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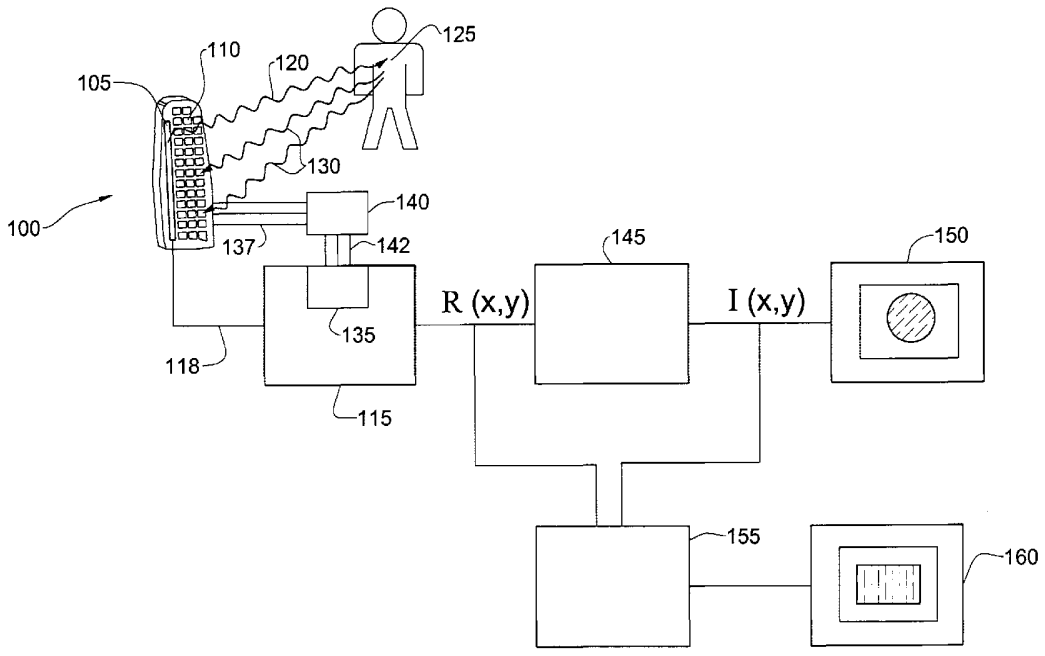
For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: SYSTEM AND METHOD FOR ANALYSIS OF A TISSUE



(57) Abstract: A method and system for assessing a spatial regularity of reflecting members in a tissue. The method comprises irradiating the tissue and detecting wave reflected or transmitted by the tissue. One or more parameters are then calculated, based upon the reflected or transmitted waves, indicative of a degree of spatial disorder of reflecting members in the tissue.

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SYSTEM AND METHOD FOR ANALYSIS OF A TISSUE

FIELD OF THE INVENTION

This invention relates to methods for analyzing data obtained by irradiating biological tissues or organs.

BACKGROUND OF THE INVENTION

Imaging methods such as ultrasound (US), magnetic resonance imaging (MRI), and computer tomography (CT), are widely used because of their ability to non-invasively image body organs and tissues with minor deleterious effects. In these techniques, an organ or tissue is irradiated with sonic or electromagnetic waves. The waves reflected or scattered by the organ or tissue are recorded and processed into a digital image.

SUMMARY OF THE INVENTION

The present invention is based upon the finding that healthy tissue may be distinguished from its malignant counterpart by the way the tissue reflects radiation energy. The organization of reflecting members in a healthy tissue is more spatially regular than in malignant tissue. The invention my thus be used in the diagnosis of cancer or other disorders involving alterations in the organization or texture of a tissue, such as the presence of a liquid filled cyst.

In accordance with the invention, a tissue is irradiated and the reflected or transmitted waves are detected. An analysis is performed on the reflected or transmitted waves in order to generate one or more parameters indicative of a degree of spatial disorder of the reflecting members in the tissue. In one

embodiment of the invention, a calculated parameter value is compared to a predetermined threshold. If the calculated parameter value exceeds the threshold, the tissue is determined to be malignant. A tissue having a calculated parameter value less than the threshold is a healthy tissue. In another embodiment, one or more calculated parameters are input to an expert system such as a neural network. The neural system makes an assessment as to whether the tissue is healthy or malignant based upon the input parameter values. Expert systems are known, for example as disclosed in Kadah et al., IEEE Transactions, vol. 15, No.4, pages 472-473, 476-477, Aug. 1996.

The invention may be carried out using any form of irradiation such as electromagnetic radiation or sonic radiation. In particular, the invention may be applied to waves reflected in an ultrasound, CT, or MRI procedure.

The analysis of the detected reflected waves may be performed using any mathematical method for evaluating a degree of periodicity. The analysis may thus involve, for example, a Fourier analysis, a wavelet analysis, or an entropy analysis. The analysis may be performed on complex raw data obtained from the reflected waves. Alternatively, an image may be generated from the complex raw data, and the analysis performed on the image.

In another of its aspects, the invention provides a method for generating an image of the tissue based upon the reflected, scattered, or transmitted waves using non-Fourier analysis. This produces an image of better resolution and contrast than is obtainable by a Fourier analysis of the reflected or scattered waves, which is the present standard of existing signal processing algorithms. Methods for non-Fourier analysis of scattered or reflected waves are known in the art, for example, as disclosed in Degraaf, S., IEEE Trasactions on Image Processing, Vol. 7, No.5, May 1998. As shown in this reference, the non-Fourier analysis may utilize for example, Capon's minimum variance method.

Thus in its first aspect, the invention provides a method for assessing a spatial regularity of reflecting members in a tissue, comprising steps of:

(a) irradiating the tissue;

(b) detecting waves reflected or transmitted by the tissue; and

(c) calculating one or more parameters indicative of a degree of spatial disorder of reflecting members in the tissue based upon the reflected or transmitted waves.

In its second aspect, the invention provides, a method for determining whether a tissue is malignant comprising steps of;

(a) irradiating the tissue;

(b) detecting waves reflected or transmitted by the tissue;

(c) calculating a parameter indicative of a degree of spatial disorder of reflecting members in the tissue based upon the reflected or transmitted waves; and

(d) comparing the parameter to a predetermined threshold;

the tissue being malignant if the parameter exceeds the predetermined threshold.

In its third aspect, the invention provide a method for determining whether a tissue is malignant comprising steps of;

(a) irradiating the tissue;

(b) detecting waves reflected or transmitted by the tissue;

(c) calculating one or more parameters indicative of a degree of spatial disorder of reflecting members in the tissue based upon the reflected or transmitted waves; and

inputting the one or more parameters into an expert system so as to generate an assessment as to whether the tissue is malignant.

In its fourth aspect, the invention provides a system for assessing a spatial regularity of reflecting members in a tissue, comprising:

(a) a wave source configured to irradiate the tissue;

(b) a wave detector configured to detect waves reflected or transmitted by the tissue; and;

(c) a processor configured to calculate a parameter indicative of a degree of spatial disorder of reflecting members in the tissue based upon the reflected or transmitted waves.

In its fifth aspect, the invention provides, a system for determining whether a tissue is malignant comprising:

(a) a wave source configured to irradiate the tissue;

(b) a wave detector configured to detect waves reflected or transmitted by the tissue;

(c) a processor configured to calculate a parameter indicative of a degree of spatial disorder of reflecting members in the tissue based upon the reflected or transmitted waves.

In its sixth aspect, the invention provides a method for determining whether a tissue is malignant comprising steps of;

(a) irradiating the tissue;

(b) detecting waves reflected, scattered, or transmitted by the tissue;

(c) performing an analysis of the reflected, scattered, or transmitted waves;

(d) inputting the results of the analysis into an expert system.

In yet another aspect, the invention provides a method for generating an image of the tissue, comprising steps of:

(a) irradiating the tissue;

(b) detecting waves reflected or transmitted by the tissue; and

performing a non-Fourier analysis of the detected waves so as to produce an image of he tissue.

BRIEF DESCRIPTION OF THE DRAWINGS

In order to understand the invention and to see how it may be carried out in practice, a preferred embodiment will now be described, by way of non-limiting example only, with reference to the accompanying drawings, in which:

Fig. 1 shows a system for analyzing reflected waves in accordance with one embodiment of the invention;

Fig. 2 shows a Fourier analysis of healthy (a,d), malignant (b,e) and benign (c,f) ovarian tissue in accordance with one embodiment of the invention;

Fig. 3 shows a wavelet analysis of healthy (a) malignant and benign (c) ovarian tissue, in accordance with another embodiment of the invention; and

Fig. 4 shows an entropy analysis of healthy malignant and benign ovarian tissue.

DETAILED DESCRIPTION OF THE INVENTION

Fig. 1 shows a system for analyzing biological tissues or organs in accordance with one embodiment of the invention. A transducer **100** contains a wave generator **105** for generating waves. The generated waves may be sonic waves or electromagnetic waves. The transducer also comprises an array of detectors **110** that detect reflected waves. A processor **115** is used to select the properties of the generated waves (e.g. amplitude and wavelength) via a signal **118** input to the wave generator **105**. The wave generator **105** is used to produce generated waves **120** that irradiate a tissue or organ **125.** Waves **130** reflected by the organ or tissue **125** are detected by the detectors **110** in the transducer **105.** The wave detected by each detector is converted by the detector into an analog voltage dependent signal that is sampled by an analog to digital converter **140.** The digital samples **142** are then input to the processor **115.** The processor **115** calculates a phase for each sample based upon the signal **118** and stores the digital samples in a memory **135** in the form of complex raw data R(x,y).

A second processor **145** is configured to receive the complex raw data R(x,y) from the memory **135** and process the complex raw data into an image I(x,y) as is known in the art. The image may be displayed on a display such as a CRT **150.**

In accordance with the invention, a third processor **155** is configured to analyze the tissue by processing either the raw data R(x,y) or the processed image data I(x,y). The results of the analysis may be displayed on a display such as the CRT **160.**

EXAMPLES

Example 1: Fourier analysis of ultrasound images.

Fig. 2 shows an ultrasound image I(x,y) of human ovary tissue from a healthy ovary (a) from a malignant ovarian tumor (b), and a benign ovarian tumor (c), as determined by histological examination of the tissues. (e) (f) and (g) show the Fourier transform $F(y,\omega)=\int I(x,y)e^{i\omega x}dx$ of a 30X30 pixel square from the image shown in (a) (b) and (c), respectively. The energy of each Fourier transform was measured by evaluating the sum $\sum|\partial F/\partial y|$ over the range of $1\leq y\leq 28$ and $34\leq\omega\leq 64$. The energy calculated for the normal tissue (a,d) was 3, for the malignant tissue (b,e) 8, and for the benign tissue, 3. An analysis of 30 ovarian tissues showed that by this method of calculating energy, healthy ovarian tissues have an energy in the range of about 2 to 4, while malignant ovarian tissues have an energy in the range of about 7-9. Ovarian tissues having a benign growth were indistinguishable from healthy ovarian tissues. The method of the invention may thus be used for identifying malignant tissues. Other methods may be used for measuring energy may also be used in accordance with the invention such as calculating a volume under the Fourier transform.

Example 2: Wavelet analysis of ultrasound images.

Fig. 3 shows a wavelet analysis of the three images I(x,y) shown in Fig. 2. The 30X30 pixel square from each image was input to the wavelet analysis software of the Matlab™ wavelet toolbox. The B-orthogonal filter was used with a decomposition level equal to 1. The output of this software is four matrices known as the principle image coefficients (A), horizontal coefficients (H), vertical image coefficients (V) and the diagonal coefficients (D). Fig. 3 shows the contour graph of the coefficients of the A matrix obtained for each image. The maximum of each contour graph was used as an index. The index of the malignant tissue is 204, of the benign tissue 162 and the healthy tissue 90. An analysis of 30 ovarian tissues showed that malignant tissues have indices 2-2.5 times those of healthy tissues. Other indices maybe also used in accordance with the invention when using wavelet analysis such as the maximum coefficient in sum of the H, V, and D

coefficient matrices. Other filters may be used in accordance with the invention such as a Mexican hat filter, as are known in the art.

Example 3: Entropy analysis of ultrasound images.

Fig. 4 shows the results of an analysis of entropy in 60 images of ovaries. The state (healthy, benign or malignant) was determined for each ovary by histological methods. For each image, a 30X30 pixel square was selected and an entropy E was calculated for each square as follows. For each pixel I(x,y), a parameter A(x,y) was calculated by $A(x,y)=\frac{1}{n}\sum\left|I(x,y)-I(x',y')\right|^2$, where the sum extends over all pixels (x',y') in the square neighboring the pixel (x,y), and n is the number of pixels neighboring the pixel (x,y). The entropy was then calculated as the average of the A(x,y) over the entire square. As shown in Fig. 4, images of healthy ovaries were found to have the lowest entropy (in the range of 2 to 4.3). Images from malignant ovaries have high entropies (6.9-8.3). Images from benign tissues have intermediate to high values of entropy (4.9-8.3).

CLAIMS:

1. A method for assessing a spatial regularity of reflecting members in a tissue, comprising steps of:
   (a) irradiating the tissue;
   (b) detecting waves reflected or transmitted by the tissue; and
   (c) calculating one or more parameters indicative of a degree of spatial disorder of reflecting members in the tissue based upon the reflected or transmitted waves.

2. The method of Claim 1 wherein the tissue is irradiated with a form of radiation selected from the group comprising:
   (a) sonic radiation; and
   (b) electromagnetic radiation.

3. The method of Claim 2 wherein the tissue is irradiated in a procedure selected from the group comprising:
   (a) an ultrasound procedure;
   (b) a CT procedure; and
   (c) an MRI procedure.

4. The method of Claim 1 wherein the one or more parameters are obtained in a calculation based upon complex raw data obtained from the detected reflected or transmitted waves.

5. The method of Claim 4 wherein the one or more parameters are obtained in a calculation involving an analysis selected from the group of:
   (a) a Fourier analysis of the complex raw data;
   (b) a wavelet analysis of the complex raw data; and
   (c) an entropy analysis of the complex raw data.

6. The method of Claim 1 further comprising a step of generating an image of the tissue based upon the detected reflected or transmitted waves and wherein the one or more parameters are obtained in a calculation based upon the image.

7. The method of Claim 6 wherein the parameter is obtained in a calculation involving an analysis selected from the group of

(a) a Fourier analysis of the image;

(b) a wavelet analysis of the image; and

(c) an entropy analysis of the image.

8. A method for determining whether a tissue is malignant comprising steps of;

(a) irradiating the tissue;

(b) detecting waves reflected or transmitted by the tissue;

(c) calculating a parameter indicative of a degree of spatial disorder of reflecting members in the tissue based upon the reflected waves; and

(d) comparing the parameter to a predetermined threshold;

the tissue being malignant if the parameter exceeds the predetermined threshold.

9. A method for determining whether a tissue is malignant comprising steps of;

(a) irradiating the tissue;

(b) detecting waves reflected or transmitted by the tissue;

(c) calculating one or more parameters indicative of a degree of spatial disorder of reflecting members in the tissue based upon the reflected or transmitted waves; and

(d) inputting the one or more parameters into an expert system so as to generate an assessment as to whether the tissue is malignant.

10. The method according to Claim 9 wherein the expert system is a neural network.

11. A system for assessing a spatial regularity of reflecting members in a tissue, comprising:

(a) a wave source configured to irradiate the tissue;

(b) a wave detector configured to detect waves reflected or transmitted by the tissue; and

(c) a processor configured to calculate a parameter indicative of a degree of spatial disorder of reflecting members in the tissue based upon the reflected or transmitted waves.

12. The system of Claim 11 wherein the wave source is configured to irradiate the tissue with a form of radiation selected from the group comprising:

(a) sonic radiation; and

(b) electromagnetic radiation.

13. The system of Claim 12 configured to carry out a procedure selected from the group comprising:

(a) an ultrasound procedure;

(b) a CT procedure; and

(c) an MRI procedure.

14. The system of Claim 11 wherein the parameter is obtained in a calculation based upon complex raw data obtained from the detected reflected or transmitted waves.

15. The system of Claim 14 wherein the parameter is obtained in a calculation involving an analysis selected from the group of:

(a) a Fourier analysis of the complex raw data;

(b) a wavelet analysis of the complex raw data; and

(c) an entropy analysis of the complex raw data.

16. The system of Claim 11 wherein the processor is further configured to generate an image of the tissue based upon the detected reflected or transmitted waves and wherein the parameter is obtained in a calculation based upon the image.

17. The system of Claim 16 wherein the parameter is obtained in a calculation involving an analysis selected from the group of

(a) a Fourier analysis of the image;

(b) a wavelet analysis of the image; and

(c) an entropy analysis of the image.

18. A system for determining whether a tissue is malignant comprising:

(a) a wave source configured to irradiate the tissue;

(b) a wave detector configured to detect waves reflected or transmitted by the tissue;

(c) a processor configured to calculate a parameter indicative of a degree of spatial disorder of reflecting members in the tissue based upon the reflected or transmitted waves.

19. The system of Claim 18 wherein the processor is further configured to compare the parameter to a predetermined threshold.

20. A method for determining whether a tissue is malignant comprising steps of;

(a) irradiating the tissue;

(b) detecting waves reflected or scattered by the tissue;

(c) performing an analysis of the reflected or scattered waves;

(d) inputting the results of the analysis into an expert system.

21. The method of Claim 20 wherein the analysis involves one or more processes selected from the group of:

(a) a Fourier analysis of the complex raw data;

(b) a wavelet analysis of the complex raw data; and

(c) an entropy analysis of the complex raw data..

22. A method for generating an image of the tissue, comprising steps of:

(c) irradiating the tissue;

(d) detecting waves reflected or transmitted by the tissue; and

(e) performing a non-Fourier analysis of the detected waves so as to produce an image of he tissue.

23. The method of Claim 22 wherein the non-Fourier analysis is a minimum variance method.

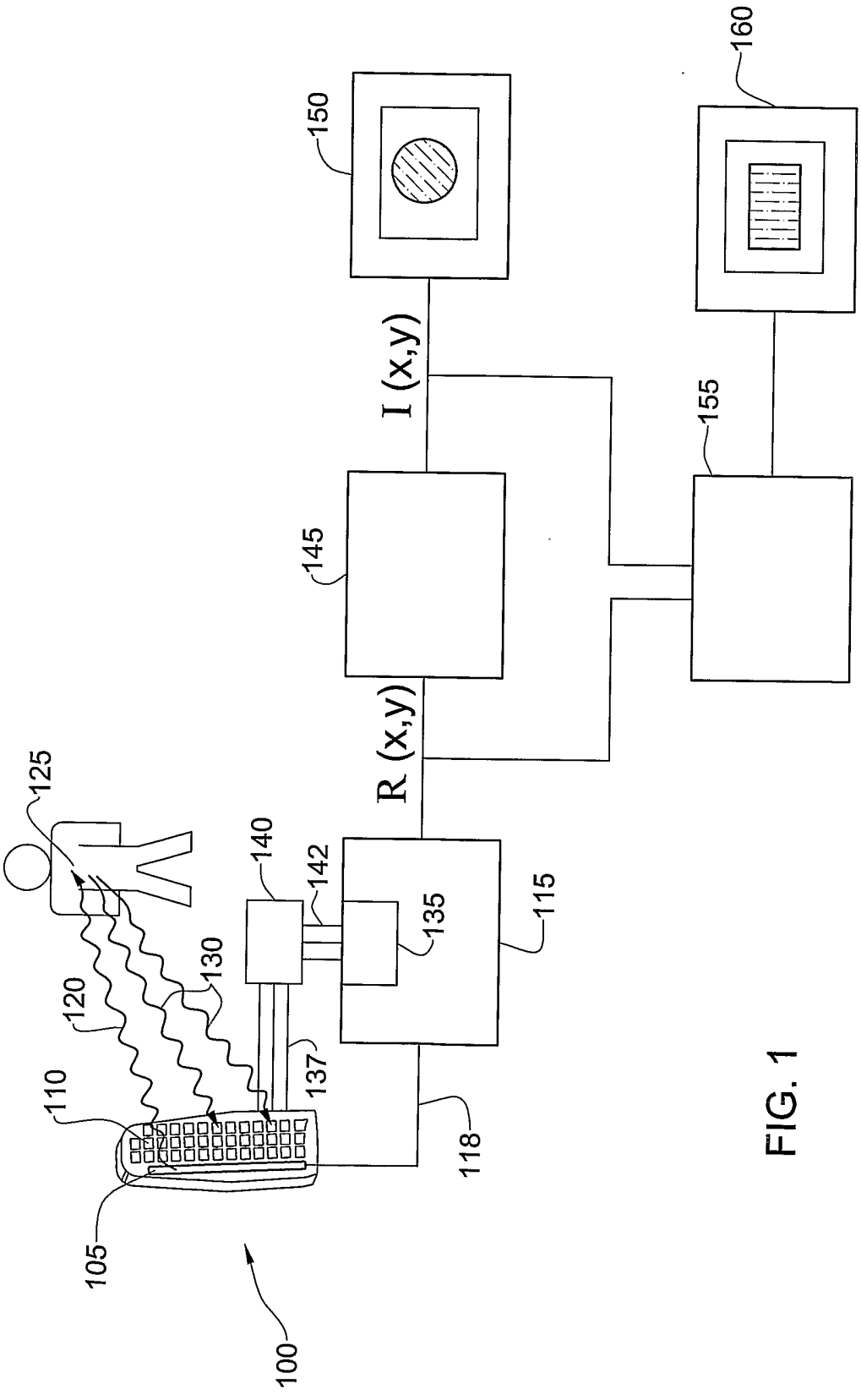
160
150
I (x,y)
155
145
R (x,y)
125
140
142
135
115
130
120
137
110
118
105
100

FIG. 1

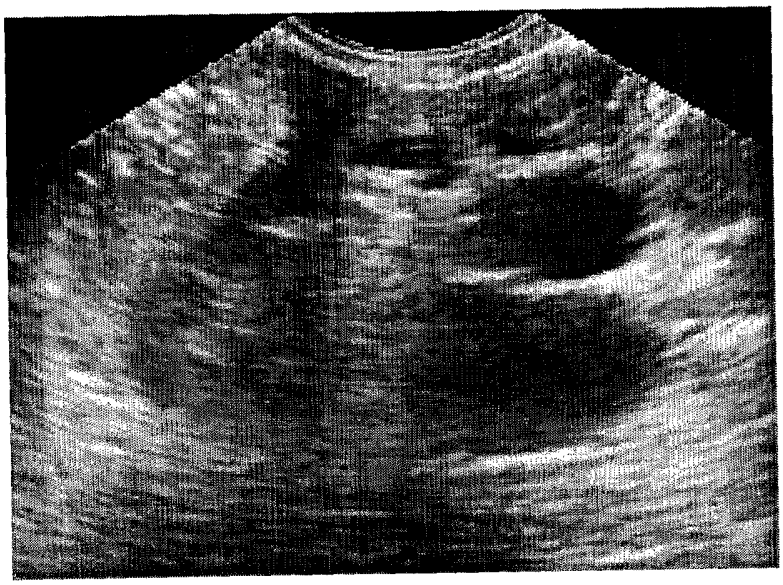

FIG. 2A

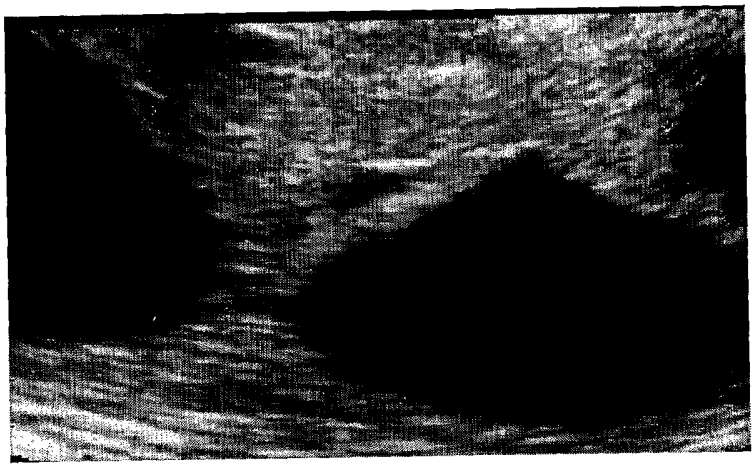

FIG. 2B

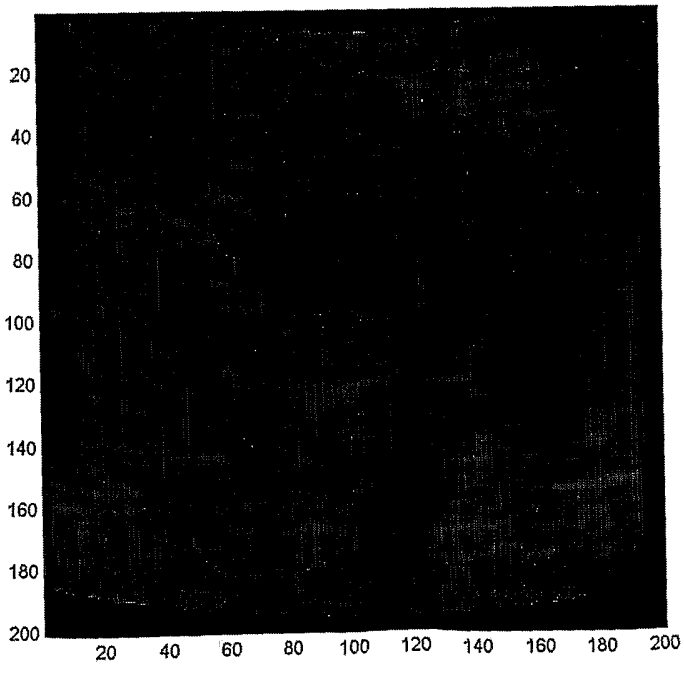

FIG. 2C

HEALTHY

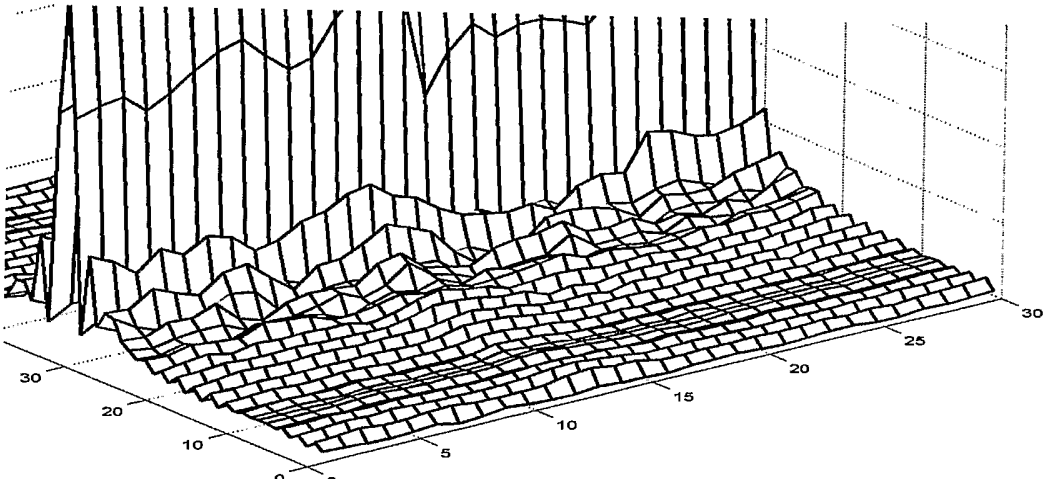

FIG. 2D

MALIGNANT

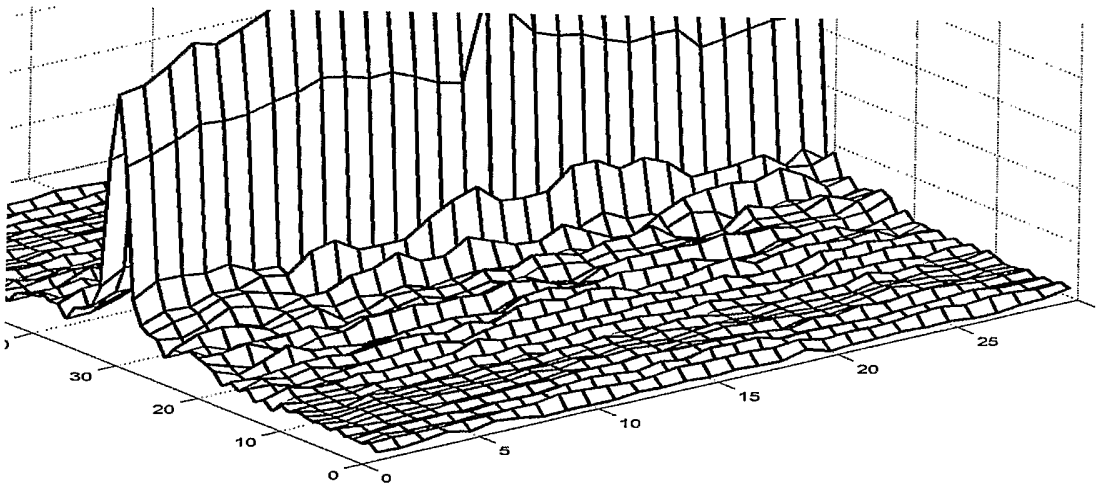

FIG. 2E

BENIGN

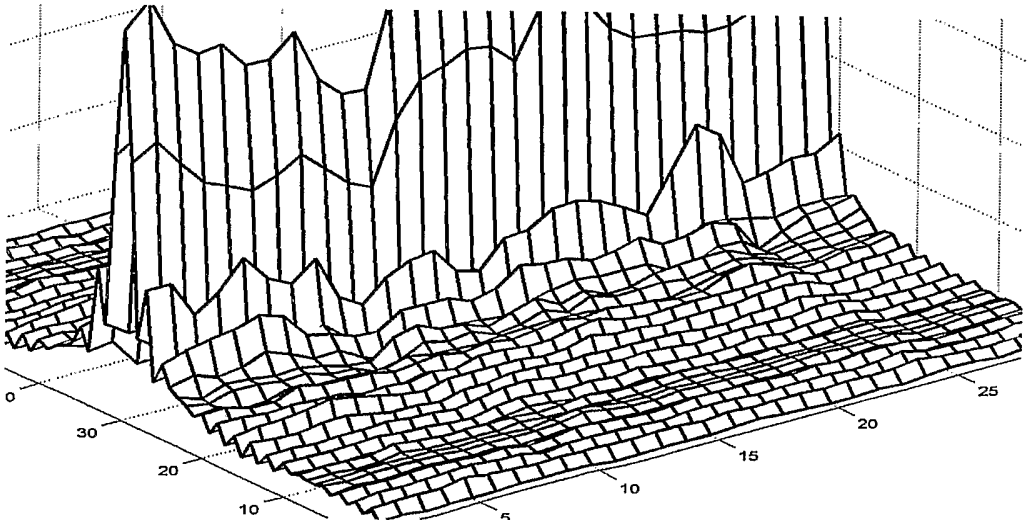

FIG. 2F

HEALTHY

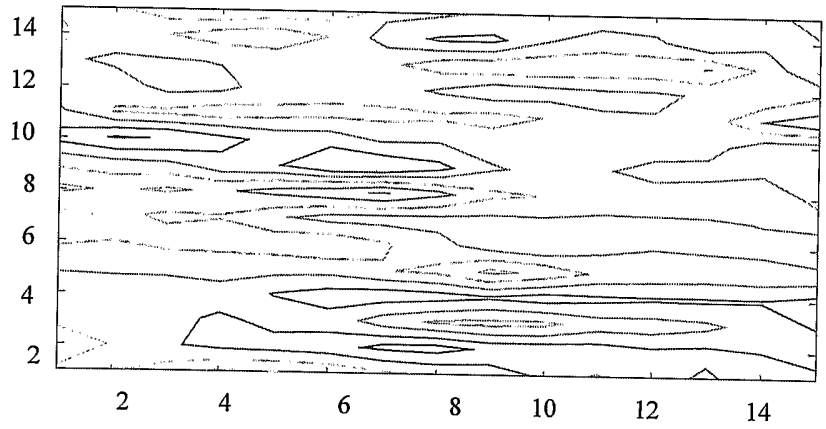

FIG. 3A

MALIGNANT

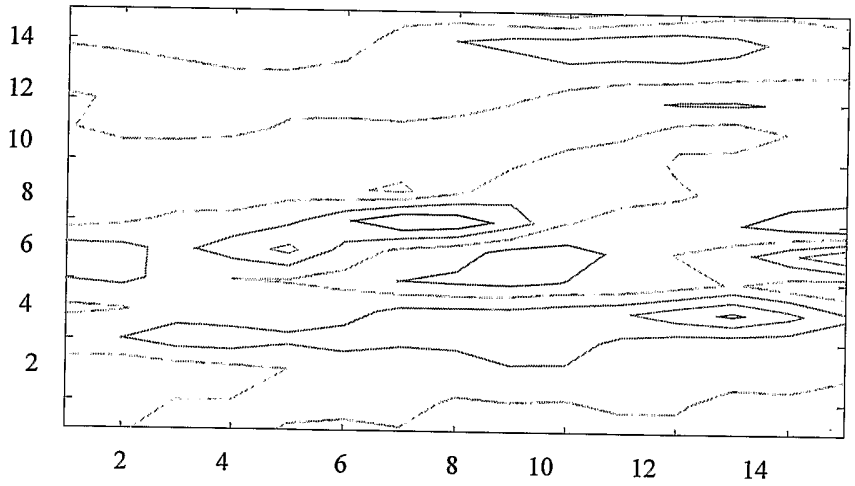

FIG. 3B

BENIGN

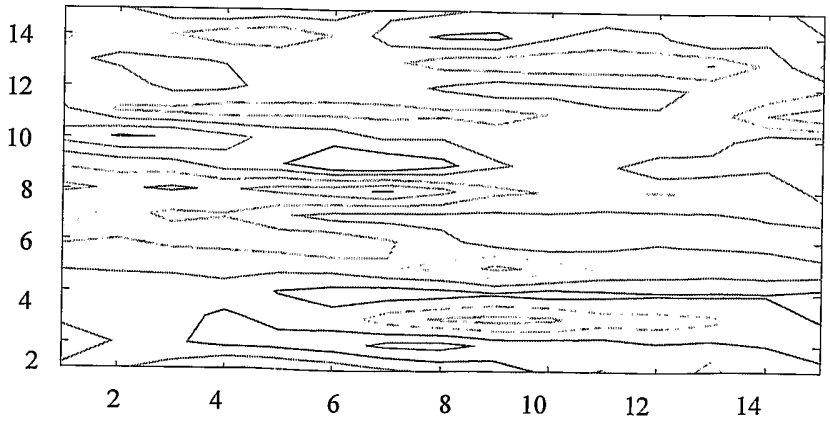

FIG. 3C

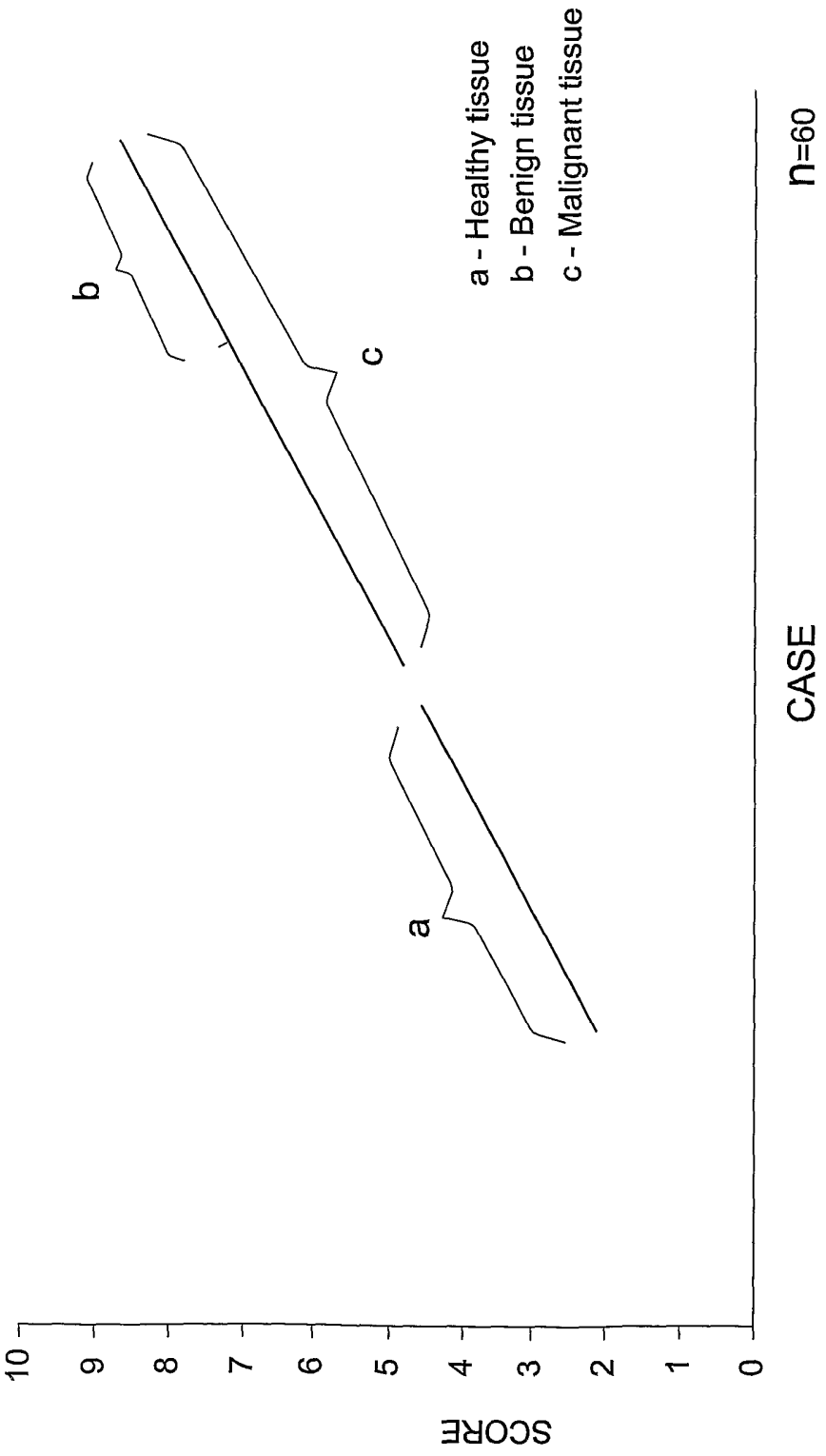
a - Healthy tissue
b - Benign tissue
c - Malignant tissue
a
b
c
SCORE
0
1
2
3
4
5
6
7
8
9
10
CASE
n=60

FIG. 4

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IL 02/00481

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61B8/08

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)
IPC 7 A61B

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, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 524 636 A (SARVAZYAN ARMEN P ET AL) 11 June 1996 (1996-06-11) column 6, line 66 -column 7, line 15 column 10, line 8 -column 11, line 13 column 14, line 37 - line 39 column 15, line 47 - line 67 ---	1-3,6, 11-13, 16,22
X Y	US 5 839 441 A (STEINBERG BERNARD D) 24 November 1998 (1998-11-24) column 4, line 48 - line 50 column 5, line 62 -column 6, line 10 column 8, line 46 - line 52 column 10, line 1 - line 11 --- -/--	1-3,6,7, 11,12, 16,17,22 4,5,14, 15,20,21

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

[X] Patent family members are listed in annex.

° 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 document 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	Date of mailing of the international search report
9 April 2003	08/05/2003

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	Martelli, L

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IL 02/00481

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	US 2002/040187 A1 (ALAM SHEIKH KAISAR ET AL) 4 April 2002 (2002-04-04) paragraphs '0016!,'0029!,'0030!,'0041!,'0042!	22,23
Y	US 6 234 968 B1 (BOLORFOROSH MIRSAID ET AL) 22 May 2001 (2001-05-22) column 2, line 58 -column 3, line 6 column 6, line 64 -column 7, line 3	4,5,14, 15
A	US 6 312 382 B1 (MIELE FRANK R ET AL) 6 November 2001 (2001-11-06) column 6, line 33 - line 45	5,7,15, 17
Y	US 5 081 993 A (STRAUGHAN KEITH ET AL) 21 January 1992 (1992-01-21) column 15, line 7 - line 12	20,21
A	US 5 107 841 A (STURGILL MICHAEL R) 28 April 1992 (1992-04-28) column 4, line 1 - line 9	5,7,15, 17

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-7,12-19

   Method and system for calculating a parameter indicative of a degree of spatial disorder.

2. Claims: 20,21

   Analysis of reflected waves using an expert system.

3. Claims: 22,23

   Method of generating an image of a tissue by performing a non-variance analysis.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IL 02/00481

Box I Observations where certain claims were found unsearchable (Continuation of item 1 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. [X] Claims Nos.: 8-10
because they relate to subject matter not required to be searched by this Authority, namely:

Rule 39.1(iv) PCT - Diagnostic method practised on the human or animal body

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 II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

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

see additional sheet

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [X] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

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.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IL 02/00481

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