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D E C I S I O N
of 13 September 2001

Case Number: T 0779/97 - 3.4.1

Application Number: 93917992.5

Publication Number: 0654146

IPC: G01R 33/62

Language of the proceedings: EN

Title of invention:
Method of obtaining images representing the distribution of paramagnetic material in solution

Applicant:
BTG INTERNATIONAL LIMITED

Opponent:
-

Headword:
-

Relevant legal provisions:
EPC Art. 123(2), 54, 56

Keyword:
"EPC Art. 56 Inventive step - (yes) after amendment"

Decisions cited:
-

Catchword:
-

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Case Number: T 0779/97 - 3.4.1

D E C I S I O N
of the Technical Board of Appeal 3.4.1
of 13 September 2001

Appellant: BTG INTERNATIONAL LIMITED
10 Fleet place
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Representative: Buttrick, Richard
BTG International Limited
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London EC4M 7SB (GB)

Decision under appeal: **Decision of the Examining Division of the European Patent Office posted 29 January 1997 refusing European patent application No. 93 917 992.5 pursuant to Article 97(1) EPC.**

Composition of the Board:

Chairman: G. Davies
Members: G. Assi
H. K. Wolfrum

Summary of Facts and Submissions

I. The appellant (applicant) lodged an appeal, received on 21 March 1997, against the decision of the Examining Division, dispatched on 29 January 1997, refusing the European patent application No. 93 917 992.5 (international publication number WO-A-94/03824). The fee for the appeal was paid on 20 March 1997. The statement setting out the grounds of appeal was received on 4 June 1997.

In its decision, the Examining Division held that the application did not meet the requirements of Articles 52(1), 54 and 56 EPC having regard to the following documents:

(D1) WO-A-90/13047,

(D2) WO-A-92/04640,

(D3) EP-A-0 409 292.

II. In appeal proceedings, the following further document was considered:

(D4) US-A-4 707 658.

III. Oral proceedings were held on 13 September 2001.

At the oral proceedings, the appellant requested that the decision under appeal be set aside and a patent be granted on the basis of the following documents:

Claims:
No. 1 to 3 filed at the oral proceedings on

13 September 2001,

Description:
Pages 1 to 9 filed with the letter of 13 August 2001,

Drawings:
Figures 1 to 4 of the published application.

IV. The wording of claim 1 reads as follows:

"A method of proton-electron double-resonance magnetic resonance imaging comprising the steps of:

subjecting a sample containing paramagnetic material to a polarising magnetic field (B_0^p) during a polarisation period;

subjecting said sample, during an evolution period following said polarisation period, to a further polarising magnetic field (B_0^e), the value of the polarising magnetic field (B_0^e) during the evolution period being lower than the value of the polarising magnetic field (B_0^p) during the polarisation period, and to radio-frequency radiation at a frequency appropriate to said further polarising magnetic field (B_0^e) so as to excite electron paramagnetic resonance in the paramagnetic material;

subjecting said sample, in a detection period after said evolution period to a yet further polarising magnetic field (B_0^d), the value of the polarising magnetic field (B_0^d) applied during said detection period being greater than the value of the field (B_0^e) applied during said evolution period

characterised in that

only a single polarisation period and evolution period is applied but the detection period comprises a series of detection cycles,

during each of said detection cycles the sample is subjected to a nuclear magnetic resonance interrogating signal, a corresponding plurality of nuclear magnetic resonance signals is derived from said sample during said detection period and said plurality of nuclear magnetic resonance image signals are combined into a complete nuclear magnetic resonance image."

Claims 2 and 3 are dependent claims.

V. The appellant argued essentially as follows:

The invention concerned a method of proton-electron double-resonance imaging (PEDRI). Such a method was known from documents D1, D2 and D3. The problem underlying the PEDRI method consisted in that a high magnetic field would improve the signal-to-noise ratio (SNR) but, at the same time, a low field would reduce the electron-paramagnetic resonance (EPR) power absorbed by the sample. These conflicting requirements were met in the prior art according to D2 by the provision of field-cycling. Document D2, which was considered as the closest prior art, disclosed a field-cycled PEDRI method, in which each cycle of the nuclear magnetic resonance (NMR) imaging sequence included an EPR pulse preceding the NMR interrogating pulse. By contrast, the present invention concerned a field-cycled PEDRI method with a single EPR pulse for each NMR imaging sequence including a plurality of cycles, each having an NMR interrogating pulse. The claimed solution was not obvious having regard to the cited prior art. Document D1 disclosed a PEDRI method without field-cycling. A single EPR pulse was provided before an echo planar imaging (EPI) sequence. Thus, there was a one-to-one relationship between the NMR interrogating

pulse and the EPR pulse. The same one-to-one relationship was disclosed by D2 and D3. Document D4 simply referred to a particular NMR fast imaging sequence that could be used in the method of the invention. Should the skilled person consider replacing the EPI sequence of D1 by another fast sequence based on a plurality of cycles, each including an NMR interrogating pulse, he would provide a plurality of EPR pulses.

Reasons for the Decision

1. The appeal is admissible.

2. *Article 123(2) EPC*

2.1 As compared with the original claim 1, the present claim 1 has been amended so as to include the following features:

(i) the field-cycling, in particular the features concerning the values of B_0^p, B_0^e and B_0^d,

(ii) the EPR single-shot, which is not clearly expressed in the original claim 1,

(iii) the NMR imaging sequence including a series of cycles, each of which comprises an NMR interrogating signal.

The amendments are supported by the disclosure of the original application. In particular, the field-cycling is disclosed on page 9, lines 20 to 33, page 11, lines 9 to 12, claim 2 and Figure 4, the EPR single-

shot on page 3, line 32, to page 4, line 5, page 9, lines 15 to 33, and Figure 4, and the NMR imaging sequence in Figure 4.

Claim 2 includes the feature that the value of B_0^d is equal to the value of B_0^p, which feature is originally disclosed on page 11, lines 9 to 12, and in claim 3.

Claim 3 includes the feature that the value of B_0^d is less than the value of B_0^p, this feature being disclosed in the original claim 3.

2.2 The original description has been amended so as to be adapted to the new claim 1 and to acknowledge the prior art, without introducing new elements.

2.3 Therefore, the application as amended meets the requirements of Article 123(2) EPC.

3. *Novelty*

3.1 Document D2, which represents the closest state of the art, discloses a PEDRI method, according to which an NMR image of a sample is obtained by means of a sequence of cycles, each including the following steps:

- during a polarisation period, subjecting the sample containing paramagnetic material to a polarising magnetic field B_0^p,

- during an evolution period following the polarisation period, subjecting the sample to a further polarising magnetic field B_0^e, the value of B_0^e being lower than the value of B_0^p, and to EPR radiation at a frequency appropriate to the field

B_0^e so as to excite electron paramagnetic resonance in the paramagnetic material,

- during a detection period following the evolution period, subjecting the sample to a yet further polarising magnetic field B_0^d, the value of B_0^d being greater than the value of the field B_0^e, and to a radio-frequency NMR interrogating signal with magnetic field gradients, an NMR output signal being thus generated and detected,

- obtaining the NMR image using the output NMR signals of all the imaging cycles.

The subject-matter according to claim 1 differs from the field-cycled PEDRI method known from D2 in that only a single polarisation period and a single evolution period are applied, which are followed by a detection period comprising a sequence of detection cycles, during each of which the sample is subjected to an NMR interrogating signal and varying field gradients.

3.2 Document D1 discloses a single-shot PEDRI method without magnetic field-cycling (see page 1, first paragraph, page 16, lines 10 to 12), wherein an image is obtained by an echo-planar imaging (EPI) technique (see claim 1) following a single EPR excitation signal (see page 9, lines 30 to 36, Figures 2 and 3).

The method of claim 1 differs from that known from D1 in that magnetic field-cycling is performed and the detection period comprises a series of detection cycles, each of which includes a radiofrequency (RF) NMR interrogating signal.

3.3 The other documents cited, D3 and D4, do not come closer to the subject-matter of claim 1 than D2 or D1.

3.4 Therefore, the subject-matter of claim 1 is new having regard to documents D1 to D4 (Article 54(1),(2) EPC).

4. *Inventive step*

4.1 According to D2 (see page 2, lines 14 to 33), the field-cycled PEDRI method represents a compromise between the conflicting requirements concerning the choice of the value of B_0, in particular the advantage of having a high field value ensuring a good SNR, on the one hand, and the need to reduce the field value in order to decrease the high frequency radiation power absorbed by the sample, while maintaining a sufficient NMR signal enhancement, on the other hand.

The present invention starts from the known field-cycled PEDRI method and aims at further reducing the power absorbed by the sample (see the present application, page 3, last paragraph). The claimed solution consists in providing a single EPR excitation before the sequence generating an image (see Figure 4 of the present application), whereas in the method according to D2, a plurality of EPR excitations is provided at different times during the same imaging sequence (see Figure 2 of the present application or Figure 3 of D2).

Document D2 does not give any explicit or implicit hint at the possibility of modifying the known method in the way according to claim 1. Nor would the combination of D2 with another document directly lead to the claimed method. In particular, the combination of D2 and D1

would be problematic in view of the different characteristics of the sequence used for obtaining an image, i.e. a sequence including a plurality of cycles, each comprising an NMR interrogating signal and field gradients, according to D2 and the EPI sequence with only one RF NMR excitation signal and rapidly switched read and phase-encoding gradients according to D1. This difference is relevant for the choice of the magnetic field, more specifically for the measure concerning field-cycling (see point 4.2 below).

4.2 The Board has also considered the possibility of regarding the method of document D1 as the starting point. In order to arrive at the claimed method, it would be necessary to introduce the field-cycling and to replace the EPI sequence.

With regard to field-cycling, this measure permits the applied EPR power to be reduced (see, for example, D2, page 7, lines 1 to 7), i.e. it permits to achieve the object underlying the present invention. However, the application as filed (see page 12, lines 6 to 9) warns that snapshot field-cycled PEDRI using EPI would probably be difficult, since it may not be possible to stabilise the magnetic field sufficiently well during the detection period, resulting in image artefacts. This difficulty has been underlined by the appellant in his letter of 2 June 1997 and the Board has no reason to dispute his point of view. Thus, it is not obvious to combine the EPI technique with the feature of field-cycling. Difficulties of a technical nature rather speak against the combination.

As regards the imaging sequence, D1 only mentions the EPI technique and does not give any explicit or

implicit hint at the possibility of replacing EPI by another known imaging sequence, for example the fast low angle shot (FLASH) method disclosed by D4 (see Figure 3), including an NMR interrogating signal together with field gradients in each detection cycle of the sequence generating the image. Replacing the EPI sequence by such an imaging sequence would thus imply departing from the teaching of D1. Nevertheless, even in case the skilled person would be prompted to make this change with the aim of overcoming the technical difficulties related to the intrinsic characteristics of the EPI method, which render difficult its application to the field-cycled PEDRI method, this would not yet lead to the claimed subject-matter. Indeed, according to D1, page 9, lines 8 to 13, the main attraction of EPI is that it is possible using this technique to reduce the number of RF NMR excitation and FID signal detection cycles necessary for the generation of NxN voxel images (see, for instance, the method of D4, Figure 3) down to as low as 1. Insofar as ESREMRI, i.e. PEDRI, is concerned, the use of the EPI technique affords the opportunity to reduce the total EPR microwave exposure of the subject by reducing the number of RF NMR excitation and FID signal detection cycles and "*thus*" the number of EPR exposure periods required for the acquisition of a single image (see page 9, lines 24 to 29). Therefore, D1 teaches that a single EPR shot is sufficient in combination with the EPI technique, in which an image is obtained by means of a detection period including only one RF NMR excitation signal and rapidly switched read and phase-encoding gradients. It may be concluded from the cited passages that, in case the image is generated by means of a detection period including many RF NMR excitation and FID signal detection cycles, an

EPR shot should precede each detection cycle (see also page 16, lines 17 to 26), as shown in Figure 3 of D2.

4.3 Document D3 (see claim 1) discloses a magnetic resonance image generating apparatus comprising a first radiation source emitting a first radiation of a frequency selected to excite NMR transitions in selected nuclei in a sample being imaged, means for detecting FID signals from the selected nuclei, and a second radiation source emitting a second radiation of a frequency selected to excite ESR transitions coupled to the nuclear spin transitions of at least some of the selected nuclei. The known apparatus is suitable for carrying out the PEDRI method using a fast imaging technique (see page 3, lines 31 to 33). The second radiation source may be a continuous wave transmitter or may be arranged to emit pulses or trains of pulses of the second radiation (see page 10, lines 21 and 22). According to page 11, lines 1 to 5, "*the sample may be exposed to the second radiation either continuously or for one or more periods between the initiating pulses of subsequent first radiation pulse sequences. Preferably, exposure to the second radiation will be in the period in which no field gradients are imposed on the sample, e.g. for at least part, and preferably all, of the delay period between the final FID signal detection period of each sequence and the initial first radiation pulse of the next*" (see also page 4, lines 35 to 39, and page 13, lines 14 to 19). This passage, however, is not clear enough to conclude that it points to the claimed method, without considering the feature of field-cycling. In particular, the alternative of a continuous exposure to the second radiation goes against the teaching of the present invention. By supposition, should an EPI sequence be used, then the

disclosure of D3 would essentially correspond to that of D1. Should instead a sequence be used, which includes a plurality of cycles, each with an RF NMR interrogating signal and field gradients, then it cannot be excluded that the teaching of D3 would correspond to that of D2 without, however, the field-cycling.

4.4 In conclusion, the disclosures of the cited prior art documents, when considered either alone or in combination, do not point to the claimed method in a clear way. On the contrary, the Examining Division's negative assessment of inventive step based on the combination of documents D2 and D1 appears to underestimate aspects of the disclosures leading away from the said combination, so that a risk of an *ex post facto* analysis cannot be excluded, apart from the fact that the combination *per se* does not cover the whole subject-matter claimed.

Therefore, the Board considers appropriate to conclude, in favour of the appellant, that the subject-matter of claim 1 involves an inventive step having regard to documents D1 to D4 (Article 56 EPC).

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the department of the first instance with the order to grant a patent on the basis

of the following documents:

Claims:
No. 1 to 3 filed at the oral proceedings on 13 September 2001,

Description:
Pages 1 to 9 filed with the letter of 13 August 2001,

Drawings:
Figures 1 to 4 of the published application.

The Registrar: The Chairman:

R. Schumacher G. Davies