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(54) **PORTABLE DEVICE FOR DETECTION OF BIOMARKERS IN EXHALED AIR AND METHOD OF BIOMARKER DETECTION IN EXHALED AIR**

(57) A portable device for monitoring of exhaled air composition provided with a mouthpiece (U) and an air duct leading the air to the outlet port (O1) through a sensor unit (M), wherein the air duct is provided with a moisture filter (F) and the sensor unit (M) is connected with a control module (S) connected to an external interface system (I). The air duct also includes a pre-concentrator (P) and a carbon dioxide sensor (CO2) installed upstream of the sensor unit (M) and connected to the control unit (S) provided with a measurement triggering module (W) triggering a measurement using the sensor unit (M).

A method of exhaled air composition analysis according to the invention is characterised in that the composition analysis starts when the sensor (CO2) indication exceeds a threshold value.

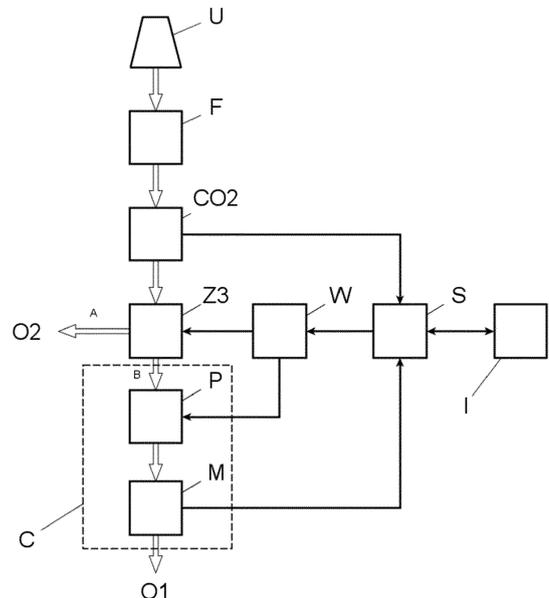


Fig. 1

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Description

[0001] Present invention is related to a portable device for detection of biomarkers and to a method of biomarker detection in exhaled air. Present invention is related, in particular, to biomarker indicating diabetes.

[0002] Current condition of the body, its dysfunctions and some medical conditions may be identified on the basis of presence and concentration of volatile organic compounds, so called biomarkers, in exhaled air. For example, presence of acetone in exhaled air is a diagnostic indication of diabetes.

[0003] Polish patent application no. P.423933 discloses a personal, portable device for exhaled air composition monitoring, which includes a housing with an inlet and an outlet for analysed air and a sensor unit system located inside the housing, provided with a system of sensors enabling gas detection and connected with a control module including a sensor signal converter, memory units and a microprocessor. The device is equipped with a first port enabling connection of a mouthpiece pipe, connected to the analysed air inlet leading to the sensor unit via an internal duct and a moisture filter. Such breath-based tests are a promising diagnostic tool which may enable early, non-invasive detection of many diseases. Their non-invasive nature makes them potentially usable directly by patients using personal devices. Unfortunately, concentration ranges of biomarkers present in exhaled air and providing potential diagnostic indications are often lower than measurement ranges of sensors enabling detection of these compounds, available on the market. Other substances present in the exhaled air, such as water present as vapour and droplet suspension, for example, trammel operation of such sensors. Advanced laboratory techniques, such as mass spectrometry or gas chromatography may not be used in portable and personal devices because of their size, working requirements and costs. The ability to test the concentration of such compounds by patients using portable and personal devices would be highly desirable.

[0004] The problem of inadequate sensitivity of semiconductor sensors was identified in European patent publication no EP2845009B1, which recommends the use of a special reaction mixture and a chemical detection method at home.

[0005] An alternative solution to this problem was proposed in the European patent application no. EP2920589, which discloses a sensor with a pre-concentrator - a device used to concentrate gases present in the sample before analysis. Use of this solution enables detection of compounds in exhaled air at concentration lower than the detection threshold of currently used sensors. However, this solution negatively impacts accuracy of detection, for two reasons. Firstly, it leads to an average concentration of detected compounds over the entire breathing cycle and secondly, it requires to include the concentration rate, which varies over time, in the result of the measurement.

[0006] Publication no. WO2009025488 of an international patent application discloses a device for analysis of gas composition provided with a control module, a display unit and a set of sensors. Gas fed to the device is dried using a filter.

[0007] The objective of the invention is to provide a portable, user-friendly and easy to manufacture device enabling independent measurements of biomarkers in the air exhaled by the patient and a method of detection of these biomarkers.

[0008] A portable device for monitoring the composition of exhaled air, provided with a mouthpiece and an air line leading the air from mouthpiece through a sensor unit to an outlet port, wherein the air line includes a moisture filter and the set of sensors is connected with a control unit connected to an internal interface system according to the invention has the air line that also includes a pre-concentrator and a carbon dioxide sensor connected with the control module, and is provided with a module triggering the measurement using a sensor set connected with the pre-concentrator. This configuration allows monitoring of carbon dioxide concentration to be used as a detection method indicating exhalation of the so called "useful air" - the air from pulmonary alveolus. This air is constituted by tidal air and part of expiratory reserve volume which usually remains in the lungs for a longer time and is ejected only if a full exhalation is forced. This air is more saturated with substances produced by the body of the patient-including biomarkers, present therein in higher and easier to detect concentrations, independent from the previous breathing cycle. By detecting high and easy to measure CO₂ concentrations we can thus determine the time at which the measurement should be performed in order to analyse useful air and improve working conditions of biomarker sensors, as well as to obtain a more reliable measurement with smaller impact of patient activity. Concentration using the pre-concentrator combined with the use of useful air allows better utilisation of the dynamic range of the sensors.

[0009] The carbon dioxide sensor is preferably located in the air line upstream of the sensor unit. This allows useful air to be detected in advance and fully utilised.

[0010] A portable device for monitoring of exhaled air composition according to the invention is provided with a valve cutting off air supply to the sensor unit located downstream of the carbon dioxide unit. The device is also preferably provided with the second outlet port, while the controlled valve is a three-way valve directing air to the second outlet port in its first position, to the pre-concentrator, the sensor unit and the first outlet port in its second position. Only useful air reaches the pre-concentrator in this configuration, thus ensuring a more precise measurement.

[0011] The carbon dioxide sensor is preferably integrated with the sensor unit in a single sensor matrix.

[0012] The pre-concentrator and the moisture filter are preferably integrated into a single module. This solution prevents detection sensitivity losses caused by filtration

and paradoxically, moisture filters heated cyclically in the pre-concentrator have an extended operational lifetime.

[0013] The sensor unit preferably includes an acetone sensor, preferably provided as a semi-conductor sensor. This allows suspected diabetes to be detected using a sensor easily fit inside a portable device.

[0014] The method of biomarker detection in exhaled air using a sensor unit, in which an exhaled air stream is fed from the mouthpiece to the outlet using an air line including a moisture filter and a sensor unit according to the invention is characterised in that the exhaled air is concentrated using a pre-concentrator and subjected to a carbon dioxide concentration measurement using a carbon dioxide sensor, while biomarker detection begins when the carbon dioxide indication exceeds a certain threshold. This allows detection in concentrated useful air, namely in conditions most favourable for the sensors.

[0015] Before biomarkers are detected using the sensor unit, a calibration measurement is preferably performed using the carbon dioxide sensor, for at least one breathing cycle or even for five breathing cycles and used to determine the threshold carbon dioxide concentration. The threshold concentration is preferably determined as a fraction in the range of 0.8 to 0.95 of the maximum carbon dioxide concentration measured during the calibration measurement.

[0016] Preferably threshold concentration is a fraction of 0.91 to 0.93 of the maximum carbon dioxide concentration. In case of significant amount of people within population in this range falls the value of fraction of maximal carbon dioxide concentration above which only useful air reach in biomarkers and relatively free of moisture is exhaled.

[0017] Before the biomarker detection, air flow to the sensor unit is preferably cut off using a valve opened again only when the sensor indication is higher than the threshold value. This prevents air other than useful air from reaching the pre-concentrator.

[0018] Exhaled air is preferably fed to the second outlet port before the carbon dioxide indication exceeds the threshold value.

[0019] The invention is explained below in detail with reference to the attached drawings in which Fig. 1 presents a block diagram of an example embodiment of the invention, Fig. 2 presents an example profile of CO₂ concentration changes in exhaled air and a correlated biomarker detection profile, Fig. 3 presents a flow diagram of the method according to the invention, and Fig. 4 presents schematically the pre-concentrator integrated with the moisture filter, intended for use in the disclosed invention.

[0020] In the first example embodiment of a portable device for monitoring the exhaled air composition, the block diagram of which is presented in Fig. 1, air exhaled by the patient, the line of which has been marked with a double arrow and the flow direction using arrows, passes through the mouthpiece U, the moisture filter F and reaches the carbon dioxide CO₂ concentration sensor and the

three-way valve Z3 controlled by a signal from the control module S, transmitted using the measurement triggering module W. The three-way valve Z3 in its position A directs the exhaled air to the outlet port O₂, while in position B, it directs the air to the measurement compartment C, where the pre-concentrator P and the sensor unit M are located. The air exits the sensor unit M and the compartment C through the outlet port O₁.

[0021] The moisture filter F is collecting - absorbing - water vapour present in the exhaled air. Vapour presence effectively interferes with gas sensor operation regardless of the detection method: semiconductors, electrochemical or optical methods, thus this interference should be eliminated. The moisture filter may also be provided in one of several forms, e.g. by using silica gel, which changes colour in contact with water vapour and thus signals the need to replace the filter. There are also membrane filters and activated charcoal filters available. Numerous commercial filters of these types are available on the market. Good results were obtained using the Hydro-Therm 1850 filter. The moisture filter is important for the operation of the pre-concentrator, as it prevents absorbing substances from being saturated with moisture from the air. Application of moisture filter allows elimination of the moisture on the result of measurement despite use of pre-concentrator.

[0022] The sensor unit M contains at least one sensor. In this particular embodiment this is an acetone sensor.

[0023] The pre-concentrator (or microconcentrator) comprises a system performing initial concentration of the exhaled air sample (pre-concentrating system). Its operation should ensure repeatable concentration factor for air samples. At negligible concentration of the tested gas in the sample, it is collected (e.g. Adsorbed) in the microconcentrator until its concentration exceeds the detection threshold of the used sensor, and then suddenly released in response to a control signal. This allows gas detection using a sensor, the detection threshold of which does not allow the gas concentration to be measured directly in the initial mixture (e.g. in mine gases, exhaled air, etc.). A pre-concentration according to the Polish patent publication PAT.225138 is used in this embodiment of the invention. It contains a duct filled with an adsorbent, heated using a heater along a section of its length, while cooling ducts open towards outside are provided along the remaining part of its length. The pre-concentrator is controlled by the control module S using the measurement triggering module W. Alternative pre-concentrator solutions available on the market are discussed in detail in the doctoral dissertation: Artur Rydosz, Detekcja gazow o malych koncentracjach z uzyciem mikroprekoncentratorow (Gas detection at low concentration using micropre-concentrators), AGH 2014, in Chapter 2: Gas sample concentrating systems.

[0024] Use of the three-way valve Z3 improves precision and repeatability of biomarker concentration detection, as only the end fraction of air exhaled by the patient saturated with biomarkers is pre-concentrated, and con-

centration of biomarkers remains relatively constant at the end of the exhalation. This facilitates restoration of the initial biomarker concentration, before concentration in the pre-concentrator, on the basis of the measurement with the pre-concentrator.

[0025] Signal connections are marked in Fig. 1 with a single line and transmission direction - using arrows. These connections may be provided as wired, optical or wireless radio connections. The control unit S is connected with a carbon dioxide CO₂ sensor, from which it receives the measurement signal and, via the measurement triggering module W, with the three way valve Z3, to which it sends the control signal, and with the sensor unit M sending biomarker indications. These connections may be provided using a dedicated I/O system, not presented in the figure. The control module S also communicates with the interface system I. This system includes buttons, wired and/or wireless communication modules, displays and other elements enabling user interaction or integration with other devices, in particular communication with a remote telemedical server. The measurement triggering module W may be provided as an electronic system adapted to generating a valve control signal and a pre-concentrator control signal. The control module S may be alternatively provided as a microcontroller or a FPGA array with adequate converters and the triggering module may be provided as a software element.

[0026] The device according to the invention enables air analysis to be performed along with changes to concentration of exhaled carbon dioxide, such that analysis of biomarker presence includes useful air exhaled at the end of the breath, richest in CO₂ and in biomarkers. Thus, CO₂ concentration is used as the reference signal, allowing the measurement to be triggered during the appropriate phase of breath. The moment when the threshold concentration is exceeded is used as the criterion in this case. An example profile of CO₂ concentration variations and a correlated profile of biomarker detection are presented in Fig. 2. The best conditions for biomarker detection during a breath cycle are indicated as 22 on the bottom graph. The wave indicated as 21 includes suboptimal conditions, under which no measurement is performed according to the invention. Limits (i) and (ii) of phases 21 and 22 are obtained analysing carbon dioxide concentration in the exhaled air - the top graph, which is much higher than biomarker concentrations and easily measured.

[0027] The method according to the invention is executed analysing air blown by the patient into the device through the mouthpiece U placed in the mouth. The sensor unit of the device includes at least one sensor of at least one biomarker, such as acetone. The analysis may be concluded with a quantitative determination - of biomarker concentration values or with a binary value indicating whether the threshold concentration was detected or not. A flow diagram of an example method according to the invention is presented in Fig. 3. During stage 1, when the measurement is initiated, the three way valve

is set in position A; this valve is then switched to position B if the indication of the carbon dioxide CO₂ sensor exceeds the specified threshold value. Stage 2 includes determination whether a threshold value has been set.

5 This value may have been stored from the previous measurement in the memory of the control unit S or may be input in advance to the device according to the invention using the interface system I.

10 **[0028]** The threshold value may also be determined using tables, according to patient data, such as e.g. age, weight or on the basis of a training measurement - calibration.

15 **[0029]** If the threshold value is not determined otherwise, calibration is performed during the calibration stage, for the given patient.

20 **[0030]** Calibration may be performed, for example, analysing indication of the carbon dioxide CO₂ sensor during a cycle of one or more exhalations and by determining the threshold value as a specific fraction of the maximum value. The specified fraction should be greater than 80%. Good efficiency of acetone determination as a biomarker was achieved in the range of 90% - 95%. For most of the population the most appropriate trigger value falls within a range of 91%-93% of maximal concentration.

25 **[0031]** Then, the actual measurement begins. During the actual measurement, stage 4 of carbon dioxide measurement, the carbon dioxide CO₂ concentration is measured and followed by stage 5, in which it is determined whether the threshold value has been exceeded. If carbon dioxide concentration measured using the carbon dioxide CO₂ concentration sensor exceeds the specified threshold value, the three way valve Z3 is switched to position B and during this stage, air is directed to the sensor unit M until the end of the exhalation, while stage 6 of biomarker detection includes triggering air release from the pre-concentrator and concentration measurement for at least one biomarker. Air exhaled at the end of the breath cycle - the so called useful air is the best material for biomarker analysis because of the higher biomarker concentrations and because of the fact that such performed measurements are much more repeatable. Concentration measurement performed for at least one biomarker may be quantitative or binary: detected/not detected.

45 **[0032]** The end of the breath is tested in stage 7 of breath end detection, which may be performed using a flow meter (if the device is provided with a flowmeter) or by detecting a drop in CO₂ concentration indicated by the carbon dioxide CO₂ concentration sensor. The method according to the invention may be performed by a human or using a software run on the device according to the invention or remotely controlling the device.

50 **[0033]** Good results were also obtained with fixed measurement time within a range of 1.5 s to 2 s. Process of exhaling air in a function of carbon dioxide concentration is relatively repeatable. End of exhalation is close to local maximum of exhaled CO₂ concentration in the breath cycle. Having reached 85% - 90% this concentra-

tion is usually stable for some time and then slightly increases to 91-93%, and finally drops. Rapid decrease of CO₂ concentration corresponds to the end of breath. Thereafter only small amount of air is exhaled.

[0034] Biomarker concentration may be determined more precisely, if measurement is performed over several exhalation, by repeating stage 4 of CO₂ concentration measurement with the three way valve set in position A. The test ends if stop criterion is met as determined during stage 8 of stop condition testing. The criterion may include the number of breaths, test time or the signal generated by the patient and recorded using the interface I.

[0035] The moisture filter F and the pre-concentrator P can be integrated within a single unit. This has an advantage as the heater of the pre-concentrator can be used to drying moisture filter F. Heating of the filter surprisingly increases its expected life span.

[0036] An example, applicable sensor unit M is provided as the integrated gas sensor array known from the disclosure of the Polish patent application P.417038 (the patent was granted on 29.04.2018). It is a monolithic array made using low temperature, co-fired ceramics LTCC, containing many ceramic layers. One of the layers includes separated arms, comprising thermal bridges with gas sensor heaters located on one side thereof. Through openings feeding gas to the sensors are provided at the layer between gas sensors and the environment, and an air compartment is provided in another layer. A list of other useful sensor types may be found in the following doctoral dissertation: Artur Rydosz, Detekcja gazow o malych koncentracjach z uzyciem mikroprekoncentratorow (Gas detection at low concentration using micropre-concentrators), AGH 2014 - p. 25. Application of such matrix in the present invention requires a branch in the airline to guarantee that not useful air is not going to be fed to pre-condenser.

[0037] The pre-concentrator P integrated with a moisture filter F is provided according to the invention as a device including an air duct filled with absorbing and adsorbing compounds. Thanks to this solution, the pre-concentrator adsorbs moisture and acts as a water vapour filter. This is advantageous in that the filtration does not reduce concentrations of analysed biomarkers. An example design of the pre-concentrator is shown schematically in Fig. 4. Gas inlet 51 continues as a quartz pipe 52 provided with polymeric adsorbing agent 52 on its walls capturing acetone molecules and with a Ni-CR heater 54. Acetone is adsorbed during exhalation and then released in a shorter time and at a higher concentration, once heated using the heater. Charcoal sieves (not shown) are used to remove acetone. Water is released at a temperature different than temperature used to release acetone. Thus, the same heater may be used to pre-concentrate acetone as a biomarker and to dry charcoal sieves, regenerating the initial condition of the moisture filter. This increases the filter lifetime. The pre-concentrator may also be adapted to biomarkers other

than acetone.

[0038] Depending on the application, the adsorbing agent may include a composite of various compounds, e.g. organic compounds such as TENAX-TA and compounds based on charcoal sieves CARBOXEN-1018, CARBOXEN-1000 or CARBOSIEVE-SIII. It is also possible to fill the pre-concentrator duct using spherical particles of various types, ensuring removal of water vapour and diabetes biomarkers. Particles with compounds responsible for water vapour adsorption are placed in the initial stage of pre-concentrator filling, such that water vapour is removed at the beginning of the process, and this part is known as the moisture filter or an RH filter. The RH filter should cover 10-30% of the device length, preferably 18-22%. The remaining volume is filled with particles containing and adsorbing agent, e.g. CARBOXEN-1018 offered by Sigma-Aldrich. Higher adsorption efficiency and shorter pre-concentrators may be achieved using a composite of at least two adsorbents TENAX-TA/CARBOXEN-1018.

[0039] Measurement interferences caused by adsorbed water vapour may be prevented by specifying a heating profile such that biomarkers are released first, at temp. lower than e.g. 220° C and after some detection time - water vapour is released at 350°-500°C, depending on materials used.

[0040] The embodiments of the invention discussed above are intended to explain the invention in a manner enabling its re-creation to people skilled in the art. People skilled in the art, who have read the disclosure, will be easily able to indicate other sensor and units which may be used, as well as other solutions distributing air within the device. Such people may also change the order of elements, use a bifurcated air line or various working compartments. The method according to the invention may be executed by a person performing the measurement using the central unit or by a person remotely communicating with the device or with the patient. This method may also be executed using a piece of software installed in the device or on a remote server. The control module (S) and the measurement triggering module (W) may be implemented as various solutions - as analogue or digital systems, including processors, microcontrollers or FPGA arrays. They may be implemented in the same or in two different hardware elements. All variations and modifications discussed in this paragraphs are covered by the scope of the claims presented below, which determine the actual scope of protection, otherwise not limited to examples, variants and embodiments discussed in the disclosure.

Claims

1. A portable device for detection of biomarkers in exhaled air, provided with a mouthpiece (U) and an air line, leading the air from mouthpiece (U) through a sensor unit (M) to an outlet port (O1), wherein the

- air line includes a moisture filter (F) and the sensor unit (M) is connected with a control module (S) connected to an interface system (I), **characterised in that** the air line also includes a pre-concentrator (P) and a carbon dioxide sensor (CO₂) connected with the control module (S), which is provided with a measurement triggering module (W) triggering a measurement executed with the sensor unit (M).
2. The portable device for monitoring of exhaled air composition according to Claim 1, **characterised in that** the sensor (CO₂) is located in the air line upstream of the sensor unit (M).
 3. The portable device for monitoring of exhaled air composition according to Claim 2, **characterised in that** it includes a controlled valve cutting off air flow to the sensor unit, located in the air line downstream of the carbon dioxide sensor (CO₂)
 4. The portable device according to claim 3, **characterised in that** it is provided with a second outlet port (O₂), while the controlled valve is a three-way valve (Z₃) directing air to the second outlet port (O₂) in its first position (A), and to the pre-concentrator (P), the sensor unit (M) and the first outlet port (O₁) in its second position (B).
 5. The portable device for monitoring of exhaled air composition according to Claim 1 or 2, **characterised in that** the carbon dioxide sensor (CO₂) is integrated with the sensor unit (M) in a single sensor matrix.
 6. The portable device for monitoring of exhaled air composition according to any of Claims 1-5, **characterised in that** the pre-concentrator (P) and the moisture filter (F) are integrated within a single module.
 7. The portable device for monitoring of exhaled air composition according to any of Claims 1-6, **characterised in that** the sensor unit (M) includes an acetone sensor.
 8. The portable device according to claim 7, **characterised in that** the acetone sensor is a semi-conductor sensor.
 9. A method of biomarker detection in exhaled air using a sensor unit (M), in which an exhaled air stream is fed from the mouthpiece (U) to the outlet (O₁) using an air line including a moisture filter (F) and a sensor unit (M), **characterised in that** the exhaled air is concentrated using a pre-concentrator (P) and subjected to a carbon dioxide concentration measurement using a carbon dioxide sensor (CO₂), while biomarker detection begins when the carbon dioxide sensor (CO₂) indication exceeds a threshold value.
 10. The method according to claim 9, **characterised in that** before biomarkers are detected using the sensor unit (M), a calibration measurement is performed using the carbon dioxide sensor (CO₂), for at least one breathing cycle, and used to determine the threshold carbon dioxide concentration.
 11. The method according to claim 10, **characterised in that** the threshold concentration is determined as a fraction in the range of 0.8 to 0.95 of the maximum measured carbon dioxide concentration.
 12. The method according to claim 10, **characterised in that** the threshold concentration is selected within a range of 0.91 to 0.93 of the maximal concentration.
 13. The method according to any of claims 9 to 12, **characterised in that** the threshold value is determined in a measurement covering at least five breathing cycles.
 14. The method according to any of claims 9 to 13, **characterised in that** air flow to the sensor unit (M) is cut off before the analysis using a valve (Z₃) opened again only when the sensor (CO₂) indication exceeds the threshold value.
 15. The method according to claim 14, **characterised in that** exhaled air is fed to the second outlet port (O₂) before the carbon dioxide sensor (CO₂) indication exceeds the threshold value.

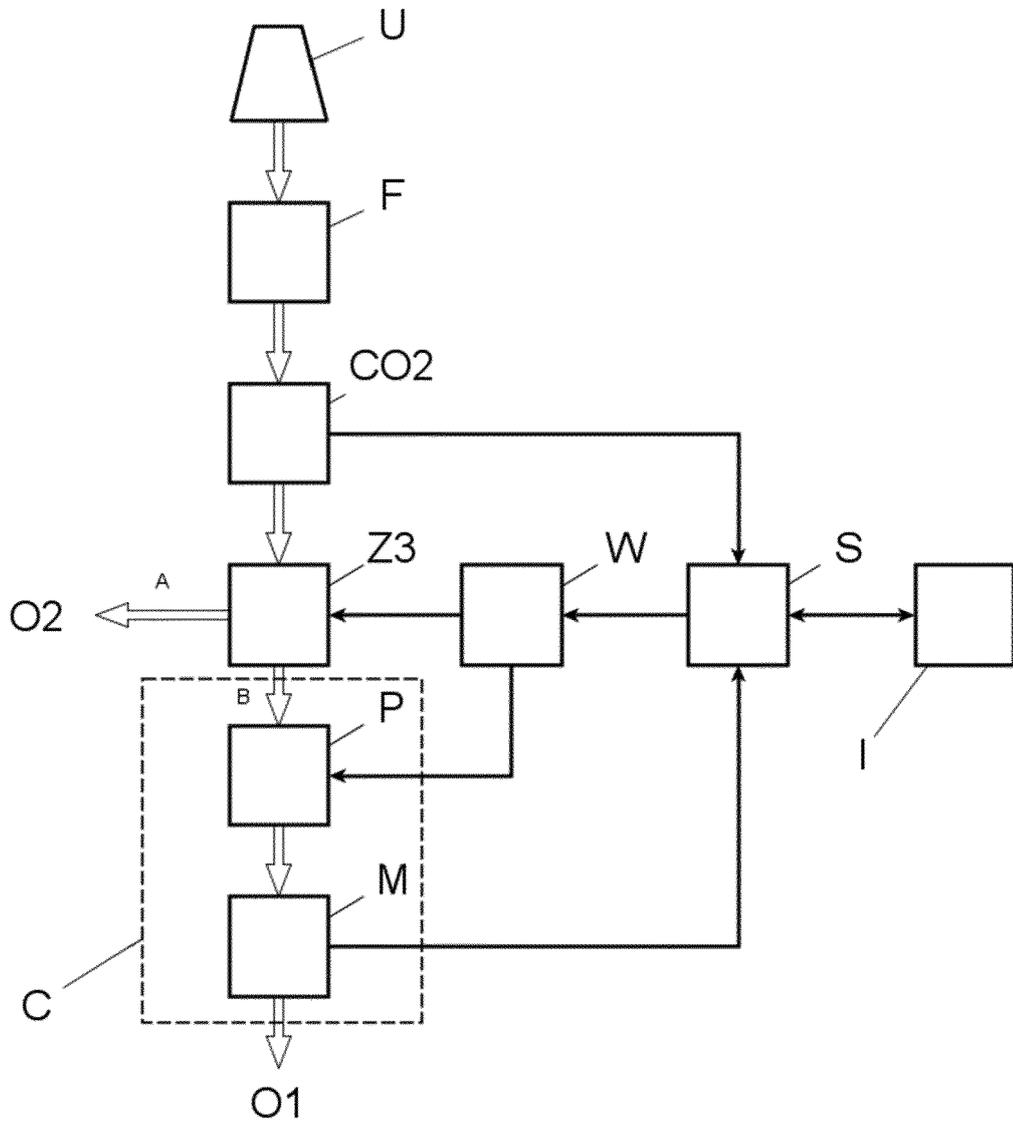


Fig. 1

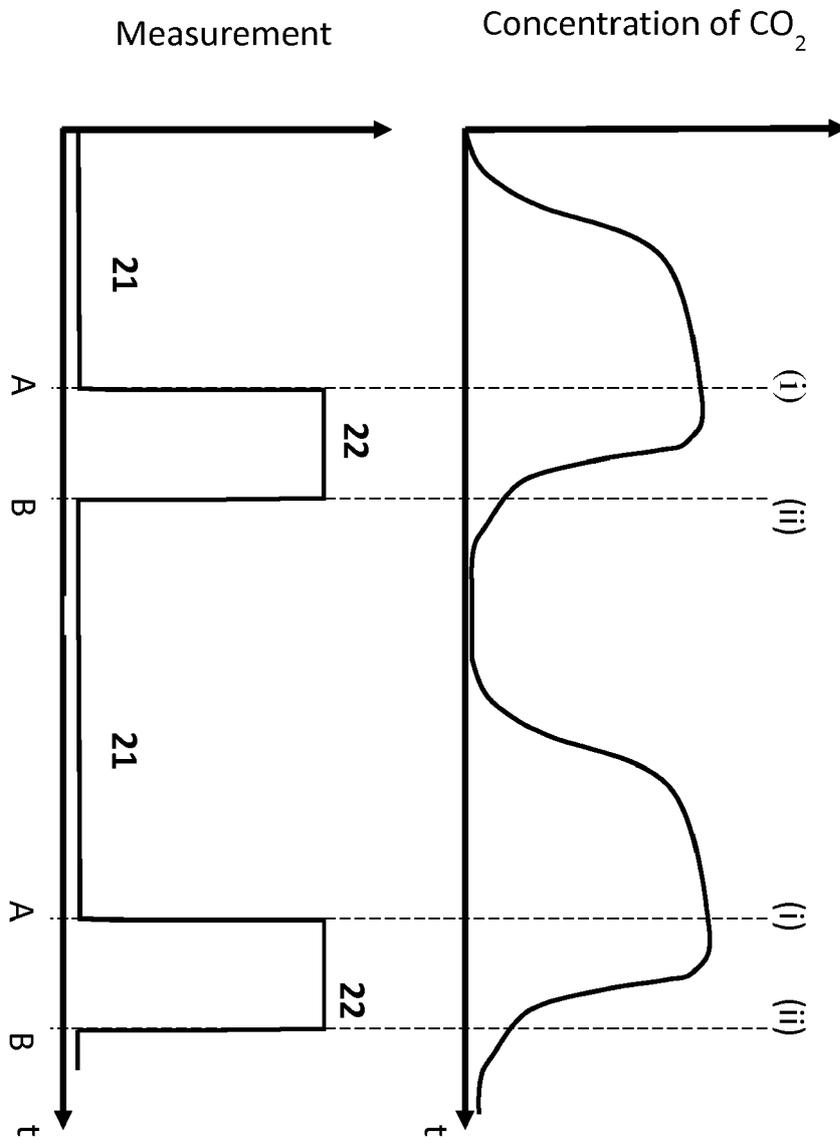


Fig. 2

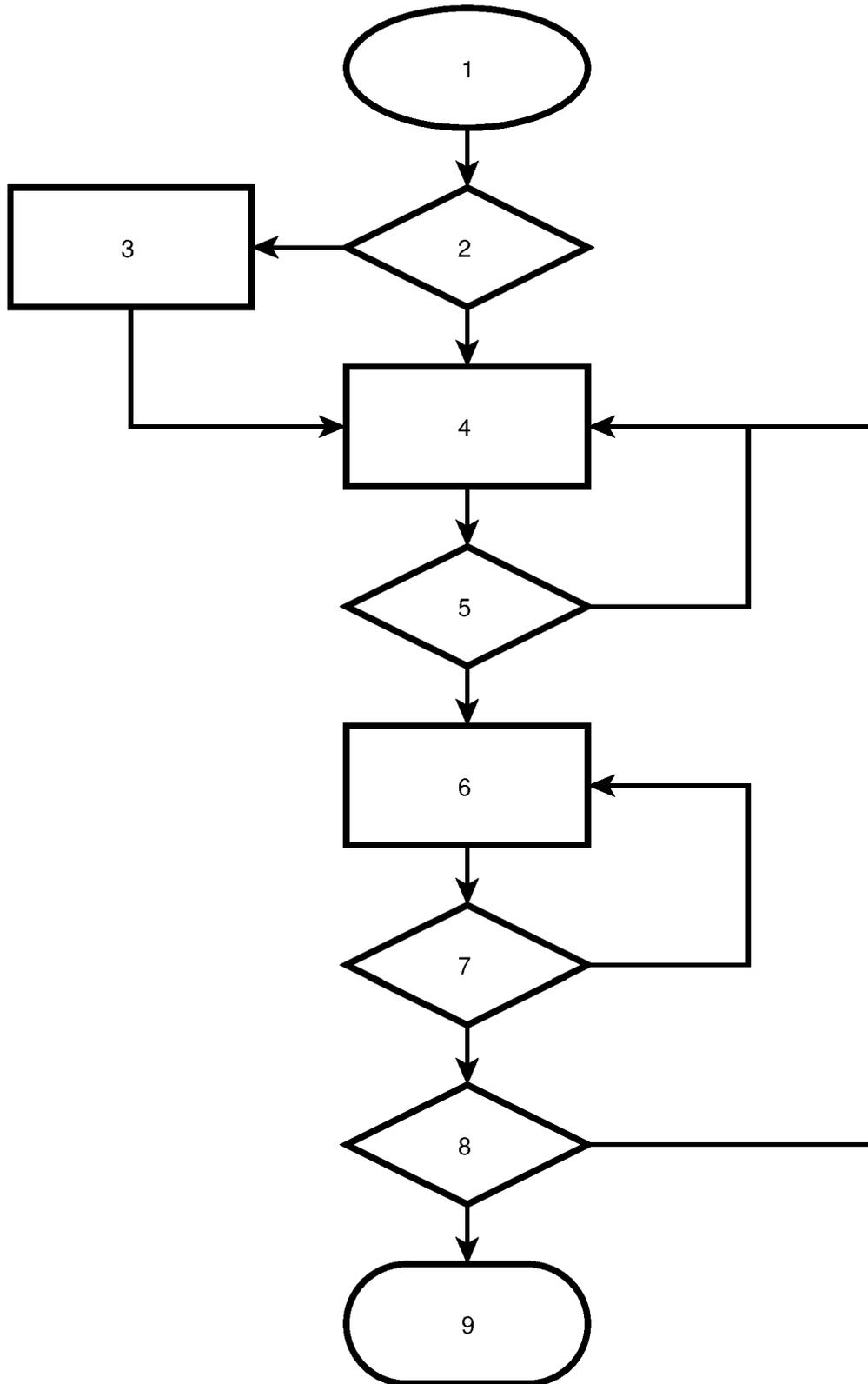


Fig. 3

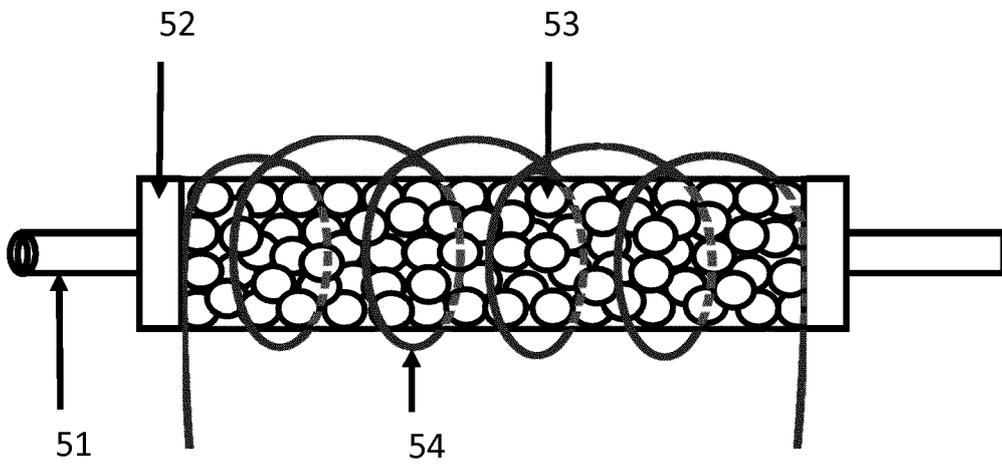


Fig. 4



EUROPEAN SEARCH REPORT

Application Number
EP 18 19 0345

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The present search report has been drawn up for all claims			
Place of search The Hague		Date of completion of the search 18 March 2019	Examiner Kraus, Leonie
CATEGORY OF CITED DOCUMENTS X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document	

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EUROPEAN SEARCH REPORT

Application Number
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ANNEX TO THE EUROPEAN SEARCH REPORT
ON EUROPEAN PATENT APPLICATION NO.

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5 This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report.
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