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(54) **Title:** ON-LINE AUTOMATIC SUBCLINICAL MASTITIS DETECTION DEVICE BASED ON OPTICAL SCATTERING AND AN AUTOMATIC MILK SAMPLING SYSTEM COMPRISING THIS DEVICE

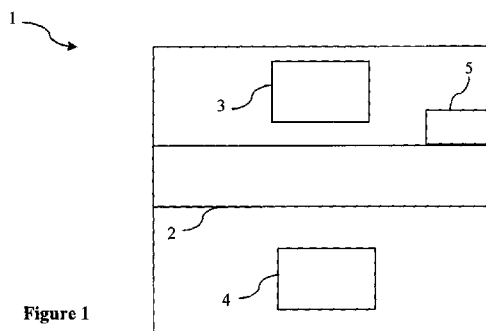
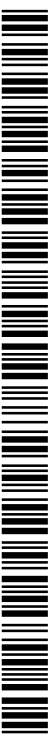


Figure 1

(57) **Abstract:** The present invention relates to a subclinical mastitis detection device which carries out evaluation based on three mastitis criteria as SHS measurement and cell type characterization and number of bacteria by optical laser scattering analysis of cow's milk, uses very little amount of sample with the help of microfluidic channel, does not use any chemical having risk of contamination to milk; and an automatic milk sampling system comprising this device.



**ON-LINE AUTOMATIC SUBCLINICAL MASTITIS DETECTION DEVICE
BASED ON OPTICAL SCATTERING AND AN AUTOMATIC MILK
SAMPLING SYSTEM COMPRISING THIS DEVICE**

DESCRIPTION

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Technical Field

The present invention relates to a subclinical mastitis detection device which carries
10 out evaluation based on three mastitis criteria as SHS measurement and cell type
characterization and number of bacteria by optical laser scattering analysis of cow's
milk, uses very little amount of sample with the help of microfluidic channel, does
not use any chemical having risk of contamination to milk; and an automatic milk
sampling system comprising this device.

15

Background of the Invention

In milk farms, burning and inflammation occur inside udder tissue due to the fact
that pathogenic (disease-causing) microorganisms contaminate to udders of cows
20 and this disease is called as mastitis. Mastitis disease has two subconditions. The
first condition is called as clinical mastitis and it occurs due to diseases caused by
some bacteria. Clinical mastitis disease is understood via symptoms which can be
seen by veterinarian and breeders externally such as redness of udder, the animal
gets bad-tempered and does not allow contact to its udders, the milk becomes
25 bloody and even the teat becomes blunt. Milk yield of cows getting clinical mastitis
disease reduces in a certain amount and they must be definitely treated with
antibiotics. If disease of a milch animal is not detected at the first and particularly
subclinical disease level, serious economic losses occur.

30 Whereas the second sub-condition of mastitis is called as subclinical mastitis. This
condition is the one before the clinical mastitis and some pathogenic
microorganisms can ensure that the animal remains only in subclinical mastitis

condition as well. Subclinical mastitis is also known as hidden mastitis and it has no symptom whereby a veterinarian or a breeder can understand occurrence of the disease with the naked eye upon microbe contamination to an animal's udder. In case of subclinical mastitis: number of somatic cell is high in these animals, loss of
5 milk production yield is in serious amount and treatment is required even if the animal is no different than a healthy animal when viewed from the outside. Both number of cows with subclinical mastitis in the herd increases and probability of occurrence of cows with clinical mastitis increases if animals with subclinical mastitis in a farm are not found out and treated, removed from the herd or cleaning
10 of the farm is not reviewed.

Counting the number of somatic cells in milk is the standard method being used at the present time in order to detect and follow-up subclinical mastitis in farms. If 200.000 or more cell number is found in 1 mL milk belonging to a single udder of a
15 single animal, this animal is accepted as having mastitis. Although this method is globally accepted, it also has many disadvantages. The most important of these disadvantages is that: total number of cells in milk also increases in cases other than mastitis or there are unidentified sudden decreases in cell number in the event of sickness.

20

Current equipment and devices used for detecting subclinical mastitis have various disadvantages. The first method of measurement enabling to diagnose mastitis disease routinely is a test which is called as California Mastitis Test (CMT), fast and cheap but has low sensitivity. In CMT method, milk from udder is put into a white
25 paddle a little and a special detergent is added on thereof. This detergent becomes gel when it is mixed with milk and consistency of the gel increases according to the excess of somatic cell number in the milk. Even though it seems simple and practical, CMT is a method which is time-consuming such that it cannot be routinely used for farms having more than 100 milch animals and it is insufficient for
30 distinguishing number of cells less than 600.000 cell/mL in milk. It is a test with low sensitivity value considering 200.000 cell/mL which is the theoretical limit of subclinical mastitis. There is CellSense device which is a CMT like device

integrated to milking automation by using the principle of CMT. Although the said device can carry out analysis by automatic sampling during milking, deficiencies underlying CMT are valid for this device as well.

- 5 Another method and technology used for diagnosis of subclinical mastitis is measuring electrical conductivity of milk. There are portable devices which use this technology and devices which make diagnosis of mastitis according to the electrical conductivity during milking by taking sample from the milk automatically. Making diagnosis of mastitis according to the electrical conductivity of the milk is based on
- 10 the information that amount of some enzymes and fat molecules change upon increase of number of cells in the milk however sensitivity ratio is approximately 60% due to the fact that electrical conductivity of milk can change, for example, according to the feed consumed by the animal on that day except for mastitis.
- 15 Upon developing technology, there are also devices which enable to make diagnosis of subclinical mastitis by counting somatic cells directly. However, none of the said devices carry out sampling automatically and it is required to take sample from each milch animal's milk manually one by one. The samples received are taken into a cartridge upon being mixed with fluorescent dye and they are read in a device
- 20 performing fluorescent reading. All these transactions require work of a person because they are not compatible with automation. In addition, due to the fact that it is worked only according to the total number of somatic cells with the said device, it has disadvantage of making diagnosis of subclinical mastitis only according to the number of somatic cells. Diagnostic sensitivity of devices running only according to
- 25 the number of somatic cells can be 80% at most and determining whether a milch cow has mastitis or not by taking into consideration only one criteria, i.e. upon number of somatic cells, lead to wrong results. It can be observed that subclinical mastitis disease occurs in some animals without cell number of 200.000 cell/mL. On the contrary, in some animals, for example 210.000 cell/mL can be a genetic
- 30 characteristic of this animal and it may not be related to mastitis.

Whereas other available mastitis analysis devices examine health status of an animal by applying indirect method. The said devices measure density of fat, protein, lactose and blood in milk by infrared spectrometry technology. Although it is stated that it is enabled to make diagnosis of subclinical mastitis by giving information of somatic cell number with this analysis, results indicate that this success lacks.

The International patent document no. **WO0119170**, an application in the state of the art, discloses a device which detects mastitis or other udder disorders in milking animals. In the invention disclosed in the said document, analysis is enabled by means of two optical sensors disposed along a conduit and each including an optical emitter and a monitoring arrangement including a detector. In addition, the vacuum pump of the device comprises waste water tank in the said invention. In the said device, it is mentioned that LED is used as optical emitter and photodetectors are used as detector. However for analysis, somatic cell count or neutrophil/macrophage ratios are not measured but lumpy particles, blood and inflammations are detected in the said device.

The United States patent document no. **US6731100**, an application in the state of the art, discloses an online system which detects diseases by using chemical via somatic cell count in raw milk collected from milked animals. It is mentioned that the invention disclosed in the said document can be integrated to a milking system. In the invention, compressed air or pump is used in order that the sample proceeds in the channel. In the said device, the sample is focused by using a light source lens such as laser and monochromatic detector is used. In the device, use of fluorescent dye is mentioned for imaging sub cells and calculating only numbers of total somatic cell is disclosed. In addition, analysis is carried out inside the sample chamber in the device.

Summary of the Invention

An objective of the present invention is to realize a subclinical mastitis detection device which has high detection sensitivity (95%), high accuracy (99%) and

provides real-time alert for enterprises having particularly farming automation; and an automatic milk sampling system comprising this device

Another objective of the present invention is to realize a subclinical mastitis
5 detection device which carries out evaluation based on three mastitis criteria as SHS (number of somatic cells) measurement and cell type characterization and number of bacteria by optical laser scattering analysis of milk, uses very little amount of sample with microfluidic chip technology, does not use any chemical having risk of contamination to milk; and an automatic milk sampling system comprising this
10 device.

Another objective of the present invention is to realize a device which has cheap operating cost, is easy-to-use with minimum farmer intervention; and an automatic milk sampling system comprising this device.

15 Another objective of the present invention is to realize a device which can be adapted or carried to any automatic milk sampling system.

Another objective of the present invention is to realize a device which can
20 distinguish neutrophil and macrophage cells according to their optical scattering characteristics without fluorescent marking; and an automatic milk sampling system comprising this device.

Detailed Description of the Invention

25 “ON-LINE AUTOMATIC SUBCLINICAL MASTITIS DETECTION DEVICE BASED ON OPTICAL SCATTERING AND AN AUTOMATIC MILK SAMPLING SYSTEM COMPRISING THIS DEVICE” realized to fulfil the objectives of the present invention is shown in the figures attached, in which:

30

Figure 1 is a schematic view of the inventive device.

Figure 2 is a schematic view of an automatic milk sampling system comprising the inventive device.

The components illustrated in the figure are individually numbered, where the
5 numbers refer to the following:

1. Device
2. Microfluidic chip channel
3. Laser source
- 10 4. Image reception unit
5. Analysis unit
6. Automatic sampling system
7. Milking pump
8. Collecting channel
- 15 9. Delivery channel
10. Milk pump
11. Valve
12. Sensor
13. Water channel
- 20 14. Water pump
15. Water valve
16. Filter
17. Waste channel

25 The device (1) enabling to detect whether a milch cow has subclinical mastitis or not by analysing cow's milk comprises:

- at least one microfluidic chip channel (2) which enables to take milk sample;
- at least one laser source (3) which sends laser beam onto the sample being included inside the channel (2);
- 30 at least one image reception unit (4) which receives the image emitted from the cells being included in the sample whereon laser beam is sent; and

at least one analysis unit (5) which enables to detect whether there is subclinical mastitis or not by analysing the image received from the image reception unit (4).

- 5 In the device (1) developed by the present invention, laser beam is sent onto the sample being included inside the microfluidic chip channel (2) and it is ensured that the light which falls over the cells being included inside the sample is subjected to optical scattering. Due to the fact that different cells reflect light to directions at different angles with varying intensity, image of this reflecting light is received by
10 the image reception unit (4) and it is ensured whether there is subclinical mastitis or not by making analysis of the sample upon being transmitted to the analysis unit (5).

- In one preferred embodiment of the invention, the microfluidic chip channel (2) is a glass microfluidic channel or a capillary tube which performs hydrodynamic
15 focusing. The said channel (2) has a curved structure in order to facilitate image reception and milk cells are enabled to flow on a line consecutively in thereof.

In one preferred embodiment of the invention, the laser source (3) is a LED lamp.

- 20 In one preferred embodiment of the invention, the image reception unit (4) is a CCD camera, CMOS camera, array photodetector, line photodetector, dot photodetector or any sensor which senses optical data and turns it into electrical signal.

- In another preferred embodiment of the invention, the device (1) comprises at least
25 one lens (not shown in the figures) which is between the laser light source (3) and the image reception unit (4) and focuses the light to the channel (2).

- In one embodiment of the invention, the analysis unit (5) distinguishes neutrophil and macrophage cells according to their optical scattering characteristics in order to
30 detect presence of subclinical mastitis and carries out the said detection by proportioning the cell numbers to one another.

In another embodiment of the invention, the analysis unit (5) performs detection of subclinical mastitis by distinguishing normal milk cells and milk cells having subclinical mastitis according to their optical scattering characteristics without making discrimination of cell types.

5

In another embodiment of the invention, the analysis unit (5) performs detection of subclinical mastitis by counting and proportioning lymphocyte and macrophage cells via optical scattering.

- 10 In another embodiment of the invention, the analysis unit (5) performs detection of subclinical mastitis by counting and proportioning lymphocyte and neutrophil cells with one another via optical scattering.

- 15 In another embodiment of the invention, the analysis unit (5) performs detection of subclinical mastitis by optical scattering and counting total somatic cell and counting total bacteria amount.

- 20 In an exemplary embodiment of the invention, the device (1) comprises at least two image reception units (4) one of which is positioned in front of the laser beam source and receives forward scattering images and the other one thereof is positioned perpendicularly to the incidence angle of the scattering images' laser beam and receives side scattering images. In this embodiment of the invention, forward scattering (FSC) images give information about both cell dimension and cell structure whereas side scattering (SSC) images give additional information about the cell's internal structure and thus it is enabled to distinguish macrophages and neutrophils.
- 25

- The inventive device (1), in one preferred embodiment of the invention, is included in an automatic sampling system (6).

30

The said automatic sampling system (6) comprises:

- at least one milking pump (7) which is connected to at least one udder of a cow and enables to milk;
- at least one collecting channel (8) wherein the milk from the milking pump (7) is collected;
- 5 at least one delivery channel (9) where the milk collected in the collecting channel (8) is delivered;
- at least one milk pump (10) which is located on the delivery channel (9) and enables to take milk sample;
- 10 at least one subclinical mastitis detection device (1) where the milk sample received from the milk pump (10) is delivered for subclinical mastitis detection.

In one preferred embodiment of the inventive system (6), the said system (6) comprises at least one valve (11) which is located on the delivery channel (9) and

15 can be switched to on/off position. Upon the said valve (11) is opened, the milk included in the delivery channel (9) is drawn by means of the milk pump (10) and it is delivered to the channel (2) of the detection device (1).

In another preferred embodiment of the inventive system (6), the system (6)

20 comprises at least one sensor (12) which is included in the delivery channel (9) and detects presence of milk and ensures that milk sample is taken with the help of the milk pump (10) by enabling to open the valve (11) after the presence of milk is detected. The said sensor (12) is a motion sensor in one preferred embodiment of the invention.

25

In an exemplary embodiment of the invention, the system (6) comprises at least one water channel (13) which is connected to the detection device (1) and provides water supply to the channel (2) included inside the device (1). On the said water channel (13), there are preferably one water pump (14) and a water valve (15) and it

30 is ensured that water is taken into the channel (2) of the device (1) with the help of the pump (14) upon the valve (15) is opened. In this embodiment of the invention, the sensor (12) ensures that water is also taken into the channel (2) of the device (1)

at the same time by triggering the valve (15) included in the water channel (13) as well while enabling to take milk.

5 In another preferred embodiment of the invention, there is at least one filter (16) enabling to clean milk from undesirable substances on the delivery channel (9).

10 In another preferred embodiment of the invention, the system (6) comprises at least one waste channel (17) which is connected to the detection device (1) in order to remove the waste water and the milk sample included in the device (1) after the detection transaction is carried out. Whereas in another preferred embodiment of the invention, the system (6) comprises at least one cleaning channel (not shown in the figures) which feeds cleaning fluid to the system (6) in order to clean the detection device (1) and the channels (2,8,9,13,17).

15 It is possible to develop a great variety of embodiments of the inventive “A Subclinical Mastitis Detection Device (1) and an Automatic Milk Sampling System Comprising This Device (6)”; it cannot be limited to the examples disclosed herein; and it is essentially according to the claims.

CLAIMS

1. A device (1) enabling to detect whether a milch cow has subclinical mastitis or not by analysing cow's milk, **comprising:**
 - 5 at least one microfluidic chip channel (2) which enables to take milk sample; and **characterized by:**
 - at least one laser source (3) which sends laser beam onto the sample being included inside the channel (2);
 - at least one image reception unit (4) which receives the image emitted from
10 the cells being included in the sample whereon laser beam is sent; and
 - at least one analysis unit (5) which enables to detect whether there is subclinical mastitis or not by analysing the image received from the image reception unit (4).
- 15 2. A device (1) according to Claim 1, **characterized by** a glass microfluidic channel (2) which performs hydrodynamic focusing.
3. A device (1) according to Claim 1, **characterized by** the channel (2) which is a capillary tube.
20
4. A device (1) according to Claim 1, **characterized by** the channel (2) which has a microchannel structure enabling to array milk cells consecutively so as to facilitate image reception
- 25 5. A device (1) according to Claim 1, **characterized by** the laser source (3) which is a LED lamp.
6. A device (1) according to Claim 1, **characterized by** the image reception unit (4) which is a CCD camera, CMOS camera, array photodetector, line
30 photodetector, dot photodetector or any sensor which senses optical data and turns it into electrical signal.

7. A device (1) according to Claim 1, **characterized by** at least one lens which is located between the laser light source (3) and the image reception unit (4) and focuses the light to the channel (2).
- 5 8. A device (1) according to Claim 1, **characterized by** the analysis unit (5) which distinguishes neutrophil and macrophage cells according to their optical scattering characteristics in order to detect presence of subclinical mastitis and carries out the detection transaction by proportioning the cell numbers to one another.
- 10 9. A device (1) according to Claim 1, **characterized by** the analysis unit (5) which performs detection of subclinical mastitis by distinguishing normal milk cells and milk cells having subclinical mastitis according to their optical scattering characteristics without making discrimination of cell types.
- 15 10. A device (1) according to Claim 1, **characterized by** the analysis unit (5) which performs detection of subclinical mastitis by counting and proportioning lymphocyte and macrophage cells via optical scattering.
- 20 11. A device (1) according to Claim 1, **characterized by** the analysis unit (5) which performs detection of subclinical mastitis by counting and proportioning lymphocyte and neutrophil cells with one another via optical scattering.
- 25 12. A device (1) according to Claim 1, **characterized by** the analysis unit (5) which performs detection of subclinical mastitis by optical scattering and counting total somatic cell and counting total bacteria amount.
- 30 13. A device (1) according to Claim 1, **characterized by** at least two image reception units (4) one of which is positioned in front of the laser beam source and receives forward scattering images and the other one thereof is positioned perpendicularly to the incidence angle of the scattering images' laser beam and receives side scattering images.

14. An automatic sampling system (6) enabling to milk automatically and detect whether there is subclinical mastitis or not;
comprising
5 at least one milking pump (7) which is connected to at least one udder of a cow and enables to milk;
at least one collecting channel (8) wherein the milk from the milking pump (7) is collected;
at least one delivery channel (9) where the milk collected in the collecting
10 channel (8) is delivered;
at least one milk pump (10) which is located on the delivery channel (9) and enables to take milk sample;
and characterized by
a subclinical mastitis detection device (1) according to any of the preceding
15 claims where the milk sample received from the milk pump (10) is delivered for subclinical mastitis detection.
15. An automatic sampling system (6) according to Claim 14, **characterized by** at least one valve (11) which is located on the delivery channel (9) and can be
20 switched to on/off position.
16. An automatic sampling system (6) according to Claim 14, **characterized by** at least one sensor (12) which is located in the delivery channel (9) and detects presence of milk and ensures that milk sample is taken with the help of the milk
25 pump (10) by enabling to open the valve (11) after the presence of milk is detected.
17. An automatic sampling system (6) according to Claim 15, **characterized by** the sensor (12) which is a motion sensor.
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18. An automatic sampling system (6) according to Claim 14, **characterized by** at least one water channel (13) which is connected to the detection device (1) and provides water supply to the channel (2) included inside the device (1).
- 5 19. An automatic sampling system (6) according to Claim 18, **characterized by** at least one water pump (14) which is located on the water channel (13).
20. An automatic sampling system (6) according to Claim 18 or 19, **characterized by** at least one water valve (15) which is located on the water channel (13).
- 10 21. An automatic sampling system (6) according to Claim 16, **characterized by** the sensor (12) which ensures that water is also taken into the channel (2) of the device (1) at the same time by triggering the valve (15) included in the water channel (13) as well while enabling to take milk.
- 15 22. An automatic sampling system (6) according to Claim 14, **characterized by** at least one filter (16) which is located on the delivery channel (9) and enables to clean milk from undesirable substances.
- 20 23. An automatic sampling system (6) according to Claim 14, **characterized by** at least one waste channel (17) which is connected to the detection device (1) in order to remove the waste water and the milk sample included in the device (1) after the detection transaction is carried out.
- 25 24. An automatic sampling system (6) according to Claim 14, **characterized by** at least one cleaning channel which feeds cleaning fluid to the system (6) in order to clean the detection device (1) and the channels (2,8,9,13,17).

Figure 1

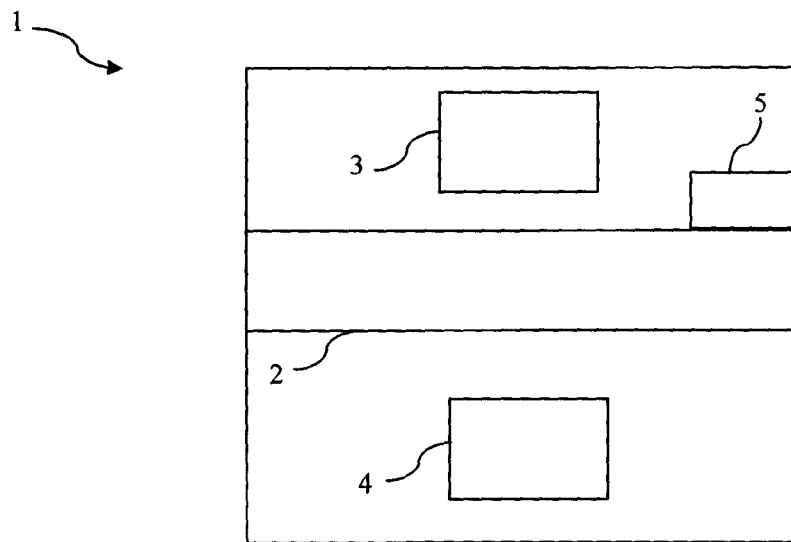
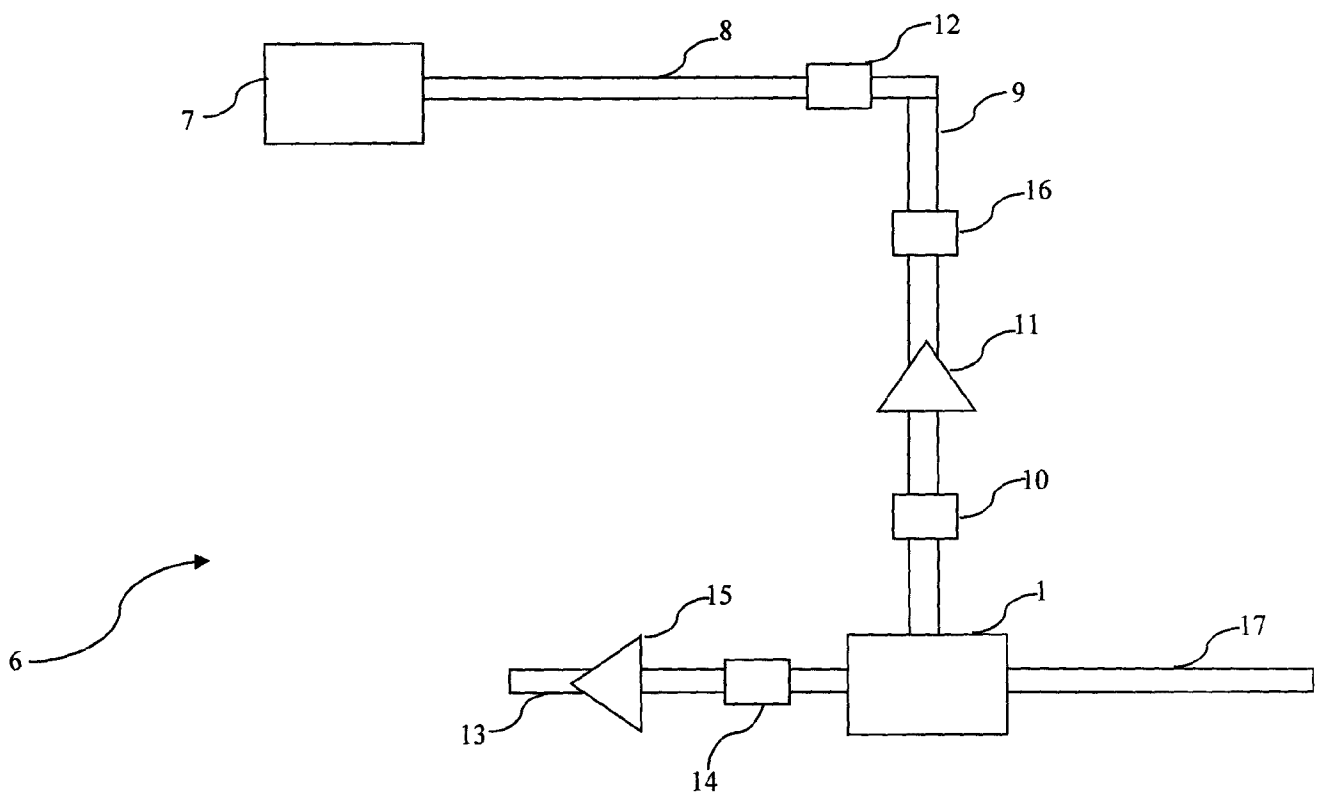


Figure 2



INTERNATIONAL SEARCH REPORT

International application No
PCT/TR2016/000134

A. CLASSIFICATION OF SUBJECT MATTER
INV. A01J5/013 G01N33/50
ADD.

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)
A01J 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 practicable, search terms used)

EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2007/289536 A1 (DUNN JAMES [CA] ET AL) 20 December 2007 (2007-12-20) paragraphs [0002], [0029], [0041]; figures 1-3	1,5-24
Y	----- WO 2012/052046 A1 (FOSS ANALYTICAL AS [DK]; HOLM CLAUS [DK]) 26 April 2012 (2012-04-26)	1,5-24
A	abstract	2-4
A	----- WO 2008/093344 A1 (E N G S SYSTEMS LTD [IL]; TUVAL ERAN [IL]) 7 August 2008 (2008-08-07) the whole document	1
	----- -/-	



Further documents are listed in the continuation of Box C.



See patent family annex.

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"&" document member of the same patent family

Date of the actual completion of the international search

1 March 2017

Date of mailing of the international search report

08/03/2017

Name and mailing address of the ISA/

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Nédélec, Morgan

INTERNATIONAL SEARCH REPORT

International application No

PCT/TR2016/000134

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2008/146276 A1 (AFIKIM S A E [IL]; PINSKY NIV [IL]; KATZ GIL [IL]; SABBAAH BENJAMIN [IL]) 4 December 2008 (2008-12-04) the whole document	1
A	----- EP 2 916 131 A1 (AMPHASYS AG [CH]) 9 September 2015 (2015-09-09) the whole document -----	1

INTERNATIONAL SEARCH REPORT

Information on patent family members

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