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- (81) **Designated States (unless otherwise indicated, for every kind of national protection available):** AE, AG, AL, AM,

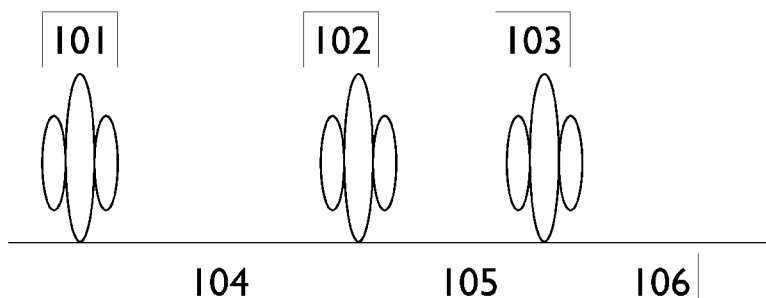
AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE,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

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- Published:**
  - with international search report (Art. 21(3))
  - before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))
- (88) **Date of publication of the international search report:**  
6 December 2012

(54) **Title:** USE OF MAGNETIC RESONANCE TECHNIQUES FOR MOLECULAR DETECTION

Fig. 1



(57) **Abstract:** System and methods are provided to perform non-invasive, real-time, continuous or episodic molecular detection and quantification of molecular species in a sample or animal or human subject using magnetic resonance. Such systems and methods may be applied to identify and quantify molecular species found in the body, which may be useful for many aspects of medical care including without limitation prenatal diagnosis, detecting deep skin infections, performing cerebral spinal fluid assessment, measuring arterial blood gases, blood glucose, cardiac biomarkers, and creatinine flow rates. The non-invasive, quantification of such molecular species continuously in real time enables significantly more attractive methods of diagnosis, monitoring and therapy than existing methods and protocols.



## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 12/28455

<b>A. CLASSIFICATION OF SUBJECT MATTER</b> IPC(8) - G01R 33/46; G01R 33/44; G01R 33/20 (2012.01) USPC - 324/312; 324/318 According to International Patent Classification (IPC) or to both national classification and IPC		
<b>B. FIELDS SEARCHED</b> Minimum documentation searched (classification system followed by classification symbols) IPC(8)- G01R 33/46; G01R 33/44; G01R 33/20 (2012.01); USPC- 324/312; 324/318 Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Patents and NPL (classification, keyword; search terms below) Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) PubWest (US Pat, PgPub, EPO, JPO), GoogleScholar (PL, NPL), FreePatentsOnline (US Pat, PgPub, EPO, JPO, WIPO, NPL); Search terms used: magnetic, resonance, stead, state, signal, background, water, substance, compound, enhance, amplify, emit, emanate, target, field, repeat, pattern, dentify, analysis, chemical, shift, resonance, alpha, glucose, BI		
<b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2010/110881 A1 (HETHERINGTON et al.) 30 September 2010 (30.09.2010), pg 1, ln 13-20; pg 9, ln 15 to pg 14, ln 21; pg 20, ln 1-21; pg 21, ln 16-19; pg 22, ln 13-20; pg 24, ln 9 to pg 25, ln 10; pg 26, ln 17-21; pg 27, ln 13-24; pg 28, ln 10-14; pg 47, ln 15-25; pg 57, ln 22 to pg 61, ln 22; pg 74, ln 18 to pg 76, ln 15; pg 78, ln 20-28; pg 93, ln 3-25; pg 109, ln 20-27; pg 110, ln 16 to pg 114, ln 17; pg 116, ln 14 to pg 117, ln 13; pg 118, ln 3-21	2, 3/(2)-6/(2)
Y		1, 3/(1)-8/(1), 7/(2), 8/(2), 9-24
Y	US 2010/0271020 A1 (DOYLE) 28 October 2010 (28.10.2010), para [0003], [0005], [0009], [0033], [0049], [0053]	1, 3/(1)-6/(1), 7/(2), 8/(2)12-24
Y	US 2008/0129298 A1 (VAUGHAN et al.) 05 June 2008 (05.06.2008), para [0005], [0061], [0169], [0185], [0214], [0225], [0230], [0232], [0256], [0285], [0325], [0433]	7/(1), 7/(2), 8/(1), 8/(2), 9-11, 17
Y	US 2007/0196280 A1 (SHEN) 23 August 2007 (23.08.2007), para [0006], [0007], [0025], [0029], [0037], [0041], [0047], [0061], [0065]	15
Y	US 2010/0286502 A1 (VAN ZIJL et al.) 11 November 2010 (11.11.2010), para [0012]-[0017], [0025], [0027], [0031], [0037]	23, 24
Y, E	US 2012/0112748 A1 (HETHERINGTON et al.) 10 May 2012 (10.05.2012), para [0019]-[0444]	1-24
Y, P	US 2011/0279117 A1 (ALFORD et al.) 17 November 2011 (17.11.2011), para [0012]-[0120]	1-24
Y	US 2007/0194788 A1 (PINES et al.) 23 August 2007 (23.08.2007), para [0020]-[0063]	1-24
Y	US 5,317,265 A (WEINSTOCK et al.) 31 May 1994 (31.05.1994), col 1-2	1-24
<input type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/>		
* Special categories of cited documents: "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier application or patent but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family		
Date of the actual completion of the international search 15 August 2012 (15.08.2012)		Date of mailing of the international search report 03 OCT 2012
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201		Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 12/28455

**Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
  
2.  Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
  
3.  Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

The following claim groups were found:

- Group I: Claims 1-24
- Group II: Claims 25-26
- Group III: Claims 27-34

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

-- Please see Extra Sheet --

1.  As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2.  As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3.  As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
  
4.  No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:  
1-24

- Remark on Protest**
- The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
  - The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
  - No protest accompanied the payment of additional search fees.

Continued from Box No. III, Observations where unity of invention is lacking:

The following claim groups were found:

Group I: Claims 1-24

Group II: Claims 25-26

Group III: Claims 27-34

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I: is drawn to a nuclear magnetic resonance steady state method with a tailored response function operable to suppress the signal from water or other substances and to enhance the signal from one or more target substances in a sample comprising determining a target resonance or resonances, generating a repeated electromagnetic field pattern comprising at least one of the following continuous, non-instantaneous pulses, soft pulses, or spin lock drives, adiabatic pulses, time varying, swept, frequency modulated, phase modulated, or amplitude modulated drives, stochastic drives, random and pseudo-random drives, combinations of drive elements and free precession delays or phase increments operable to enforce or approach closed loop magnetization trajectories after one or more pulse group operations, one or more time delays, stochastic time delays, phase increments, time-varied magnetic field gradients, time-varied magnetic fields, exposing a portion of said sample to said electromagnetic field pattern operable to drive the said target substance system toward or in a steady state cycle, suppress the signal from water, other metabolites, or non-target resonances, enhance the signal from the target resonance or resonances, cause fields to emanate from the said target substance in said sample, detecting said emitted fields from said target substance, analyzing said emitted fields.

Group II: is drawn to a method to alter the approach to a steady state cycle in a SSFP-like sequence using a sequence of elements comprising at least one of time varied magnetic field gradients, discrete RF pulses at least partially in the transverse plane, continuous drive patterns causing adiabatic transformations, spin lock drives, non-uniform in time, amplitude, phase, or frequency pulse trains and further comprising: modulating the static magnetic field or reference frequency, detecting in a phase sensitive manner the response signals, frequency filtering the detected signals, adjusting the modulation amplitude or frequency based on the detected signals.

Group III: is drawn to a system to detect a target substance in a sample using magnetic resonance comprising: a source of electromagnetic field patterns that can cause fields to emanate from said target substance in a said subject, a detector to measure said emitted fields from said target substance and, a processor to analyze the said emitted fields.

The inventions listed in the above-mentioned groups do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Groups I-III lack unity of invention, because even though the inventions of these groups require the technical features of a source generating electromagnetic field patterns that can cause fields to emanate from said target substance in a said subject, a detector detecting emitted fields from said target substance and, a processor to analyze the said emitted fields, these technical features are not special technical features as they do not make a contribution over the prior art in view of US 5,317,265 A to Weinstock et al. (hereinafter Weinstock), which discloses a source generating electromagnetic field patterns (col 1, ln 23-25; col 2, ln 5-7) that can cause fields to emanate from said target substance, a detector detecting emitted fields from said target substance (col 2, ln 25-33) and, a processor to analyze the said emitted fields (col 2, ln 46-49).

Groups I and II lack unity of invention, because even though the inventions of these groups require the technical feature of time varied magnetic field gradients, this technical feature is not a special technical feature as it does not make a contribution over the prior art in view of US 2007/0194788 A1 to Pines et al. (hereinafter Pines), which discloses time varied magnetic field gradients (para [0057]; claim 5).

It would have been obvious to use the time varied magnetic field gradients, as disclosed by Pines, in generating the electromagnetic field patterns, as taught by Weinstock, to improve signal-to-noise ratios while compensating for magnetic field inhomogeneities (see Pines, para [0005]).

Groups I-III therefore lack unity under PCT Rule 13 because they do not share a same or corresponding special technical feature.