



(43) International Publication Date
20 March 2014 (20.03.2014)

(51) International Patent Classification:

G01N 9/00 (2006.01) G01N 29/02 (2006.01)
G01N 5/02 (2006.01) G01N 29/36 (2006.01)

(21) International Application Number:

PCT/IT2013/000238

(22) International Filing Date:

10 September 2013 (10.09.2013)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

TO2012A000789 14 September 2012 (14.09.2012) IT

(71) Applicants: **POLITECNICO DI TORINO** [IT/IT]; Corso Duca degli Abruzzi 24, I-10129 Torino (IT). **FONDAZIONE ISTITUTO ITALIANO DI TECNOLOGIA (II)** [IT/IT]; Via Morego 30, I-16163 Genova (IT).

(72) Inventors: **RICCIARDI, Carlo**; c/o Politecnico di Torino, Corso Duca degli Abruzzi 24, I-10129 Torino (IT). **FERRANTE, Ivan**; c/o Politecnico di Torino, Corso Duca degli Abruzzi 24, I-10129 Torino (IT). **MURA, Andrea**; c/o Politecnico di Torino, Corso Duca degli Abruzzi 24, I-10129 Torino (IT). **CANAVESE, Giancarlo**; c/o Fondazione Istituto Italiano di Tecnologia (IIT), Via Morego 30, I-16163 Genova (IT).

(74) Agent: **GARAVELLI, Paolo**; A.Bre.Mar. s.r.l., Via Servais 27, I-10146 Torino (IT).

(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, BN, 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, 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, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, 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.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

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))

(54) Title: AUTOMATIC MEASURING DEVICE, MEASURING PROCESS THROUGH SUCH DEVICE AND SYSTEM EQUIPPED WITH SUCH DEVICE

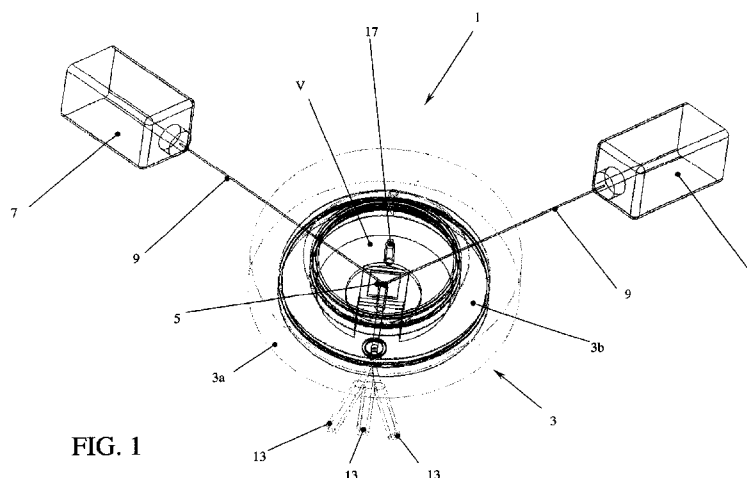


FIG. 1

(57) Abstract: An automatic measuring device (1) is described, comprising at least one measuring chamber (3) having therein at least one measuring volume (V) containing therein at least one cantilever sensor (5) for analysing at least one sampling fluid inserted inside such volume (V); at least one projecting means (7) of at least one laser light beam (9) incident onto such cantilever sensor (5), such chamber (3) being equipped with at least one window (11) transparent to such laser light beam (9); inserting and withdrawing means of such at least one sampling fluid into and from such volume (V) of such chamber (3). A system equipped with such device (1) and a measuring process through such device (1) are further described.

AUTOMATIC MEASURING DEVICE, MEASURING PROCESS**5 THROUGH SUCH DEVICE AND SYSTEM EQUIPPED WITH SUCH
DEVICE**

The present invention refers to an automatic measuring device, aimed in particular to locate in
10 real time pathogens and/or contaminants in liquid phases. The present invention further refers to a measuring process through such device and to a system equipped with such device.

Measuring devices are known in the art which
15 are equipped with mechanical nanosensors which operate as chemical or bio-chemical detectors, typically defined as "cantilevers" or "micro-cantilevers", which allow identifying and measuring the mass of pathogens and/or contaminants: the
20 cantilever surface in fact is functionalised with particular probe molecules, which have the capability of selectively linking themselves to particular target molecules (such as the pathogen and/or contaminant agents which have to be
25 identified and/or whose mass has to be measured).

Typically, the mass measure is performed by detecting, through a laser light beam, the movement of the cantilever (in terms of static flexure or variation of the oscillating resonance frequency
5 due to a mass variation of the cantilever determined by the possible deposition of the pathogens and/or contaminants being investigated).

Examples of such known devices are disclosed in US2005121615, US007671511, US2008034840,
10 CN2857015, CN1975432, US2009/0235746, US2010/0136556, US2011212511.

Such known devices are however designed and built for a manual use aimed for laboratory measures and therefore they are scarcely practical
15 for being used in line along with industrial processes, since they would imply constant interruptions of such processes in order to withdraw the samples and perform their measure.

Such known devices, moreover, do not allow
20 automatising either the functionalisation / activation procedure of the cantilever surface, or the measuring or managing modes of liquids and gases, or the chance of portability and real time measures, possibly even remotely, consequently
25 resulting scarcely practical for an efficient and

effective industrial use.

Therefore, object of the present invention is solving the above prior art problems, by providing a device, a system and a process which allow
5 performing measures in line (for example in the agricultural-foodstuff field), without interfering with productivity.

Another object of the present invention is providing a device, a system and a process which
10 allow monitoring the fluid to be analysed through an automatic sampling on its production line.

Moreover, an object of the present invention is providing a device, a system and a process which allow a high sensitivity of the mass measure based
15 on the evaluation of the variation of the resonance frequency of microbeams coupled with an automated fluidic system of necessary reagents for measuring the pathogens and/or contaminants of interest.

Another object of the present invention is
20 providing a device, a system and a process which allow automating necessary operations for measuring, high repeatability and reproducibility and absence of specialised personnel for measuring, allowing to standardise the measuring procedure and
25 therefore being able to obtain calibration curves.

Moreover, an object of the present invention is providing a device, a system and a process which allow performing the measure in a vacuum environment.

5 Another object of the present invention is providing a device, a system and a process which allow remotely managing the measures.

Moreover, an object of the present invention is providing a device, a system and a process which
10 avoid the possible alteration of a measure by an operator, since all steps of the measuring process are automatically carried out without manipulating the sensor, the sample and the reagents.

The above and other objects and advantages of
15 the invention, as will appear from the following description, are obtained with a measuring device, a system and a process as claimed in the respective independent Claims.

Preferred embodiments and non-trivial
20 variations of the present invention are the subject matter of the dependent claims.

It is intended that all enclosed claims are an integral part of the present description.

It will be immediately obvious that numerous
25 variations and modifications (for example related

to shape, sizes, arrangements and parts with equivalent functionality) could be made to what is described, without departing from the scope of the invention as appears from the enclosed claims.

5 The present invention will be better described by some preferred embodiments thereof, provided as a non-limiting example, with reference to the enclosed drawings, in which:

- Figure 1 shows a top perspective and partially
10 sectioned view of a preferred embodiment of the device according to the present invention;
- Figure 2 shows a side and partially sectioned view of the device according to the present invention of Figure 1;
- 15 - Figure 3 shows a top view of a component of the device according to the present invention;
- Figure 4 shows a top perspective and sectional view of the component of the device of Figure 3;
- Figure 5 shows a top side sectional view of
20 the component of the device of Figure 3 in a first operating position; and
- Figure 6 shows a top side sectional view of the component of the device of Figure 3 in a second operating position.

25 With reference to the Figures, it is possible

to note that the automatic measuring device 1 according to the present invention comprises:

- at least one measuring chamber 3 having therein at least one measuring volume V containing
5 therein at least one cantilever sensor 5 for analysing at least one sampling fluid inserted into such volume V;
- at least one projecting means 7 of at least one laser light beam 9 incident onto such
10 cantilever sensor 5, such chamber 3 being equipped with at least one window 11 transparent to such laser light beam 9.

In particular, each projecting means 7 operatively cooperates with suitable processing
15 means (not shown), preferably equipped with at least one "photo detector" device receiving the luminous flow reflected by the cantilever sensor 5, in order to preferably detect the variation of the oscillating resonance frequency due to a mass
20 variation of the cantilever sensor 5 determined by the possible deposition of the pathogen(s) and/or contaminant(s) present inside the sampling fluid inserted inside the volume V of the chamber 3.

Such processing means are therefore managed by
25 at least one software, which takes care of

analysing the vibration width in frequency, automatically performing the fit of the resonance curve with a Lorentz expression and computes frequency and quality factor. For a continuous
5 monitoring of the cantilever sensor 5, such software is capable of centering itself on the resonant frequency of the previous, newly-computed measure and perform a new measure: in this case, it is possible to analyse the variations of the
10 resonant frequency in real time, namely of the mass adsorbed by the sensor, and therefore quantifying the target and studying also its bond kinetics.

In addition, it is possible to provide that at least one disk made of piezoelectric material (not
15 shown) is arranged below the cantilever sensor 5 in order to energise its respective microbeam at the desired frequencies: moreover, such sensor 5 and possibly such disk can be arranged on at least one thermostating device for checking the temperature.

20 Due to redundancy reasons and/or to have the chance of performing multi-parameter measures in order to detect the presence of different types of pathogen and/or contaminant agents, the measuring chamber 3 can comprise therein a plurality of such
25 cantilever sensors 3, which can be mutually equal

and/or different.

The device 1 according to the present invention can further comprise inserting and withdrawing means of such at least one sampling
5 fluid into and from the volume V of the chamber 3: possibly, the device 1 according to the present invention can comprise a plurality of such inserting means in order to allow inserting different sampling fluids inside the volume V of
10 the chamber 3. In a possible preferred embodiment, such inserting and withdrawing means are respectively composed of a corresponding single duct which, by means of suitable valve control means, allows using them both for inserting the
15 sampling fluid inside the volume V of the chamber 3 and for withdrawing the fluid from such volume V at the end of the measure. Alternatively, as shown for example in the preferred embodiment of the device 1 of the Figures, such inserting and withdrawing
20 means can be composed of different inserting means and extracting means, preferably composed of respective inserting ducts 13 of at least one of such sampling fluids inside such volume V and extracting ducts 15 from such volume V towards
25 outside.

Such inserting and withdrawing means can also be used to insert and withdraw at least one washing fluid into and inside such volume V, for example after having inserted the sampling fluid and before
5 measuring such fluid. Alternatively, it is possible to provide that the device 1 according to the present invention comprises at least one dedicated inserting means for such washing fluid different from the inserting means of the sampling fluid.

10 Such inserting and withdrawing means can further be used to insert and withdraw at least one drying fluid into and from inside such volume V, for example after inserting the sampling fluid to dry the fluid arranged on the cantilever sensor 5.
15 Alternatively, it is possible to provide that the device 1 according to the present invention comprises at least one dedicated inserting means of such drying fluid different from the inserting means of the sampling fluid.

20 In addition, it is possible to provide that the device 1 according to the present invention further comprises vacuum creating means inside such volume V of the chamber 3 in order to allow performing surveys and measures of possible
25 pathogens and/or contaminants contained in the

sampling fluid under vacuum conditions in order to increase the sensitivity of the measure itself. Preferably, such vacuum creating means comprise at least one vacuum duct 17 having at least one end
5 communicating with such volume V of such chamber 3 and connected to at least one vacuum pump (not shown).

In a preferred embodiment, like the one shown for example in the Figures, the chamber 3 of the
10 device 1 according to the present invention is composed of at least one external envelope 3a and at least one internal container 3b, such external envelope 3a and such internal container 3b being mutually moving along at least one movement
15 direction V_1 - V_2 coaxial with such external envelope 3a and such internal container 3b between a rest position and a measuring position, and vice versa. Still more preferably, such external envelope 3a is fixed while such internal container 3b is moving
20 and slides along such movement direction V_1 - V_2 inside such external envelope 3a between the rest position (like the one, for example, shown in Figure 5) and the measuring position (like the one, for example, shown in Figure 6), and vice versa. In
25 particular, such external envelope 3a comprises the

window 11 while the internal container 3b comprises the cantilever sensor 5 and at least one perimeter edge 18 adapted to go against such window 11 when such chamber 3 is in the measuring position, in order to further increase the internal seal of the volume V during the measuring steps. On the perimeter, such internal container 3b can be externally equipped with at least one, radial first retaining means 19 interposed between the external surface of such internal container 3b and the internal surface of such external envelope 3a. Moreover, such internal container 3b can be equipped with at least one second retaining means 21 arranged externally above such perimeter edge 18 and interposed in contact between such internal container 3b and the internal surface of the window 11 when the chamber 3 is in the measuring position.

The passage of the internal container 3b from the rest position to the measuring position (for example according to a movement having the direction shown by arrow V_1 in Figure 5) can be spontaneously generated by the creation and maintenance of vacuum inside the volume V: in parallel, breaking of vacuum inside the volume V at the end of the measure generates, due to gravity,

the spontaneous return of the internal container 3b to the rest position from the measuring position (for example according to a movement having the direction shown by arrow V_2 in Figure 6).

5 Alternatively, the device 1 according to the present invention can further comprise suitable actuating means (not shown) adapted to take such chamber 3 from the rest position to the measuring position and vice versa: possibly, such actuating
10 means can cooperate with such processing means in order to automatise the movement of the chamber 3 and suitably coordinated with all other steps of the measuring process through the device 1 according to the present invention.

15 The present invention further deals with at least one automatic system for detecting and measuring pathogen and/or contaminant agents in a fluid comprising:

- at least one source of such fluid;
- 20 - at least one device 1 according to the present invention like the previously described one;
- withdrawing means of at least one aliquot of such fluid from such source as sampling fluid;
- supplying means of such sampling fluid from
25 such withdrawing means to such inserting means of

the device 1;

- processing means comprising managing means of the sampling of such fluid adapted to control the operation of such withdrawing means and of such supplying means and managing means of the operation of the device 1: in particular, such processing means allow automatically performing in a controlled way the operations of withdrawing the sampling fluid, filling, emptying, drying, moving the chamber 3 and forming vacuum inside the chamber 3 of the device 1.

Obviously, such withdrawing means, such supplying means and such processing means can be composed of any combination of fluid pumping systems, electro-served valves, fluid connections, PLC, etc. per se known in the art, which guarantee the chance of managing at the operator's will the different steps necessary for preparing the measure through the device 1 according to the present invention.

The present invention further deals with an automatic measuring process through at least one device 1 according to the present invention like the previously described one. In particular, the process according to the present invention

comprises the steps of:

- a) providing at least one amount of a sampling fluid, for example withdrawn through the withdrawing means from the source of the system
5 according to the present invention;
- b) inserting such sampling fluid inside the volume V of the chamber 3 of the device 1 according to the present invention like the previously described one, for example through the supplying
10 means of the system according to the present invention and the inserting means of the device 1;
- c) incubating such sampling fluid inside such volume V, for example for a period of time included between 5 minutes and 25 minutes: during such
15 incubating period, the pathogens and/or contaminants possibly present inside the sampling fluid are allowed to be deposited on the beam of the cantilever sensor 5;
- d) withdrawing the sampling fluid from the volume
20 V of the chamber 3, for example through the extracting means of the device 1; possibly inserting and withdrawing at least one washing fluid in and from such volume 3; possibly inserting and withdrawing at least one drying fluid in and
25 from such volume 3; possibly creating vacuum inside

such volume 3, for example through such vacuum creating means of the device 1; possibly taking such chamber 3 from the rest position to the measuring position; and

- 5 e) performing the measure through such projecting means 7; possibly breaking vacuum inside such volume V of the chamber 3; possibly taking again such chamber 3 from the measuring position to the rest position.

10 As described above, the device 1, the system and the process according to the present invention allow, in particular, to automatically locate pathogen and/or contaminant agents under liquid and aerial phases, for example:

- 15 - for quality and safety control in the agricultural-foodstuff field;
- for quality and safety control of water ducts;
- for analyzing biomarkers in the biomedical field (molecular biology, oncology, "-omics",
- 20 etc.);
- for monitoring health and safety in sensitive environments (airports, hospitals, etc.) in addition to revealing bioterrorism acts or dangerous gases.

25

CLAIMS

1. Automatic measuring device (1) characterised in that it comprises:

- at least one measuring chamber (3) having
5 therein at least one measuring volume (V) containing therein at least one cantilever sensor (5) for analysing at least one sampling fluid inserted inside said volume (V);
- at least one projecting means (7) of at least
10 one laser light beam (9) incident onto said cantilever sensor (5), said chamber (3) being equipped with at least one window (11) transparent to said laser light beam (9);
- inserting and withdrawing means of said at
15 least one sampling fluid into and from said volume (V) of said chamber (3);

characterized in that:

- the device (1) further comprises at least one inserting means of at least one washing fluid
20 and/or at least one drying fluid inside said volume (V);

and in that:

- said inserting and withdrawing means are composed of different inserting means and
25 extracting means, composed of respective inserting

ducts (13) of at least one said sampling fluid inside said volume (V) and extracting ducts (15) from said volume (V) towards outside.

2. Device (1) according to the previous claim,
5 characterised in that said projecting means (7) operatively cooperate with processing means equipped with at least one "photo detector" device receiving a luminous flow reflected from said cantilever sensor (5) to detect a variation of the
10 oscillating resonance frequency due to a mass variation of said cantilever sensor (5).

3. Device (1) according to claim 1, characterised in that it comprises at least one disk made of piezoelectric material arranged below said
15 cantilever sensor (5) to energise a respective microbeam at desired frequencies.

4. Device (1) according to claim 1 or 3, characterised in that it comprises at least one thermostating device for controlling the
20 temperature, said sensor (5) and possibly said disk being arranged on said thermostating device.

5. Device (1) according to claim 1, characterised in that it comprises vacuum creating means inside said volume (V) of said chamber (3).

25 6. Device (1) according to any one of the

previous claims, characterised in that said chamber (3) is composed of at least one external envelope (3a) and at least one internal container (3b), said external envelope (3a) and said internal container (3b) being mutually moving along at least one movement direction (V_1 - V_2) coaxial with said external envelope (3a) and said internal container (3b) between a rest position and a measuring position, and vice versa.

7. Device (1) according to the previous claim, characterised in that said external envelope (3a) is fixed while said internal container (3b) is mobile and slides along said movement direction (V_1 - V_2) inside said external envelope (3a) between said rest position and said measuring position, said external envelope (3a) comprising said window (11) while said internal container (3b) comprises said cantilever sensor (5) and at least one perimeter edge (18) adapted to go against said window (11) when said chamber (3) is in said measuring position.

8. Device (1) according to the previous claim, characterised in that said internal container (3b) is externally equipped with at least one, radial first retaining means (19) interposed between an

external surface of said internal container (3b)
and an internal surface of said external envelope
(3a), and in that said internal container (3b) is
equipped with at least one second retaining means
5 (21) externally arranged above said perimeter edge
(18) and interposed in contact between said
internal container (3b) and an internal surface of
said window (11) when said chamber (3) is in said
measuring position.

10 9. Device (1) according to any one of claims 6 to
8, characterised in that it comprises actuating
means adapted to take said chamber (3) from said
rest position to said measuring position, and vice
versa.

15 10. Automatic system for detecting and measuring
pathogen and/or contaminant agents in un fluid
characterised in that it comprises:

- at least one source of said fluid;
- at least one device (1) according to any one
20 of the previous claims;
- withdrawing means of at least one aliquot of
said fluid from said source as sampling fluid;
- supplying means of said sampling fluid from
said withdrawing means to said inserting means of
25 said device (1);

- processing means comprising managing means of a sampling of said fluid adapted to control an operation of said withdrawing means and of said supplying means and managing means of an operation
5 of said device (1).

11. Automatic measuring process through at least one device (1) according to any one of claims 1 to 9 or a system according to claim 10, characterised in that it comprises the steps of:

- 10 a) providing at least one amount of one of said sampling fluids;
- b) inserting said sampling fluid inside said volume (V) of said chamber (3) of said device (1);
- c) incubating said sampling fluid inside said
15 volume (V);
- d) withdrawing said sampling fluid from said volume (V) of said chamber (3); and
- e) performing the measure through said projecting means (7) and possibly breaking vacuum inside said
20 volume (V) of said chamber (3).

12. Process according to the previous claim, characterised in that it comprises, between step d) and step e), the steps of inserting and withdrawing at least one washing fluid into and from said
25 volume (3), inserting and withdrawing at least one

drying fluid into and from said volume (3),
creating vacuum inside said volume (3), taking said
chamber (3) from said rest position to said
measuring position, and, after step e), the step of
5 taking back said chamber (3) from said measuring
position to said rest position.

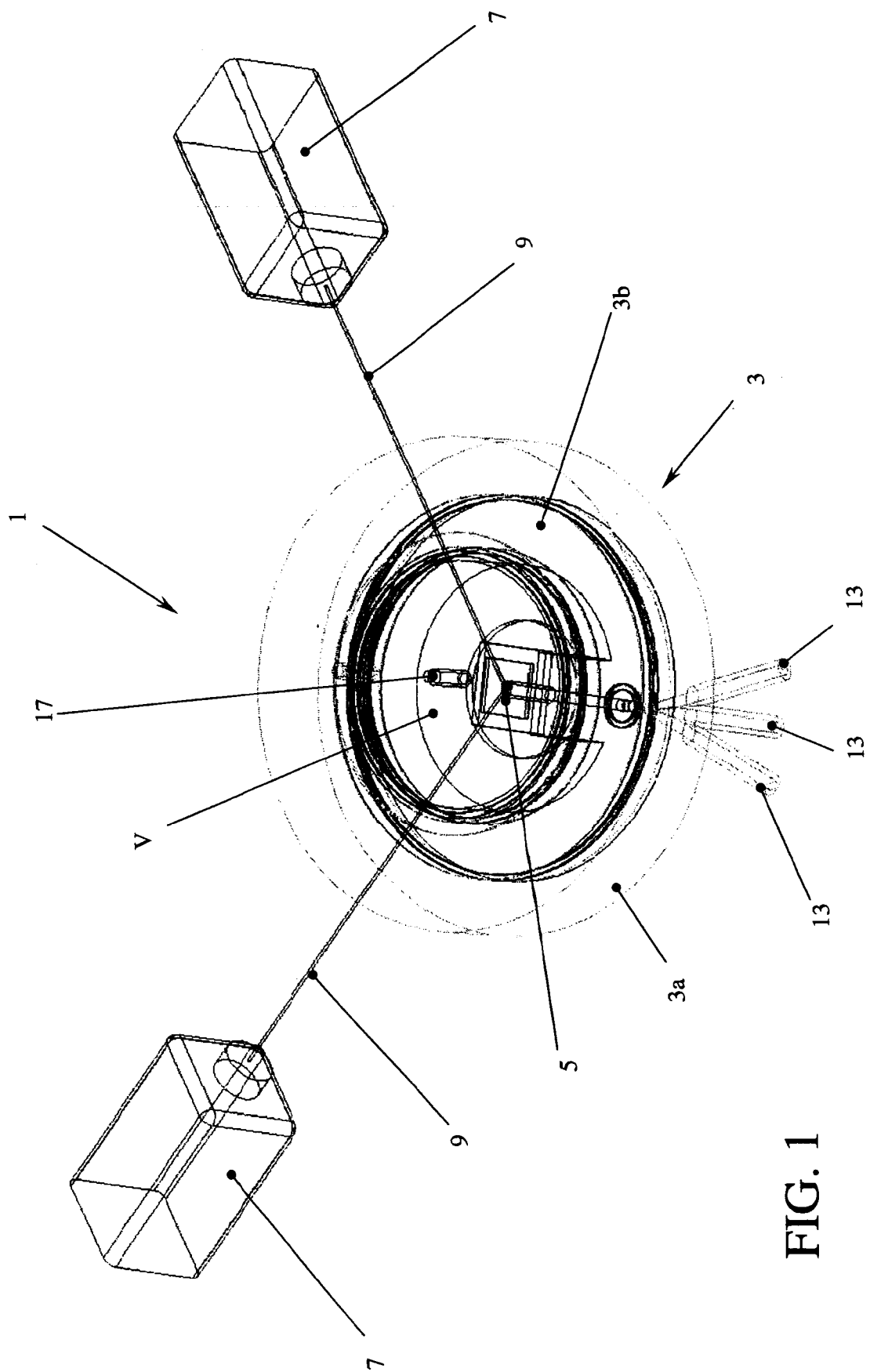


FIG. 1

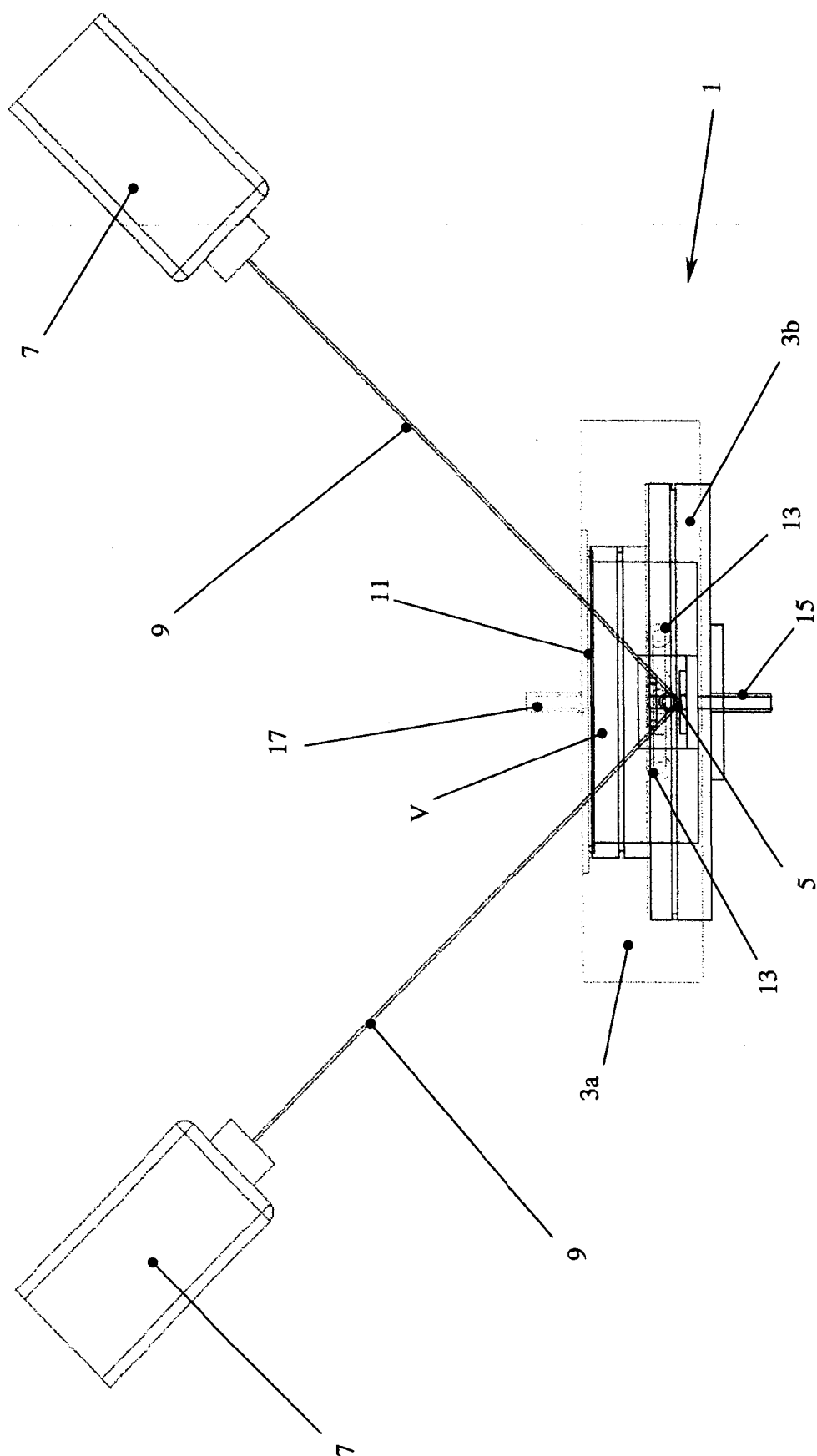


FIG. 2

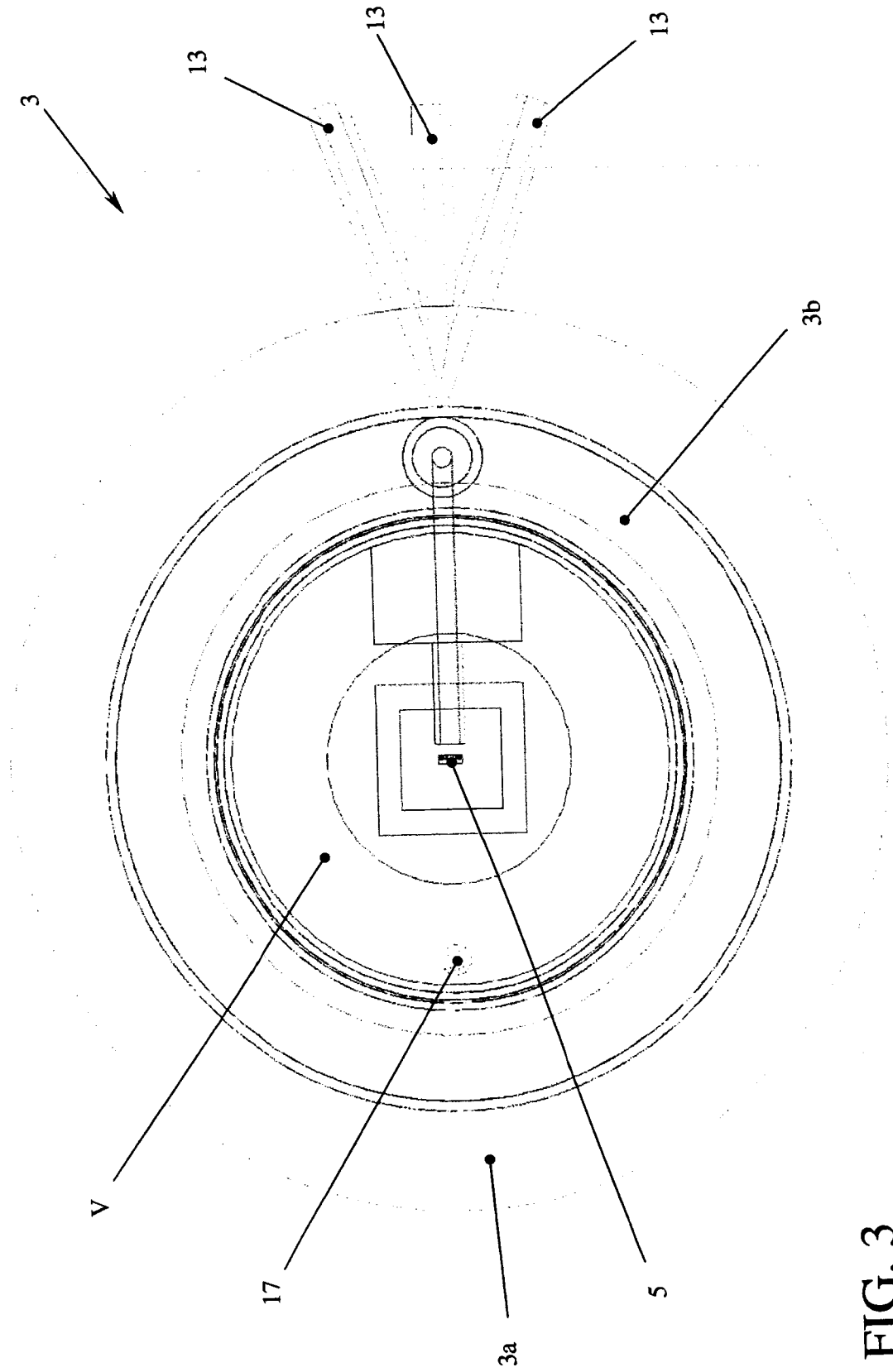


FIG. 3

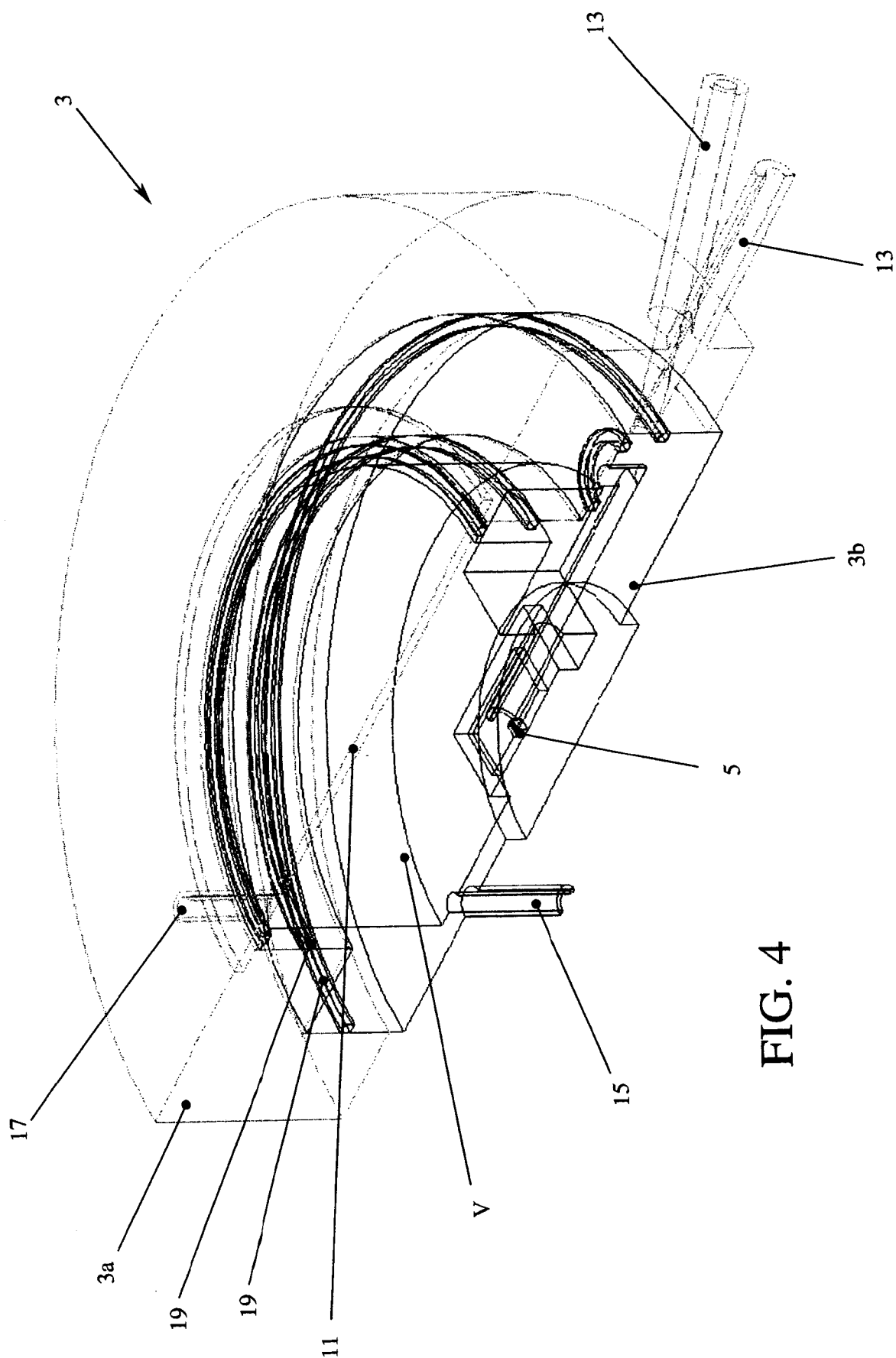


FIG. 4

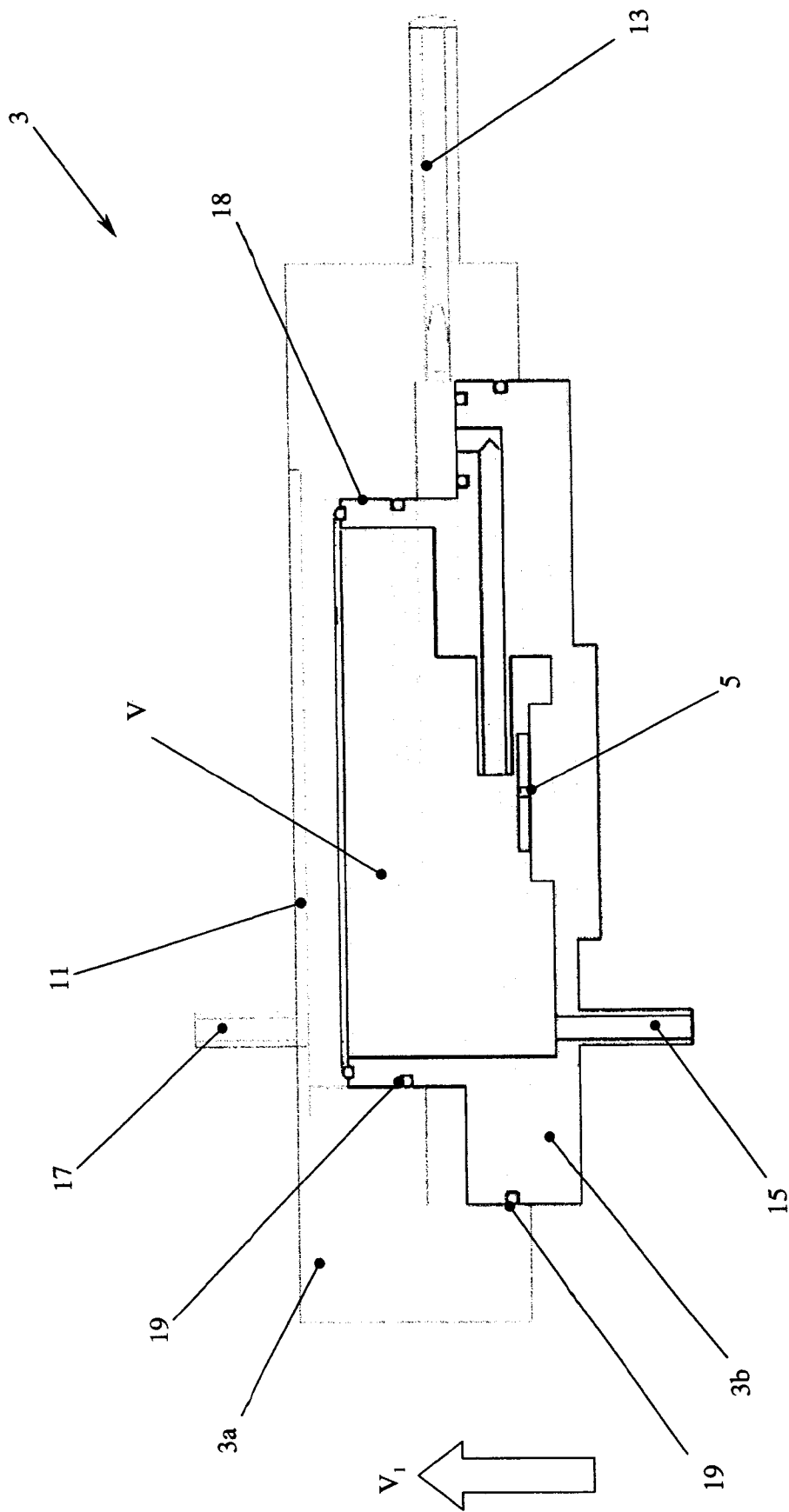


FIG. 5

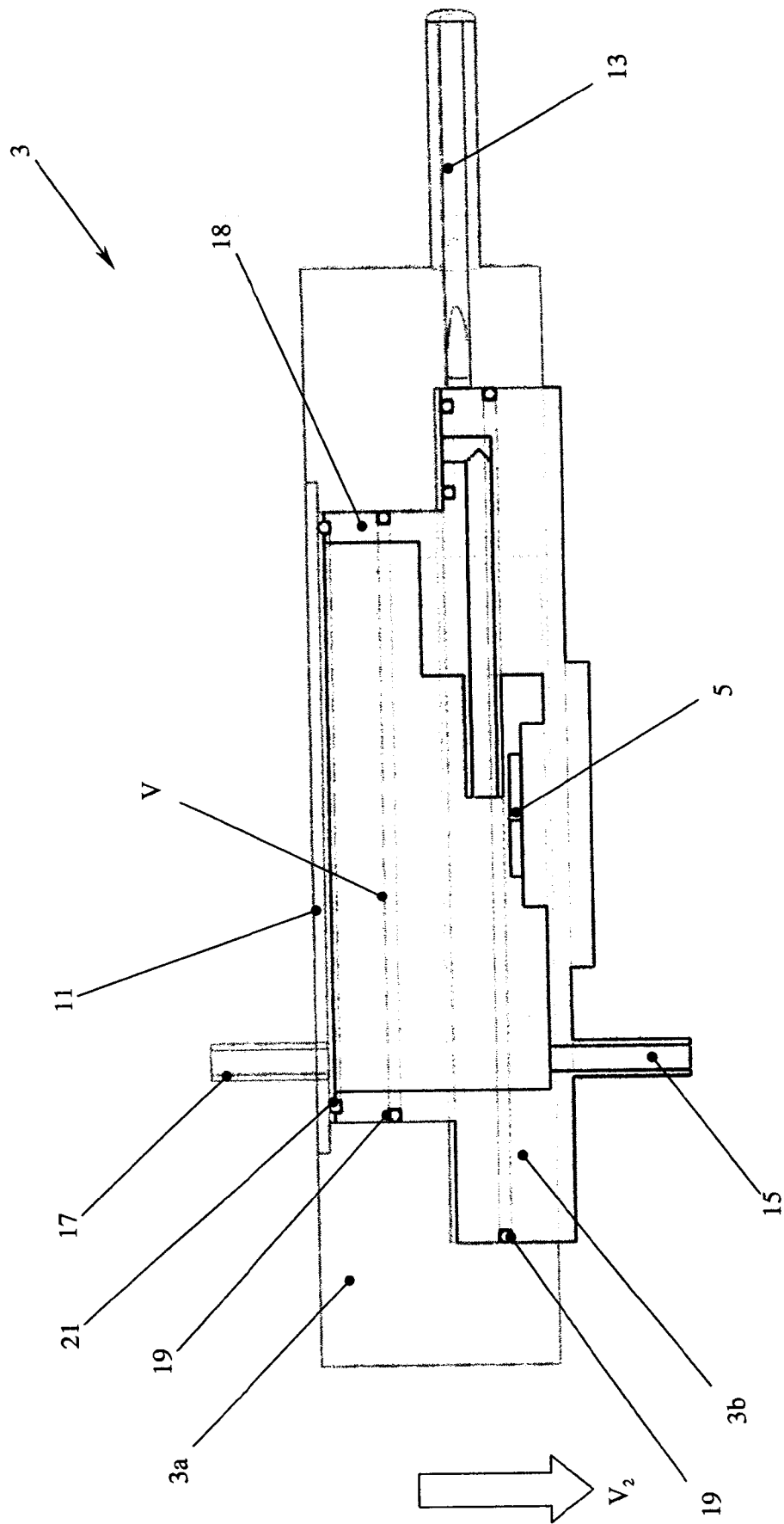


FIG. 6

INTERNATIONAL SEARCH REPORT

International application No
PCT/IT2013/000238

A. CLASSIFICATION OF SUBJECT MATTER INV. G01N9/00 G01N5/02 G01N29/02 G01N29/036 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) G01N B82Y		
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.
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☒ Further documents are listed in the continuation of Box C. ☒ See patent family annex.		
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Date of the actual completion of the international search 29 January 2014		Date of mailing of the international search report 10/02/2014
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016		Authorized officer Cantalapiedra, Igor

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