and semi-solid materials, and on complex samples such as porous rocks impregnated by liquids, foodstuffs, biological tissues, etc. The measurement of relaxation times is done analyzing the relaxation curves which show the temporal evolution of the nuclear magnetization of the sample. The latter are represented by graphs which plot signal amplitudes for a number of scans of an employed pulse sequence with a variable temporal parameter. In the case of complex samples, the difficulty of the analysis consists in the fact that such a curve is a superposition of many components with an almost continuous distribution.

It is customary to analyze the relaxation curves by numerical methods of Laplace transform inversion which, however, are not always capable of providing numerically stable results due to elevated sensitivity to experimental noise.

The magnetic resonance imaging, instead, permits to generate images of internal parts of investigated objects. Notoriously, this technique is used in medical applications where the object to be investigated is a human body. It is also widely used, however, in applications linked to other environments, such as

petrophysics, food industry, archeometry, diagnosis of monuments, etc.

An MRI data acquisition procedure provides, apart from the use of a traditional excitation pulses sequence, for the use of a pulse sequence of three different magnetic field gradients which linearly vary along the three spatial directions. The transient response signal is acquired in the form of points of a grid, whose two-dimensional or three-dimensional Fourier transform allows to build an image of the sample in terms of spatial density of the nuclides. By weighing the density images as a function of the different relaxation times of the nuclear magnetization of the nuclides in the sample, it is possible to modify the contrast of the image.

Due to the complexity of the sample, invasive measures have often recourse to, such as physical separation of various parts or infiltration, into the parts of interest, of contrast agents which modify the relaxation times. In medical applications, two example of these measures are known: the sampling of a tissue (biopsy) and its following analysis by means of in vitro nuclear magnetic resonance; and the intravenously introduction into human body of contrast agents which reduce relaxation times of parts of internal organs, of tissues and of the blood. Unfortunately, once the invasive operation has been carried out made, the system remains modified for a considerable lapse of

time, thus interfering with the possibility of carrying out a number of subsequent analyses.

DISCLOSURE OF INVENTION

The purpose of the present invention is to provide a method for acquiring nuclear magnetic resonance data from a sample, and a nuclear magnetic resonance apparatus implementing such a method, which will be free of the drawbacks described above.

According with the present invention there is provided a method for acquiring nuclear magnetic resonance data from a sample, as defined in Claim 1, or in any one of the Claims which depends directly or indirectly on the Claim 1.

According with the present invention there is further provide nuclear magnetic resonance apparatus, as define in Claim 14.

BRIEF DESCRIPTION OF THE DRAWINGS

The present invention will be now described with reference to the enclosed drawings, which illustrate a non-limiting example of embodiment thereof and in which:

- Figure 1 shows a block diagram of a nuclear magnetic resonance apparatus;

- Figure 2 shows schematically a temporal progress of a generic preparation pulse sequence transmitted by the apparatus of Figure 1 according to the present invention and a corresponding response signal of the

sample received by the apparatus of Figure 1.

- Figure 3 shows an example of a preparation pulse sequence according to a third preferred embodiment of the present invention;

- Figure 4 shows a logarithmic diagram which expresses an example of the sample response obtained by a determined parameter setting of the preparation pulse sequence of Figure 3;

- Figure 5 shows a logarithmic diagram which expresses a further example of the sample response obtained by a further parameter setting of the preparation pulse sequence of Figure 3;

- Figures 6 and 7 show an experimental verification of the effectiveness of the preparation pulse sequence of Figure 3

- Figure 8 shows an example of a preparation pulse sequence according to a fourth preferred embodiment of the present invention;

- Figure 9 shows a logarithmic diagram which expresses an example of the sample response obtained by a determined parameter setting of the preparation pulse sequence of Figure 8;

- Figure 10 shows a logarithmic diagram which expresses an further example of the sample response obtained by a further parameter setting of the preparation pulse sequence of Figure 8;

- Figure 11 shows an example of a preparation pulse sequence according to a fifth preferred embodiment of the present invention;

- Figure 12 shows a logarithmic diagram which expresses an example of the response obtained by a determined parameter setting of the preparation pulse sequence of Figure 11; and

- Figure 13 shows a logarithmic diagram which expresses an example of the response obtained by a further parameter setting of the preparation pulse sequence of Figure 11.

BEST MODE FOR CARRYING OUT THE INVENTION

In Figure 1, the reference number 1 designates, as a whole, a nuclear magnetic resonance apparatus comprising a magnet 2 designed to generate a static magnetic field between its two poles , between which an housing (not shown) is provided for a sample 3 to be analyzed; a radiofrequency generator 4 designed to emit radiofrequency pulses at a frequency close to the so-called "Larmor Frequency" of the nuclides of interest of the sample 3 (resonance condition) in order to excite the nuclear magnetization of the said sample 3; a radiofrequency receiver 5 which can be tuned so that to receive nuclear magnetic resonance transient response signals emitted by the sample 3 in response to the excitation; a probe 6, for example of the type of

an induction coil or of the type of a resonant cavity, located by the housing of the magnet 3; and a separator unit 7 which connects in a known manner the probe 6 to the radiofrequency generator 4 and to the radiofrequency receiver 5 in order to isolate the said radiofrequency generator 5 from the radiofrequency generator 4 during the transmission of pulses.

The nuclear magnetic resonance apparatus 1 comprises, in addition, a data buffer 8 for accumulating the response signals in digital format; a memory 9 for storing a library of sequences 10, where sequence of operations for the acquisition of nuclear magnetic resonance data are programmed; a control unit 11, which is known as "pulser", connected to the radiofrequency generator 4, the radiofrequency generator 5, the data buffer 8 and the memory 9for coordinating the activity of said devices according to the sequence of operations programmed in the library of sequences 10 in order to excite the magnetization of the sample 3 and to receive and accumulate the response signals originating from the sample 3. Moreover, the control unit 11 is connected to a computer 11a in order to make it possible to download the contents of the data buffer 8 for subsequent evaluations and to program the library of sequences 10.

Each of the sequence of operations programmed in

the library of sequences 10 comprises operations corresponding to the transmission, by the radiofrequency generator 4, of at least one sequence of radiofrequency pulses 12 (Figure 2), and other operations corresponding to the reception, by the radiofrequency receiver 5, and the accumulation, by the data buffer 8, of a relative transient response signal 13 (Figure 2) emitted by the sample 3 in response to the excitation caused by the radiofrequency pulse sequence 12.

According to the present invention, as illustrated in Figure 2, the preparation pulse sequence 14 comprises a determined number N, particularly equal to 2, of elementary sequences 17 arranged in succession and containing respective inversion pulses 18 followed by idle intervals 19, which have respective durations δ_i independently programmable, whose index "i" assumes integer values comprised between 1 and N.

By an inversion pulse 18 one intends any radiofrequency pulse capable to produce an overall nutation by 180° (indicated by π in Figure 2) of the nuclear magnetization of the sample 3 with respect to the equilibrium situation or, in other words, a total longitudinal inversion of the nuclear magnetization. This category of pulses contains, for example, a simple pulse causing a nutation of 180°, or a so-called

"composite" pulse composed, for example, of three successive pulses, of which the central one is in quadrature phase with respect to the first and the last one and which induce respective nutations of 90°, 180° e 90°. According to a known notation, such a composite inversion pulse is indicated as follows:

$\{90_x-180_y-90_x\}$

For the sake of simplicity the exposition, in the following we will consider an inversion pulse 18 as being composed of a simple pulse with nutation angle of 180°, without any loss of generality due to this simplification. An elementary sequence 17 can be therefore indicated as

$$\{180_x - \delta_i\}, \quad (1)$$

so that the preparation pulse sequence 14 according to the present invention can be represented in the following way:

$$\{180_x-\delta_1-180_x-\delta_2-\ldots-180_x-\delta_N\}. \quad (2)$$

Every elementary sequence 17 therefore causes a longitudinal inversion of the nuclear magnetization of the sample 3, followed by an idle delay 19 of duration δ_i, during which each component of the nuclear magnetization of the sample 3, henceforth indicated generically as M, evolves according to a known exponential law

$$M(t) = M_0 - [M_0 - M(0)]\cdot\exp(-t/T_1), \quad (3)$$

towards an equilibrium nuclear magnetization value

M_0: the parameter T_1 is known as "longitudinal relaxation time" of the nuclear magnetization M.

Considering that, in practice, the inversion of the nuclear magnetization M is imperfect, one defines an effectiveness η which is smaller than unity and typically assumes values between 0.75 and 0.95. Normalizing the relaxation law (3) with respect to the field-dependent equilibrium nuclear magnetization M_0, including η and applying the modified equation (3) to the succession of N elementary sequences 17, one obtains that at the end of the preparation pulse sequence 14 every normalized nuclear magnetization component m will be longitudinally modulated according to the function

$$\begin{aligned} m(r,\delta_1,\delta_2,...,\delta_N) &= 1-[1+\eta\cdot m(r,\delta_1,\delta_2,...,\delta_{N-1})]\cdot\exp(-r\delta_N) \\ &= 1-(1+\eta)\cdot\left[\sum_{n=0}^{N-1}(-\eta)^n\cdot\exp\left(-r\sum_{i=N-n}^{N}\delta_i\right)\right] \end{aligned} \qquad (4)$$

where r denotes the "relaxation rate" which is equal to $1/T_1$.

For every value of N it is in general possible to obtain at least one linear combination F_N of a number NF of repetitions of (4), differing among themselves in the values of at least one of the delays δ_i, such that the said linear combination can be factored into two terms, one dependent only on the inversion effectiveness η and the other only on the relaxation rate r. In this way, the linear combination F_N assumes

the characteristics of a "filter" on the nuclear magnetization of the sample 3 in terms of the relaxation rate r, whose pass-band has a profile which can be modified choosing suitable values of the delays δ_i. In other words, the linear combination F_N defines a "filter function" which permits to select freely a band of longitudinal nuclear magnetization components on the basis of their relaxation rates r or, equivalently, their longitudinal relaxation times T_1.

In actual use, the acquisition of nuclear magnetic resonance data starts with the transmission of a preparation pulse sequence 14 according to (2) at the end of which the longitudinal nuclear magnetization is modulated according to (4). At this point one applies an excitation pulse sequence 15 which brings the nuclear magnetization from the initial state given by (4) to a final state in which it can be detected by the radiofrequency receiver 5. Finally, during the accumulation period 16, the sample 3 emits the transient response signal which is detected by the radiofrequency receiver 5 and accumulated in the memory buffer 8.

The sequence of radiofrequency pulses 12 is repeated for a number K of scans in order to reduce the effects of instrumental and pulse imperfections, alternating cyclically combinations of radiofrequency

phases of the pulses according to a pre-defined phase cycle composed of NP phase combinations. In other words, the sequence of NP phase combinations is repeated K/NP times. The correct phase cycle is determined for each employed excitation pulse sequence 15 following known methods.

To implement the generic filter function F_N, the sequence of radiofrequency pulses 12 is repeated for a number of scans equal to the product of K by NF, repeating the K scans for each of the NF combinations of the delays δ_i which define the required filter cycle.

According to the first preferred form of the implementation of the present invention, the filter cycle is nested within the phase cycle. In other words, one passes from one combination of pulse phases to the next one only after the completion of the repetitions, or scans, required by the filter cycle. The accumulation sequence consists in summing or subtracting the consecutive response signals 13 pertinent to the filter cycle according to the linear combinations which define the filter function F_N. This way to proceed is best indicated in cases where one wants to make sure that there are no variations in the sample while varying the said delays δ_i.

According to a second embodiment of the present

invention, the filter cycle is carried out externally with respect to the phase cycle. In other words, for every of the NF scans which differ by the value of at least one of the delays δ_i, one executes consecutively all the K scans foreseen by the phase cycle. In this case, the linear combination which gives rise to the filter function F_N is carried out a-posteriori with respect to accumulation sequence based merely on the phase cycle.

In order to remove the effects of instrumental and inversion pulse 18 imperfections, as an alternative to the phase cycle, it is possible to use a sequence of field gradient pulses, traditionally known as "homospoil pulses", each of which is applied just after a respective inversion pulse 18. Moreover, the durations of the gradient pulses should be somewhat randomized in order to prevent the formation of so-called "echoes". The imperfections of the inversion pulses 18, being essentially link to the generation of spurious perpendicular components of nuclear magnetization, are efficiently neutralized by the de-phasing effect of the gradient pulses.

According to a third embodiment illustrated in Figure 3, the preparation pulse sequence 14 is composed of two elementary sequences 17 (N=2) and indicated as

$$\{180_x - \delta_1 - 180_x - \delta_2\}. \qquad (5)$$

At the end of the preparation pulse sequence 14 indicated by (5) every longitudinal relaxation component will be modulated by (4) which, for N=2, becomes

$$m(r,\delta_1,\delta_2) = 1-(1+\eta)\cdot\exp(-r\delta_2)\cdot[1-\eta\cdot\exp(-r\delta_1)]. \quad (6)$$

To obtain the filter function F_2, i.e., filter function F_N as explained above written for N=2, one needs to execute two scans (NF=2) of the pulse sequence 12 in which the respective preparation pulse sequences 14 set-up according to (5) have two different values of the delay δ_1, indicated by δ_1^A e δ_1^B, and one combines two respective versions of the function (6) according to the scheme

$$F_2(r,\delta_1^A,\delta_1^B,\delta_2) = m(r,\delta_1^A,\delta_2) - m(r,\delta_1^B,\delta_2) = \\ = 1-(1+\eta)\cdot f_2(r,\delta_1^A,\delta_1^B,\delta_2), \quad (7)$$

where the function f_2, expressed as

$$f_2(r,\delta_1^A,\delta_1^B,\delta_2) = \exp(-r\delta_2)\cdot[\exp(-r\delta_1^A)-\exp(-r\delta_1^B)]$$

defines the profile of the filter function F_2 and can be freely varied by selecting suitable values of the delays δ_1^A, δ_1^B e δ_2.

Figure 4 shows, using a logarithmic-scale diagram, an example of the effect of parameter settings on the profile f_2 of the filter function F_2, as given by (7), of the high-pass filter type (in terms of the relaxation rate r) obtained with the parameters δ_2=0, δ_1^A=0 and δ_1^B which, for the respective curves traced in Figure 4, left to right, assumes the values 0.1, 0.01,

0.001 and 0.0001.

Figure 5 illustrates, instead, an example of the effect of parameter settings on the profile f_2 of the filter function F_2, as given by (7), of the type band-pass obtained with $\delta_2=0.1$, $\delta_1^A=0$ and δ_1^B which, for the respective curves traced in Figure 5, top to bottom, assumes the values 1, 0.1 and 0.01.

As anticipated above, to define an appropriate phase cycle it is necessary to consider the employed excitation pulse sequence 15.

As an example, consider a preparation pulse sequence 14 according to (5), followed by an excitation pulse sequence 15 consisting of a single excitation pulse with nutation angle of 90° and followed by an accumulation period 16. Using known notation, the complete pulse sequence composed in this way can be written as

$$\{180_x - \delta_1 - 180_x - \delta_2 - 90_x - Acc_x\}. \qquad (8)$$

Using known methods of determination of proper phase cycles, based on the observation of response signals 13 emitted in response to all possible combinations of pulse phases of the preparation pulse sequence 14 as well as those of the excitation pulse sequence 15, it is possible to find the optimal combination of phases for both the preparation pulse sequence 14 and the excitation pulse sequence 15

indicated in (5), i.e. one which suppresses all instrumental imperfections as well as all undesired signal components.

In particular, considering a sequence of radiofrequency pulses 12 containing three pulses P1, P2 and P3 with a generic nutation angle, the phase cycle suitable for instruments with radiofrequency receivers 5 not in quadrature turns out to consist of four scans according to the notation

$$\{P1_{x,x,-x,-x} - \delta_1 - P2_{-x,x,x,-x} - \delta_2 - P3_{x,-x,x,-x} - Acc_{x,-x,x,-x}\}, \quad (9)$$

and the phase cycle suitable for instruments with quadrature radiofrequency receivers 5 turns out to consist of eight scans according to the notation

$$\{P1_{x,x,-x,-xy,y,-y,-y} - \delta_1 - P2_{-x,x,x,-x,-y,y,y,-y} - \delta_2 - P3_{x,-x,x,-x,y,-y,y,-y} - Acc_{x,-x,x,-x,y,-y,y,-y}\}. \quad (10)$$

Applying the phase cycle according to (9) and a filter cycle according to the filter function F_2 given by (7) to the sequence (2), one obtains the following combined cycle of sequences

$\{180_x - \delta_1^A - 180_{-x} - \delta_2 - 90_x - Acc_x\}$;

$\{180_x - \delta_1^B - 180_{-x} - \delta_2 - 90_x - Acc_{-x}\}$;

$\{180_x - \delta_1^A - 180_x - \delta_2 - 90_{-x} - Acc_{-x}\}$;

$\{180_x - \delta_1^B - 180_x - \delta_2 - 90_{-x} - Acc_x\}$;

$\{180_{-x} - \delta_1^A - 180_x - \delta_2 - 90_x - Acc_x\}$;

$\{180_{-x} - \delta_1^B - 180_x - \delta_2 - 90_x - Acc_{-x}\}$;

$\{180_{-x} - \delta_1^A - 180_{-x} - \delta_2 - 90_{-x} - Acc_{-x}\}$; e

$\{180_{-x} - \delta_1^B - 180_{-x} - \delta_2 - 90_{-x} - Acc_x\}$.

Figures 6 and 7 finally show the experimental verification of the effectiveness of the preparation pulse sequence 14, implemented according to (5), using the phase cycle according to (9) and the filter function according to (7). In the particular case, the verification was carried out under the following conditions:

- $\delta_2=0$;
- the sample has a single longitudinal relaxation time of 13.4 ms;
- the filter function F_2 given by (7) is applied varying a value Δ upon which, in turn, depend δ_1^A e δ_1^B; and
- the filter function F_2 given by (7) is normalized with respect to its maximum value obtained for sufficiently large δ_1^B.

Figure 6 shows the filter function F_2 with $\delta_1^B=\Delta$ and $\delta_1^A=0$, and Figure 7 shows the filter function with $\delta_1^B=4\cdot\Delta/3$ e $\delta_1^A=2\cdot\Delta/3$. In both Figures 6 and 7, the value of Δ is expressed in seconds.

According to the fourth preferred embodiment illustrated in Figure 8, the preparation pulse sequence 14 is composed of three elementary sequences 17 (N=3) as indicated by

$$\{180_x - \delta_1 - 180_x - \delta_2 - 180_x - \delta_3\}. \quad (11)$$

At the end of the sequence, each longitudinal component of the nuclear magnetization of the sample will be modulated according to (4) which, for N=3, becomes

$$m(r,\delta_1,\delta_2,\delta_3) = 1-(1+\eta)\cdot\exp(-r\delta_3)\cdot \cdot[1-\eta\cdot\exp(-r\delta_2) + \eta^2\cdot\exp(-r(\delta_1+\delta_2))]. \quad (12)$$

To obtain the filter function F_3, i.e., a filter function F_N as described above and written for N=3, one executes four scans (NF=4) of the radiofrequency pulse sequence 12 in which the respective preparation pulse sequences 14, implemented according to (11), differ by two values of the delay δ_1, indicated as δ_1^A and δ_1^B, and two values of the delay δ_2, indicated as δ_2^A and δ_2^B, and the respective versions of function (12) are combined following the scheme

$$\begin{aligned} F_3(r,\delta_1^A,\delta_1^B,\delta_2^A,\delta_2^B,\delta_3) &= \\ &= [m(r,\delta_1^A,\delta_2^A,\delta_3) - m(r,\delta_1^B,\delta_2^B,\delta_3)] - \\ &- [m(r,\delta_1^A,\delta_2^A,\delta_3) - m(r,\delta_1^B,\delta_2^A,\delta_3)] = \\ &= \eta^2\cdot(1+\eta)\cdot f_3(r,\delta_1^A,\delta_1^B,\delta_2^A,\delta_2^B,\delta_3), \end{aligned} \quad (13)$$

where the function f_3, given by

$$\begin{aligned} f_3(r,\delta_1^A,\delta_1^B,\delta_2^A,\delta_2^B,\delta_3) &= \exp(-r\delta_3)\cdot \\ &\cdot[\exp(-r\delta_2^B)-\exp(-r\delta_2^A)]\cdot \\ &\cdot[\exp(-r\delta_1^B)-\exp(-r\delta_1^A)], \end{aligned}$$

defines the profile of the filter function F_3 and can be freely varied by selecting suitable values of the delays δ_1^A, δ_1^B, δ_2^A, δ_2^B and δ_3.

The filter function F_3, unlike the filter function F_2, is a function of second order in terms of the

relaxation rate r, i.e., the filter function F_3 is proportional to r^2 instead of to r, for small values of the relaxation rate r.

Figure 9 illustrates, using a logarithmic-scale diagram, an example of the effect of parameter settings on the profile f_3 of the filter function F_3, build according to (13), of the high-pass filter type (in terms of the relaxation rate r) obtained with the parameters δ_3=0, δ_2^B=0, δ_1^B=0 while $\delta_2^A = \delta_1^A$ assume for the respective curves traced in Figure 9, left to right, the values 1, 0.1, 0.01 and 0.001.

Figure 10 shows, instead, an example of the effect of parameter settings on the profile f_3 of the filter function F_3 as of (13), of the type band-pass obtained with δ_3=0.1, δ_2^B=0, δ_1^B=0 while $\delta_2^A = \delta_1^A$ assume the values 1 (top curve in Figure 10) and 10 (bottom curve in Figure 10).

Following the same procedure as the one used for preparation pulse sequences 14 build according to (5), it is possible to set up an optimal phase cycle also for preparation pulse sequences 14 build according to (11) or, alternatively, use a sequence of gradient pulses. For what regards the filter cycle, one applies also the same considerations as those brought up for the preparation pulse sequence of (5).

According to a variant on the fourth embodiment described above one can design a filter function F_3 of

second order by combining versions of function (12) corresponding to just three scans ($NF=3$) or the radiofrequency pulse sequence 12, in which the preparation pulse sequences 14 build according to (11) use respective pairs of values of the pair of delays δ_1 and δ_2, denoted as δ_1^A and δ_2^A, δ_1^B and δ_2^B, δ_1^C e δ_2^C and the same value of the third delay, according to the scheme

$$F_3(r,\delta_1^A,\delta_1^B,\delta_2^A,\delta_2^B,\delta_3) = k^A.m(r,\delta_1^A,\delta_2^A,\delta_3) + k^B.m(r,\delta_1^B,\delta_2^B,\delta_3) + k^C.m(r,\delta_1^C,\delta_2^C,\delta_3),$$

where the coefficients k^A, k^B e k^C must satisfy the following condition:

$$k^A\cdot exp(-r\delta_2^A) + k^B\cdot exp(-r\delta_2^B) + k^C\cdot exp(-r\delta_2^C) = 0.$$

According to a fifth preferred embodiment illustrated in Figure 11, the preparation pulse sequence 14 is composed of four elementary sequences 17 ($N=4$), and in particular of two preparation pulse sequences 14, build as in (5), applied in succession ("cascade", and can be written as

$$\{180_x-\delta_1\ -180_x-\delta_2\ -180_x-\delta_3\ -180_x-\delta_4\}, \quad (14)$$

At the end of the preparation pulse sequence 14 build according to (14), each component of the longitudinal relaxation will be modulated as defined in (4) which, for $N=4$ and $\delta_4=\delta_2$, becomes

$$m(r,\delta_1,\delta_3,\delta_2) = 1-(1+\eta)\cdot exp(-r\delta_2)\cdot[1-\eta\cdot exp(-r\delta_3)+ +\eta^2\cdot exp(-r(\delta_3+\delta_2))-\eta^3\cdot exp(-r(\delta_1+\delta_3+\delta_2))]. \quad (15)$$

To obtain the filter function F_4, i.e., a filter function F_N as described above and written for N=4, one executes two scans (NF=2) of the radiofrequency pulse sequence 12 in which the respective preparation pulse sequences 14, implemented according to (14), contain distinct combinations of the values of the delays δ_1 and δ_3, obtained by permutations of two values, indicates as δ_1^A and δ_1^B, and combines the respective versions of the function (15) according to the scheme

$$\begin{aligned} F_4(r,\delta_1^A,\delta_1^B,\delta_2) &= \\ &= [m(r,\delta_1^A,\delta_1^A,\delta_2) - m(r,\delta_1^A,\delta_1^B,\delta_2)] - \\ &- [m(r,\delta_1^B,\delta_1^A,\delta_2) - m(r,\delta_1^B,\delta_1^B,\delta_2)] = \\ &= \eta^3 \cdot (1+\eta) \cdot f_4(\delta_1^A,\delta_1^B,\delta_2), \end{aligned} \qquad (16)$$

where the function f_4, written as

$$f_4(\delta_1^A,\delta_1^B,\delta_2) = \{\exp(-r\delta_2) \cdot [\exp(-r\delta_1^A) - \exp(-r\delta_1^B)]\}^2,$$

defines the profile of the filter function F_4 which can be freely modified by choosing suitable values of the delays δ_1^A, δ_1^B, and δ_2. It follows that the filter function F_4, like the filter function F_3, is of second order in terms of the relaxation rate r.

Figure 12 shows, using a logarithmic-scale diagram, an example of the effect of parameter settings on the profile f_4 of the filter function F_4, build according to (16), of the high-pass filter type (in terms of the relaxation rate r) obtained with the parameters δ_2=0, δ_1^B=0.1 and δ_1^A *which* assumes for the respective curves traced in Figure 9, left to right,

the values 1, 0.1, 0.01, 0.001 and 0.0001.

Figure 13 illustrates, using again a logarithmic graph, another example of the effect of parameter settings on the profile f_4 of the filter function F_4 defined by (16) which, however, has a third-order behavior achieved by means of a suitable combination of specific versions of (15) corresponding to a certain number of scans of the radiofrequency pulse sequence 12 and satisfying a condition which links between themselves the combination coefficients.

Following the same procedure as the one used for preparation pulse sequences 14 build according to (5), it is possible to set up an optimal phase cycle also for preparation pulse sequences 14 build according to (14) or, alternatively, use a sequence of gradient pulses. For what regards the filter cycle, one applies also the same considerations as those brought up for the preparation pulse sequence of (5).

From what has been described so far, in particular with reference to Figures 4, 5, 9, 10, 12 and 13 one readily observes that the pass band, in terms of the relaxation rate r, of the generic filter function F_N which can be assigned, in the above described way, to the generic preparation pulse sequence 14 formed by a number N of inversion pulses 18 according to (2) can be modified varying the durations δ_i of the intervals between consecutive inversion pulses 18 and exhibits an

increasing selectivity with increasing number N. In particular, the generic preparation pulse sequence 14 composed of number N inversion pulses 18 according to (2) permits to obtain a multitude of filter functions F_N up to the (N-1)-th order and defined by the respective sets of the durations δ_i.

The evident analogy with digital frequency filters widely used in electronics makes it possible to identify the preparation pulse sequences 14, defined according to (2), as a new category of longitudinal relaxation T_1 filters denotes as "Parametrically Enabled Relaxation Filters with Double or multiple Inversion", the contraction of which leads to the acronym "PERFIDI".

The use of preparation pulse sequences 14 as defined by (2) turns out to be advantageous in all the widely used nuclear magnetic resonance techniques since, applying a particular preparation pulse sequence 14 defined by (2) to any traditional excitation pulse sequence 15, one selects only those components of sample 3 whose longitudinal relaxation times T_1 fall into a band defined by the filter function F_N and its parameters given by the durations δ_i, simplifying nuclear magnetic resonance measurements of complex samples 3, such as heterogeneous mixtures, porous systems, tissues, biological fluids, etc.

With advantage, in nuclear magnetic resonance spectroscopy it is possible to carry out different

measurements selecting each time different subsets of longitudinal relaxation times T_1 and obtaining spectra of Larmor frequencies which are sufficiently simple to be extrapolated and analyzed by means of Fourier transform. For example, applying a preparation pulse sequence 14 with two inversion pulses 18 according to (5) to the traditional sequence COSY, it is possible to produce, by means of a 2D Fourier transform, a series of qualitatively distinct bi-dimensional spectra, each of which corresponding to a single fraction of relaxation components selected by means of a suitable setting of the parameters of the filter function F_2.

With advantage, in nuclear magnetic resonance relaxometry, it is possible to carry out different measurements selecting each time different subsets of longitudinal relaxation times T_1 which permit to unravel the quasi-continuous distribution of relaxation components which would be obtained from a traditional measurement of a complex sample 3. For example, applying a preparation pulse sequence 14 with two inversion pulses 18 according to (5) to the traditional sequence CPMG for the measurement of perpendicular relaxation times T_2, one selects the various relaxation components according to their respective longitudinal relaxation times T_1, whose perpendicular relaxation times T_2 are then measured by the traditional sequence CPMG. This simplifies enormously the determination of correlation's between the longitudinal (T_1) and

perpendicular (T_2) relaxation times which would be otherwise extremely difficult to obtain.

With advantage, in magnetic resonance imaging, with a particular reference to the medical field, it is possible to carry out different measurements selecting each time different subsets of longitudinal relaxation times T_1 which permit to produce a multitude of images of the analyzed subject which carry qualitatively different information content. Keeping in mind that, for example, tumoral tissues differ from healthy ones particularly in their longitudinal relaxation times T_1, the importance of such a discrimination is crucial. Moreover, since the image contrast is strongly related to the longitudinal (T_1) and perpendicular (T_2) relaxation times, it is possible to limit or avoid introduction of contrast agent into the subject's body. Alternatively, the preparation pulse sequences 14 according to (2) can be used in synergy with the contrast agent and accentuate its effectiveness.

Finally, the use of preparation pulse sequences 14 according to (2) appears advantageous with respect to known pulse sequences capable to discriminate between relaxation components on the basis of the perpendicular relaxation time T_2 since imperfections related to the generation of the inversion pulses 18 are easier to control, by means of phase cycling techniques or by sequences of homospoil pulses, than imperfection related to impulses with 90° nutation angles.

C L A I M S

1.- A method for acquiring nuclear magnetic resonance data from a sample (3), the method comprising:

- emitting at least one sequence of radiofrequency pulses (12) comprising a preparation pulse sequence (14) to prepare the nuclear magnetization of the sample (3), and a consecutive excitation pulse sequence (15) to excite the nuclear magnetization of the sample (3); and

- accumulating, during a subsequent and respective accumulation period (16), a response signal (13) emitted by the sample (3) in response to the excitation pulse sequence (15);

the method **being characterized in that** the preparation pulse sequence (14) comprises a plurality of elementary sequences (17) arranged in a succession and comprising respective inversion pulses (18), which are followed by respective idle periods (19), to invert longitudinally the nuclear magnetization of the sample (3); the idle periods (19), during which no radiofrequency pulse is emitted, having respective durations (δi) so as to permit a longitudinal relaxation of the nuclear magnetization of the sample (3).

2.- The method according to Claim 1, wherein the

said durations (δi) are variable independently of each other.

3.- The method according to Claim 1 or to Claim 2, wherein the said durations (δi) are programmable independently of each other.

4.- The method according to any one of Claims 1 to 3, further comprising:

- emitting a first plurality of repetitions of the said sequence of radiofrequency pulses (12), the respective preparation pulse sequences (14) of the repetitions differing among themselves in the values of at least one of the durations (δi); and

- accumulating the said response signals (13) emitted by the sample (3) in response to the repetitions of the said excitation pulse sequence (15) corresponding to the repetitions of the sequence of radiofrequency pulses (12).

5.- The method according to Claim 4, further comprising:

- combining the said response signals (13) emitted by the sample (3) in such a way as to achieve a filter effect on the nuclear magnetization of the sample (3) in terms of the longitudinal relaxation rate of the said nuclear magnetization.

6.- The method according to Claim 5, wherein combining the said response signals (13) emitted by the

sample (3) comprises:

- combining linearly the response signals (13).

7.- The method according to Claim 5 or to Claim 6, further comprising:

- emitting, for each repetition of the said first plurality of repetitions of the said sequence of radiofrequency pulses (12), a second plurality of repetitions of the sequence of radiofrequency pulses (12), alternating cyclically the phases of the pulses of the said sequence of radiofrequency pulses (12) following a phase cycle determined as a function of the excitation pulse sequence (15); and

- accumulating the said response signals (13) emitted by the sample (3) in response to the repetitions of the excitation pulse sequence (15) corresponding to the repetitions of the sequence of radiofrequency pulses (12).

8.- The method according to Claim 5 or to Claim 6, further comprising:

- emitting a second plurality of repetitions of the said sequence of radiofrequency pulses (12) alternating cyclically combinations of phases of the pulses of the said sequence of radiofrequency pulses (12), following a phase cycle determined as a function of the excitation pulse sequence (15), and alternating cyclically the said repetitions of the said first

plurality of repetitions of the sequence of radiofrequency pulses (12), whose respective preparation pulse sequences (14) differ among themselves in the values of at least one of the durations (δi); and

- accumulating the said response signals (13) emitted by the sample (3) in response to the repetitions of the excitation pulse sequence (15) corresponding to the repetitions of the sequence of radiofrequency pulses (12).

9.- The method according to Claim 8, wherein emitting a second plurality of repetitions of the said sequence of radiofrequency pulses (12) comprises:

- switching from one of the said combinations of phases of the sequence of radiofrequency pulses (12) to a following one after having alternated all the said preparation pulse sequences (14) which differ among themselves in the values of at least one of the durations (δi).

10.- The method according to Claim 8 or to Claim 9, wherein accumulating the said response signals (13) emitted by the sample (3) in response to the said repetitions of the excitation pulse sequence (15) comprises:

- combining linearly the response signals (13).

11.- The method according to any one of Claims 5

to 10, wherein the said preparation pulse sequence (14) comprises two of the said elementary sequences (17); the said idle period (19) of the first of the two elementary sequences (17) having a first duration (δ_1) and the said idle period (19) of the following one of the two elementary sequences (17) having a second duration (δ_2).

12.- The method according to Claim 11, wherein the said first plurality of repetitions of the said sequence of radiofrequency pulses (12) comprises two repetitions of the sequence of radiofrequency pulses (12); the respective said preparation pulse sequences (14) of the two repetitions differing among themselves in the value of the first duration (δ_1).

13.- The method according to Claim 12, wherein combining the said response signals (13) emitted by the sample (3) comprises:

- subtracting among themselves the said response signals (13) emitted by the sample (3) in response to the said repetitions of the excitation pulse sequence (15) emitted subsequently to the said preparation pulse sequences (14) which differ among themselves in the value of the first duration (δ_1).

14.- Nuclear magnetic resonance apparatus comprising a radiofrequency generator (4) designed to emit radiofrequency pulses for preparing and exciting

the nuclear magnetization of the sample (3); a radiofrequency receiver (5) tunable in such a way as to receive the transient nuclear magnetic resonance response signals (13) emitted by the sample (3); accumulation means (8) for accumulating the response signals (13) in digital format; storage means (9) for storing a library of sequences of operations (10), among which sequences of radiofrequency pulses; and control means (11) connected to the radiofrequency generator (4), the radiofrequency receiver (5), the accumulation means (8) and the storage means (9); the apparatus (1) **being characterized in that** the control means (11) are configured to implement the method of acquiring nuclear magnetic resonance data according to any one of the Claims 1 to 13.

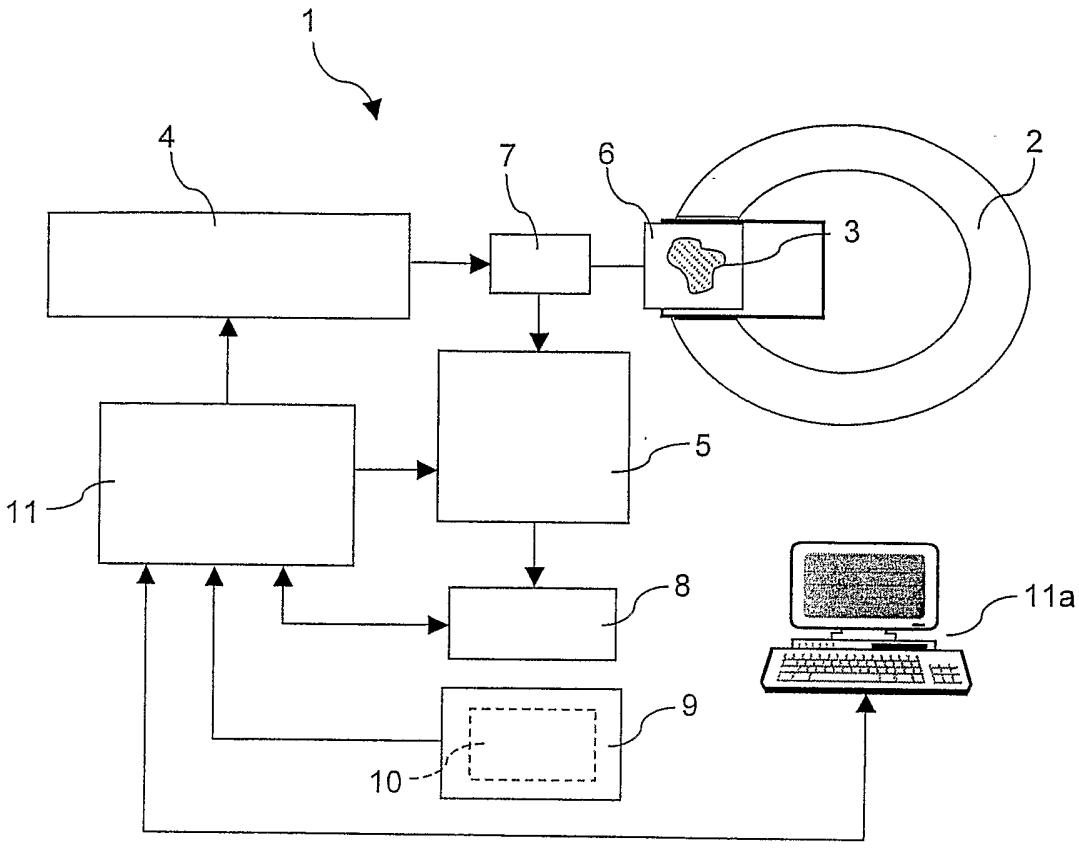
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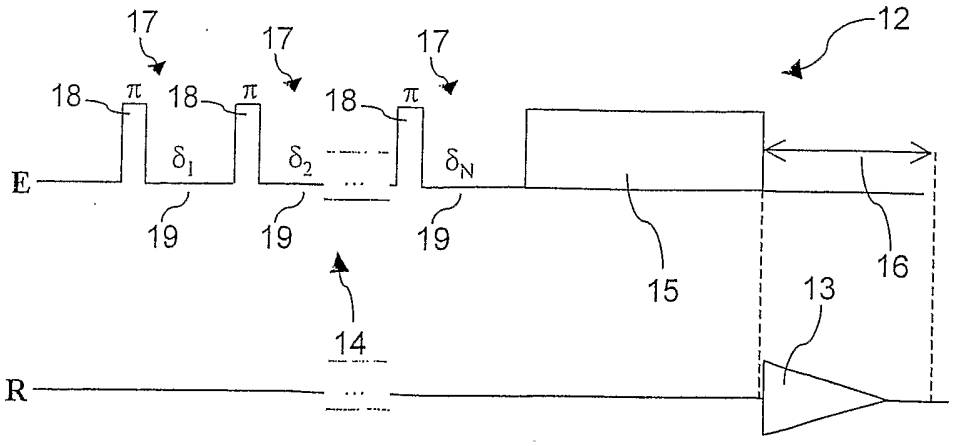
Fig. 1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δ2
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16
14
13
R

Fig. 2

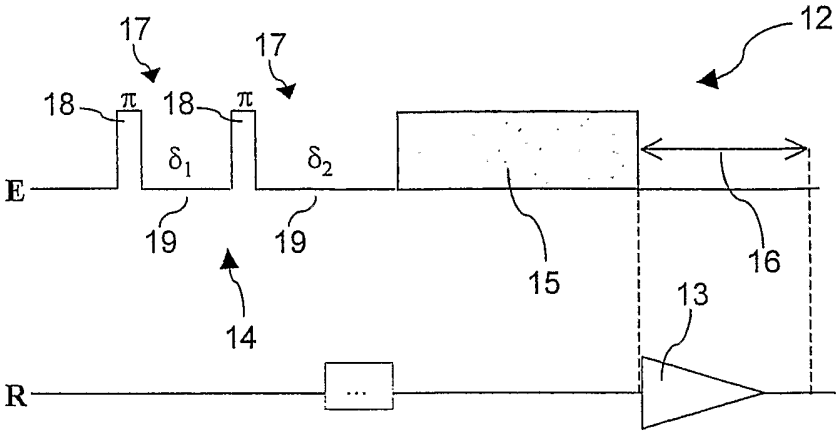


Fig. 3

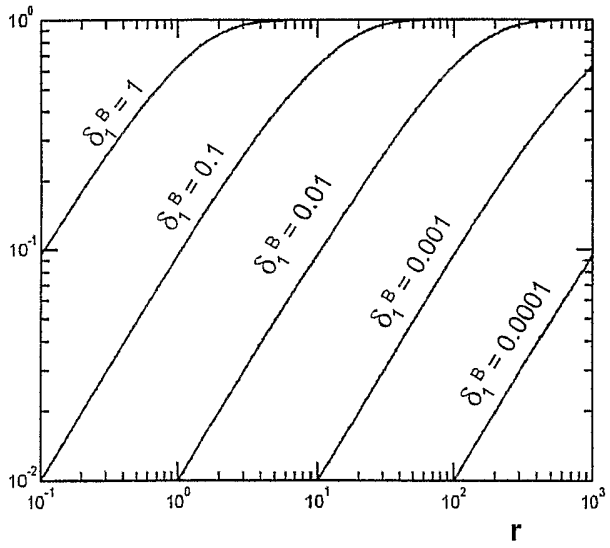


Fig. 4

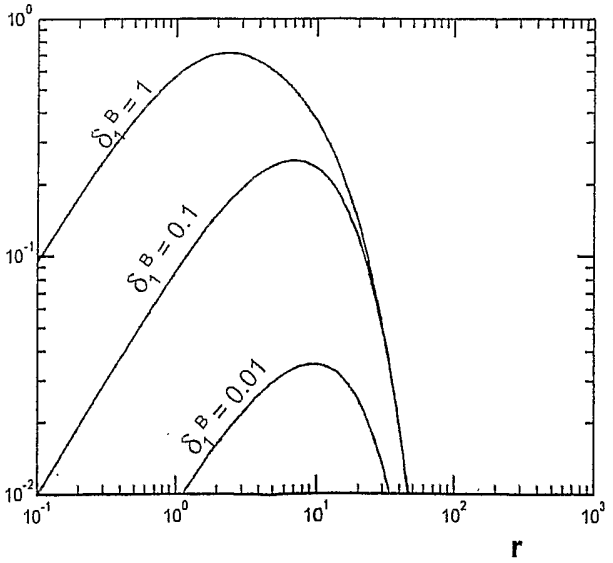
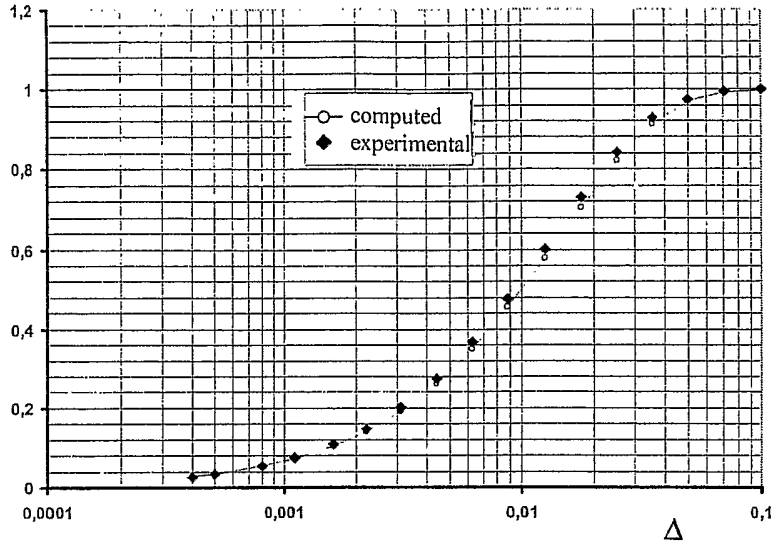


Fig. 5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0,001
0,01
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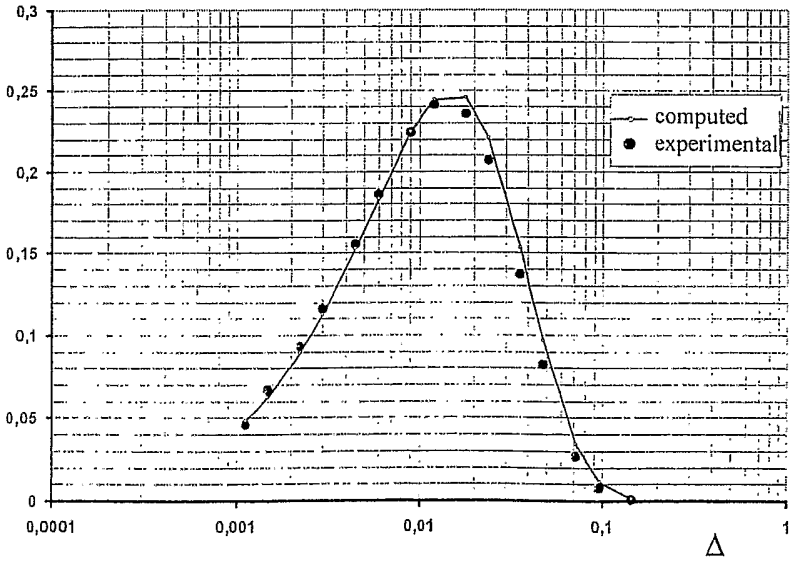
Δ
computed
experimental

Fig. 6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Δ
computed
experimental

Fig. 7

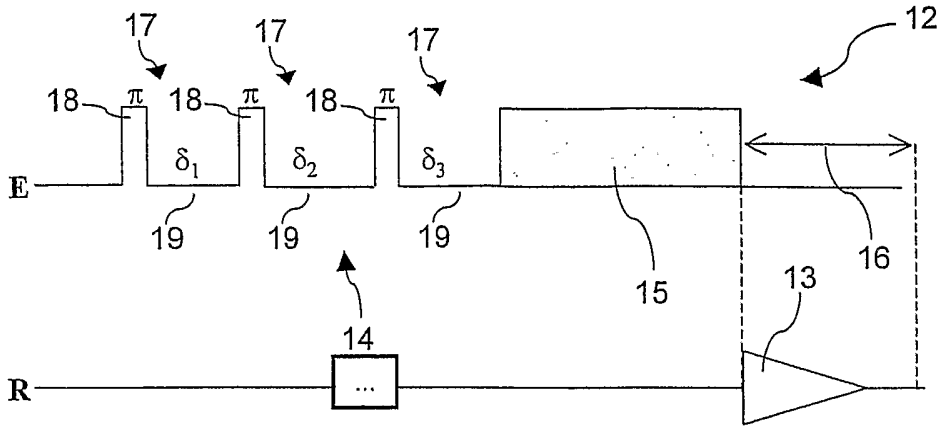

Fig. 8

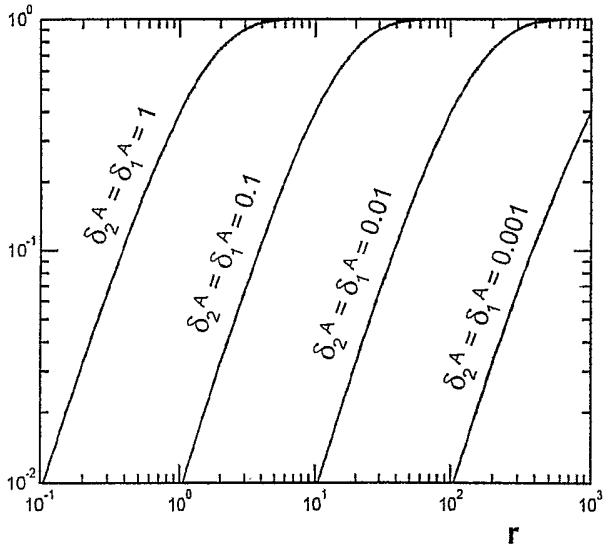

Fig. 9

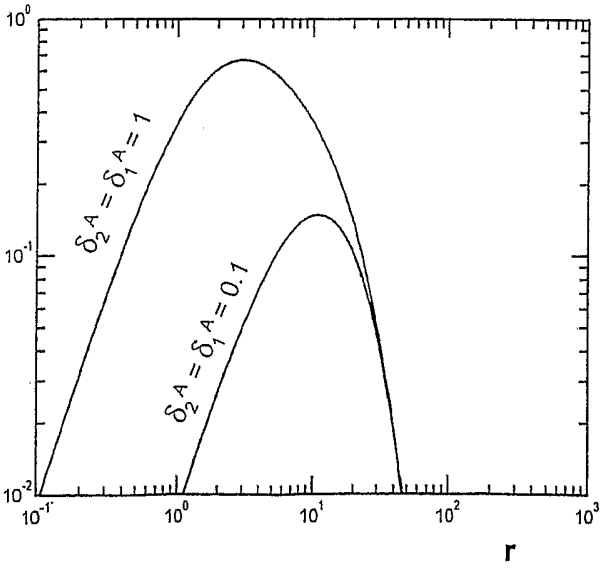

Fig. 10

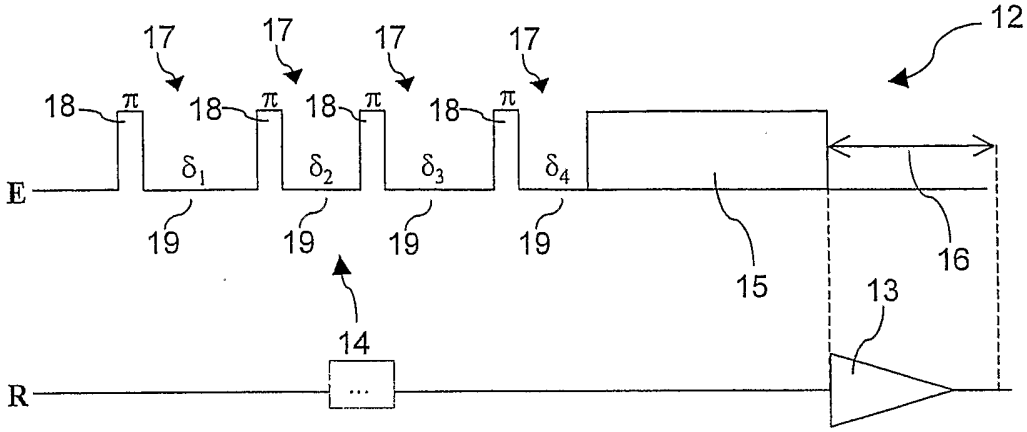

Fig. 11

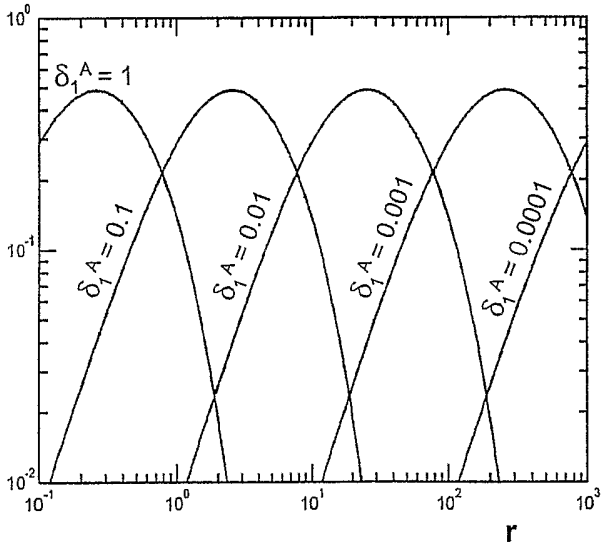

Fig. 12

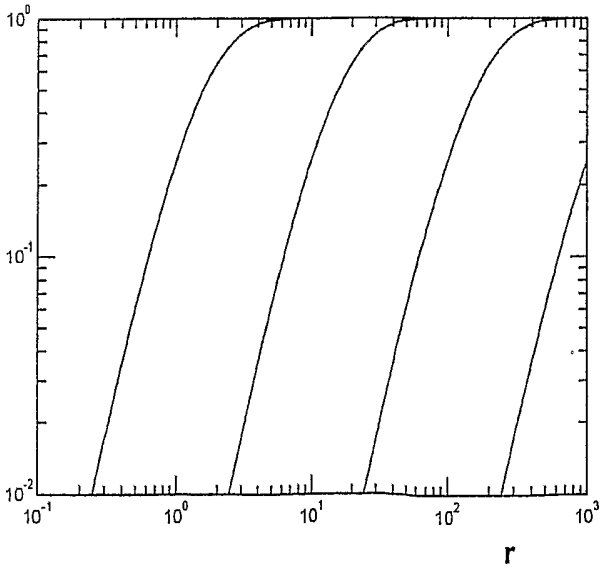

Fig. 13

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2006/001839

A. CLASSIFICATION OF SUBJECT MATTER
INV. G01R33/50
ADD. G01N24/08

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
G01R G01N

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, INSPEC, EMBASE, BIOSIS, WPI Data, PAJ, COMPENDEX, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	BLÜMICH B.: "NMR Imaging of Materials" 2002, CLARENDON PRESS , OXFORD , XP002408067	1-3,14
A	pages 242-301 pages 490-505	4-13
X	GB 2 330 658 A (WESTERN ATLAS INT INC [US]) 28 April 1999 (1999-04-28) figure 3	1-3,14
X	US 5 655 531 A (NISHIMURA DWIGHT G [US] ET AL) 12 August 1997 (1997-08-12) column 3, line 35 - line 55	1-3,14

-/--

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

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"A" document defining the general state of the art which is not considered to be of particular relevance

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"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
20 November 2006	04/12/2006

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, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Skalla, Jörg

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2006/001839

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
T	SYKORA S. ET AL: "New Universal NMR Sequences PERFIDI and LAPSR" POSTER PRESENTED AT THE XXXVI NATIONAL CONGRESS ON MAGNETIC RESONANCE, [Online] 20 September 2006 (2006-09-20), XP002408040 Retrieved from the Internet: URL:http://www.ebyte.it/library/downloads/Poster_Perfidi_Lapsr.pdf> [retrieved on 2006-11-16] the whole document	1-14

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2006/001839

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