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Datasheet for the decision of 27 October 2020

Case Number: T 0407/15 - 3.4.01

Application Number: 09719907.9

Publication Number: 2252901

IPC: G01R33/48, G01R33/38, G01R33/381, A61K49/10, G01R33/50, G01R33/44

Language of the proceedings: EN

Title of invention:
SYSTEM AND METHOD FOR MAGNETIC RESONANCE IMAGING

Applicant:
The University Of Western Ontario

Headword:
Protein-binding contrast agent for MRI / The University of Western Ontario

Relevant legal provisions:
EPC Art. 87(1), 56
RPBA 2020 Art. 13(1)

Keyword:
Priority - transfer of priority right - no evidence provided
Inventive step - (no)

Decisions cited:
T 0205/14, T 0788/05

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Case Number: T 0407/15 - 3.4.01

D E C I S I O N
of Technical Board of Appeal 3.4.01
of 27 October 2020

Appellant: (Applicant)	The University Of Western Ontario Gordon Mogenson Building 100 Collip Circle Suite 105 London, Ontario N6G 4X8 (CA)
Representative:	Faulkner, Thomas John Cleveland 10 Fetter Lane London EC4A 1BR (GB)
Decision under appeal:	**Decision of the Examining Division of the European Patent Office posted on 2 October 2014 refusing European patent application No. 09719907.9 pursuant to Article 97(2) EPC.**

Composition of the Board:

Chairman	P. Scriven
Members:	P. Fontenay
	J. Geschwind

Summary of Facts and Submissions

I. The present decision relates to the applicant's appeal of the Examining Division's decision to refuse European patent application 09 719 907.

II. The decision held that the claims on file were unclear (Article 84 EPC) and defined subject-matter extending beyond the content of the original application (Article 123(2) EPC). It further held that the subject-matter of independent claims 1 and 4, and of the dependent claims, was not inventive in the sense of Article 56 EPC in view of document:

D3: S. Ungersma et al., "In Vivo MR Imaging with T1 Dispersion Contrast", Proceedings of the International Society of Magnetic Resonance in Medicine, Berkeley (US), vol. 13, May 2005, page 414.

III. The appellant requested that the decision be set aside and that a patent be granted on the basis of a new set of claims according to a main request or, in the alternative, one of a first, second, or third auxiliary requests. All requests were new with the grounds of appeal.

IV. In the statement of grounds, the appellant explained that claim 1 of each of the new requests was amended with regard to claim 1 underlying the impugned decision so as to address the objections of clarity and added

subject-matter which had led to the refusal of the application.

V. The appellant argued that the objection of lack of inventive step relied on a fundamentally flawed interpretation of the teaching of D3. In particular, nothing justified equating proteins present in tissues to be imaged (muscles) with a contrast agent, as the Examining Division had done. It was also not justified simply to disregard the uniform static polarising field of 0,5 T present in the process of D3 and, instead, to equate such a static polarising field in the intermediate field strength of 52 mT.

VI. The Board arranged oral proceedings.

VII. In a communication under Article 15(1) RPBA, setting out its provisional view, the Board drew the attention of the appellant to the following article:

D9: J. K. Alford et al., "Delta relaxivity enhanced MR (dreMR): Theory of T1-sloped weighted contrast", Proceedings of International Society of Magnetic Resonance in Medicine, Vol. 16, May 2008, page 1443.

VIII. This article refers to the 16th meeting of the ISMRM that took place in Toronto in May 2008, i.e. during the interval between the priority dates (11 March 2008 deriving from US 61/035540, or 12 March 2008 deriving from US61/035777) and filing date (11 March 2009). Its authors include the three inventors named in the

present application. In order to allow the Board to decide on whether D9 belongs to the prior art in the sense of Article 54(2) EPC or not, the appellant was requested to provide evidence that it was indeed entitled to claim priority rights from the earlier US applications.

IX. Its contents reproduce paragraphs [0106] to [0108] as well as figures 6, 7a and 7b of the published application, and the Board considered it particularly relevant to the subject-matter of the requests on file.

X. With regard to the objection of lack of an inventive step, it was acknowledged that the arguments put forward by the appellant regarding document D3 appeared convincing, but the attention of the appellant was drawn to various other issues regarding lack of clarity and added subject-matter.

XI. As to the inventions claimed in the auxiliary requests, the Board noted that the statement of grounds did not provide any reason as to why there would be an inventive step, if the main request did not; and stated that their admissibility would be an issue.

XII. Oral proceedings took place as scheduled before the Board in the presence of the appellant's representative.

XIII. The appellant confirmed that the requests filed with the statement of grounds constituted its final requests on which the Board had to decide.

XIV. Claim 1 of the main request reads:

A magnetic resonance imaging (MRI) method comprising:
acquiring images of target tissue of a subject, wherein the target tissue has a contrast agent therein, using an MRI machine (120), said contrast agent binding to target molecules in the target tissue of said subject and demonstrating magnetic field-dependent variation in MRI relaxation properties, characterized in that said acquiring comprises shifting the strength of the static, uniform polarizing magnetic field (B_0) generated by a polarizing electromagnet (128) of said MRI machine (120) in one of a positive and negative direction ($\pm\Delta B$) to expose the subject to one of an increased or decreased polarizing magnetic field, returning the polarizing magnetic field to its static strength and then acquiring an image (I^+, I^-) of the target tissue in the presence of said static, uniform polarizing magnetic field (B_0) by scanning the target tissue using an RF pulse sequence and sensing signals radiated by excited nuclei in the target tissue in intervals between consecutive pulses of said RF pulse sequence and then shifting the strength of the static polarizing magnetic field (B_0) of said MRI

machine (120) in the other of the positive and negative direction (±ΔB) to expose the subject to the other of the increased or decreased polarizing magnetic field, returning the polarizing magnetic field to its static strength and then acquiring an image (I^+, I^-) of the target tissue in the presence of said static, uniform polarizing magnetic field (B_0) by scanning the target tissue using the RF pulse sequence and sensing signals radiated by excited nuclei in the target tissue in intervals between consecutive pulses of said RF pulse sequence;
normalizing the acquired images; and subtracting one of the normalized acquired images from the other to yield a difference image (I_{Diff}) of the target tissue that is sensitive to variations in the MRI relaxation properties.

XV. Claim 1 of auxiliary request 1 differs from claim 1 of the main request in the step of normalising, which here reads:

... normalizing the acquired images to account for differences in equilibrium magnetization; ...

XVI. Claim 1 of auxiliary request 2 differs from that of auxiliary request 1 in that the contrast agent is *activatable*, which is binding to target molecules in the target tissue, and demonstrates *relaxivity slope changes upon recognition of the target molecules*.

XVII. Claim 1 of auxiliary request 3, in comparison to that of auxiliary request 2, further specifies that the static uniform polarizing magnetic field is allowed to stabilize before acquiring each of both images I^+ and I^-.

XVIII. Each of the main and auxiliary requests includes an independent claim 4 directed to a corresponding MRI system.

Reasons for the Decision

Entitlement to priority

1. The application was initially filed as an international PCT application on 11 March 2009 by The University of Western Ontario. It claims priority rights from the earlier US applications 61/035 540 and 61/035 777 of 11 March 2008 and 12 March 2008, respectively. The application entered into the European phase on 9 September 2010. The entitlement to claim said priority rights is to be assessed on the basis of the relevant provisions of the EPC.

2. Article 87(1) EPC stipulates that

> *A person who has duly filed [...] an application for a patent [...], or his successors in title, shall enjoy, for the purpose of filing a European patent*

application in respect of the same invention, a right of priority [...].

It follows that the applicant who claims a priority right from an (earlier) application must be the same as or, alternatively, the *successor in title* to the applicant who filed said application.

3. US applications 61/035 540 and 61/035 777 were filed jointly by three persons, who happen to be the inventors mentioned in relation to present application. The right of priority belongs to them jointly, as in T 788/05 (point 2).

4. As the applicants of the earlier US applications and later PCT application are not the same, a valid priority claim would require a transfer or rights from the original applicants jointly to the present applicant, before the filing date of the international application.

5. Article 87 EPC does not require an express assignment in writing or exclude a transfer by operation of law or by conduct of the parties concerned implying such transfer (cf. T 205/14, points 3.3 and 3.6). Independently, however, of the form that the transfer of the priority right might have taken, evidence of such a transfer must be provided in order for the Board to decide on the issue. The standard of proof applied is the balance of probabilities.

6. Despite having been invited to do so by the Board, the appellant failed to provide any evidence that such a transfer took place and that it was entitled to claim these priority rights.

7. Both US applications 61/035 540 and 61/035 777 contain a section entitled "Assignee information", identifying "The University of Western Ontario" as assignee. This is, however, not sufficient to establish that the priority rights derived from either application have also been transferred to the applicant.

8. This is a consequence of the fact that the filing of a first application gives rise to two different and independent rights, namely the right to the application in question, and the right of priority. While the sections of the priority documents referred to above appear to provide evidence of a transfer of the right to a patent, it is silent as to any right of priority based on said filings.

9. The fact that the inventors in US applications 61/035 540 and 61/035 777 and the present application are identical, is without any bearing on the legal situation regarding priority, given the absence of evidence of a transfer of priority rights.

10. In the absence of any evidence establishing that the rights of priority have been validly transferred to the applicant, the status of successor in title to the applicants who filed the earlier applications must be denied to the present applicant.

11. In consequence, the applicant is not entitled to either priority.

Main request, novelty

12. It follows that 11 March 2009, the date of filing of the international application, constitutes the

effective date for defining the prior art relevant for deciding on the patentability of the claimed subject-matter.

13. The teaching of document D9 was made available to the public in May 2008. This was not contested by the appellant. The content of D9 is thus prior art in the sense of Article 54(2) EPC.

14. Document D9 discloses a relaxivity-enhanced MR imaging method. It relies on the use of activatable contrast agents that demonstrate steep relaxivity slope changes upon recognition of target molecules. The method takes advantage of the different relaxation rates resulting from said activated contrast agent being exposed to different magnetic field strengths, while non-activated tissues do not.

15.

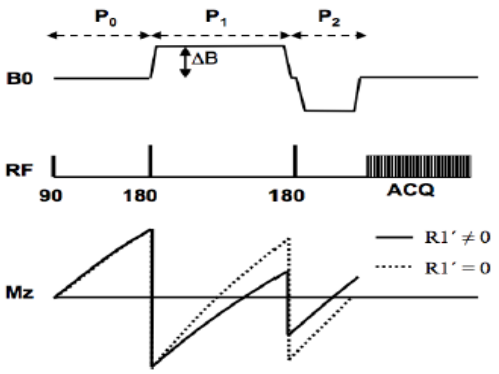


Figure 2 in D9

The pulse sequence presented in D9 (cf. Figure 2, second line) is defined so as to null the longitudinal magnetization of all non-activated tissues while maximising magnetization of activated tissue by the beginning of the acquisition period (cf. Figure 2, lower time series). This is achieved by alternately shifting the strength of the (otherwise) static polarizing magnetic field (B_0) of said MRI machine

(120) in the positive and negative direction (±ΔB) after each of the two inversion pulses (180°), thus amplifying the effect resulting from different relaxations of activated and non-activated tissues.

16. In contrast to this known method, the claimed method requires two successive imaging sequences with, first, the strength of the static polarizing magnetic field shifted in a first direction, followed by a similar imaging sequence with the strength shifted in the opposite direction. The contrast image is eventually obtained from the difference between the two previously obtained images.

17. The claimed method is, therefore, new with regard to the imaging method of D9.

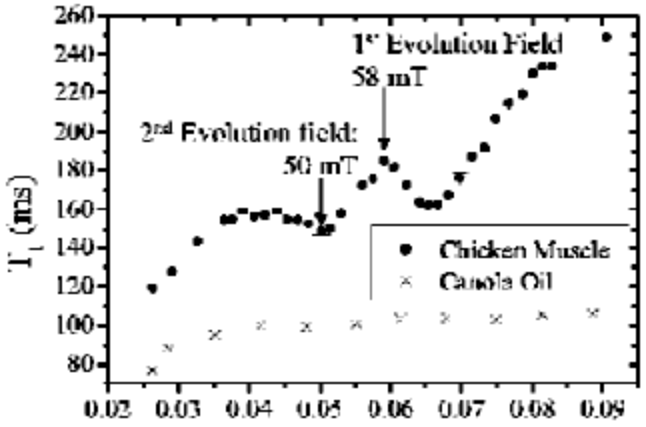
Main request - inventive step

18. D9 discloses a realistic starting point for the assessment of the inventive merits of the claimed invention. In particular, it shares the common principle of relying on contrast agents whose relaxivity properties substantially vary, in dependence on magnetic field strength.

19. The claimed method differs from the method of D9, essentially, in that it relies on two successive imaging phases, during which the strength of the static polarizing magnetic field is shifted in opposite directions. The claimed method is further distinguished from the method disclosed in D9, in that it comprises the steps of normalizing the obtained images before subtracting one from the other.

20. The claimed method defines an alternative pulse sequence implementation of delta relaxation enhanced MRI (cf paragraph [00106] of the published application) that does not require the nulling of longitudinal magnetization of all non-activated tissues.

21. Document D3 belongs to the same field as the invention, and relies on the very same principle that substances with relaxivity depending on the strength of the polarizing magnetic field may provide the basis for contrast images. D3 takes advantage of the presence of proteins in body tissues. This endogenous agent, mostly present in muscles, has the required property, showing a rapidly varying relaxivity in the range 50 mT to 58 mT.



D3, Figure 1
(Relaxation rate versus magnetic polarizing field)

Figure 1 of D3 shows T1 dispersion measurements for muscles and fat samples.

22. As underlined by the appellant, D3 does not rely on the presence of a contrast agent binding to target molecules in the tissues to be imaged. Concretely, no contrast agent in the sense of the present application

is required in the context of D3, since the proteins already present in said tissues show the required magnetic-field-dependent variation in their relaxivity in the range 50 mT to 58 mT (cf. section "Introduction", penultimate sentence).

23. The skilled person would nevertheless have recognised that the principle relied upon in D3 would apply similarly to any contrast agent with a similar dependency, whether it has an endogenous origin or not. This is acknowledged by the applicant in paragraph [0049] of the published application where contrast agents and endogenous substances are presented as alternatives insofar as they provide the required property. That applies to the contrast agent of D9.

24. When applying the imaging method of D3 to the contrast agent of D9, the skilled person would have had no other choice than to select the strength of the magnetic fields for the two successive imaging phases so as to highlight this MRI relaxivity variation of the protein-binding gadolinium chelate used as contrast agent in the context of D9. Instead of the range of 50 - 58 mT adapted to proteins, and an intermediate magnetic strength of 52 mT for the readout phase, the skilled person would have selected values adapted to the activated contrast agent.

25. A characteristic of the relaxivity curve of the activated contrast agent in D9 is its slope in the range 0,5 T - 1,5 T (cf. D9, section "Introduction", penultimate sentence). The simulation carried out in D9 is based on a static polarizing magnetic field of 1,5 T with a shift in the opposite directions of $\pm\Delta B = 0{,}15$ T (cf. section "Methods", two last sentences).

26. Taking account of the fact that, in D9, the values of the static polarizing magnetic field and opposite strength shifts actually selected are satisfactory for discriminating between blood (with activated contrast agent) and other tissues such as fat, muscles, white matter and grey matter, the skilled person would have had no incentive to select other values.

27. It is stressed, in this respect, that the ability of the method of D9 to discriminate between, on the one hand, enhanced blood, and, on the other hand, fat and other unenhanced biological tissues, is a direct consequence of the steep slope of the relaxivity curve for the activated agent and the corresponding rather flat characteristic of the non-activated agent or surrounding tissues.

28. Concretely, when searching for alternative methods to emphasise contrast resulting from the protein-binding gadolinium chelates disclosed in D9 binding to proteins, the skilled person would have had no other choice than to carry out measurements in the range around 1,5 T for which variation of the relaxation rate are expected to be highest.

29. Relying, then, on the teaching of D3, the skilled person would have considered carrying out two successive image acquisition processes, each comprising shifting the strength of the static, uniform polarizing magnetic field of 1,5 T generated by the polarizing electromagnet of said MRI machine of D9 in one of the positive and negative directions. The shift required depends on the contrast agent actually used. It follows from the assumption made above, with regard to the protein-binding gadolinium chelate, that a shift of ±0,15 T, as proposed in D9, is perfectly adapted.

30. As further suggested in D3, the polarizing magnetic field is then returned to its intermediate static strength of 1,5 T before acquisition of an image of the target tissue in the presence of said static, uniform polarizing magnetic field of 1,5 T by scanning the target tissue using an RF pulse sequence and sensing signals radiated by excited nuclei in the target tissue in intervals between consecutive pulses of said RF pulse sequence.

31. In order to obtain a final image indicative of the presence of the target molecules, subtraction of one of the acquired images from the other is carried out, as suggested in D3.

32. D3 is silent as to the necessity of normalizing the two images obtained before the subtracting step. This is an additional distinguishing feature of the claimed method, compared to the method of D9, for which no such step is actually required.

33. The Board, however, considers that image normalization is common practise in the field of image processing, when images are to be compared. It would have thus been straightforward to carry out such a step on each of the successively obtained images, and the skilled person would have done it when needed.

34. Claim 1 does not specify which criterion is to be considered when carrying out the step of normalisation. It might rely on a large variety of criteria depending on the information that should be emphasised in the resulting images. In the context of the invention, and taking account of the fact that modifications of the static polarizing magnetic field strength B_0 directly affects the steady-state longitudinal magnetization M_0

(cf. equations 3 and 4, page 17) and consequently also the voxel intensity images (I^+, I^-) (cf equations 5, 6 page 17), it would have been obvious to normalize said images in order, specifically, to take into account the different equilibrium magnetizations in the two intermediate images.

35. For these reasons, the claimed method results in an obvious manner from the teaching of D9, adapted in the light of the imaging process disclosed in D3.

36. The MRI method of claim 1 is thus not inventive in the sense of Article 56 EPC.

Auxiliary requests 1, 2 and 3

37. Since Document D9 was introduced into the appeal proceedings by the Board, the statement of grounds does not explain why, if the invention defined in the claims of the main request does not involve an inventive step with regard to D9, those of the auxiliary requests do. They were, apparently, submitted to address the Examining Division's objections under Article 123(2) EPC and do not address the objection raised above with regard to the main request. This was not contested by the appellant.

38. For the following reasons, the Board does not consider these requests suitable for overcoming a lack of inventive step, and declines to admit them.

39. Claim 1 of auxiliary request 1 specifies that the steps of normalizing are performed in order to account for differences in equilibrium magnetization.

40. As observed above with regard to claim 1 of the main request, it would have been obvious, considering that voxel magnetizations are proportional to the steady state longitudinal magnetization M_0, to normalise the intermediate images to account for differences in said equilibrium magnetizations.

41. Claim 1 of auxiliary request 2 specifies that the contrast agent is activatable, and that the activatable contrast agent binding to target molecules in the target tissue demonstrates changes in relaxivity slope upon recognition of the target molecules.

42. The additional feature reflects a key aspect of the teaching of D9. As elaborated above, the objection of lack of inventive step of claim 1 of the main request, starts from the use of the protein-binding contrast agent disclosed in D9. Thus the amended feature does not affect the reasoning developed above.

43. Claim 1 of auxiliary request 3 further specifies that the static uniform polarizing magnetic field is allowed to stabilize before the acquisition of images I^+ and I^-.

44. The skilled person was well aware that the stability of the static uniform polarizing magnetic field is a prerequisite for reliable measurement. It was well known that spatial or temporal fluctuations of the field directly influence the measurements carried out in terms of location of the voxels actually contributing to the measured signal.

45. In conclusion, the amendments to claim 1 in auxiliary requests 1, 2 and 3 do not affect the conclusion

reached above with regard to claim 1 of the main request as to the lack of an inventive step.

Order

For these reasons it is decided that:

The appeal is dismissed

The Registrar: The Chairman:

H. Jenney P. Scriven

Decision electronically authenticated