



(51) International Patent Classification:

A61B 5/097 (2006.01) G06F 19/00 (2018.01)  
A61B 5/00 (2006.01)

(21) International Application Number:

PCT/IB2017/055322

(22) International Filing Date:

05 September 2017 (05.09.2017)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

109617 12 September 2016 (12.09.2016) PT

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(81) Designated States (unless otherwise indicated, for every  
kind of national protection available): AE, AG, AL, AM,  
AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ,  
CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO,

(54) Title: SYSTEM FOR CONTROLLED AND SELECTIVE SAMPLING OF EXHALED AIR AND CORRESPONDING OPER-  
ATING PROCEDURE

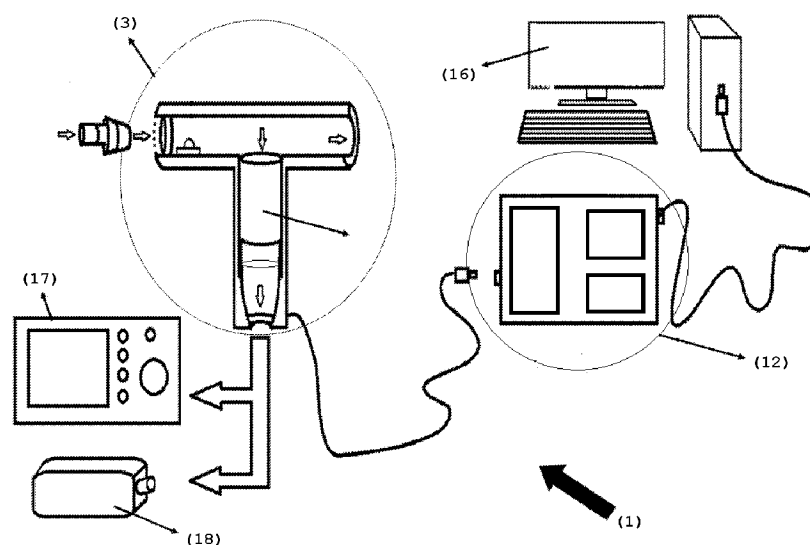


Figure 1

(57) Abstract: The present application is related with a system (1) and respective method of operation, for controlled and selective sampling of exhaled air from a predetermined part of the respiratory tree. The system (1) is comprised by two attachable modules: a portable sampling device (3) and a hardware module (12), controlled by a machine learning software (16) loaded on a processing device. The technology developed detects and imposes a breathing rhythm to the subject according to its characteristics (age, genre and physiological condition) and to synchronize the subject's breathing cycle with a representative modelled breathing cycle using the machine learning process (16). Then, it is predicted the instants for opening/closing the valve (9) to conduct the selected breath portion into the analyser (17) or collector (18). The system (1) disclosed allows monitoring, diagnosing and assessing medical conditions of the patient, as well as assessing the inflammation degree of the respiratory airways of the subject.

DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, 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, ST, 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))*

## D E S C R I P T I O N

**"SYSTEM FOR CONTROLLED AND SELECTIVE SAMPLING OF EXHALED AIR AND  
CORRESPONDING OPERATING PROCEDURE"****TECHNICAL FIELD**

The present application is concerned with a system, and corresponding method of operation, for selectively and controllably collect pre-determined fractions of exhaled air, for real time and on-line or posterior (offline) analysis of its composition.

**BACKGROUND ART**

For decades, the mammalian exhaled air, containing a complex mixture of gases, has been analysed as a diagnosis and monitoring method for multiple diseases. Even so, the understanding of the clinical importance of these gases is still increasing. For example, the detection of a variety of volatile components in breath, such as ammonia or sulphur compounds, provides information that can be related with a wide range of clinical conditions including diabetes, kidney dysfunction and liver impairment. More specifically, carbon dioxide is a known marker of the gas-exchange function of the lungs; ammonia has been identified as a marker of gastric disorders; and certain volatile organic compounds (VOCs) present in exhaled air can be useful for the diagnosis of several chronic diseases, including chronic inflammatory, lung cancer and intestinal diseases, as they have been linked to residual metabolites. Nitric oxide has also been linked to inflammation in the airways.

Thus, the detection and measurement of exhaled substances may be useful as a diagnostic and prognostic tool in a wide variety of medical conditions to assess different vital organ functions. Furthermore, the concentration of the substances in the exhaled

air varies depending on the respiratory origin of exhaled air to be analysed, including oral and nasal cavities, esophageal air and alveolar air. The concentration of most of the VOCs present in the exhaled air is very low (parts per billion (ppb<sub>v</sub>) or microgram per litre (µg/L) to parts per trillion (ppt<sub>v</sub>) or nanogram per litre (ng/L)). The detection of such small amounts in fractions of exhaled air from different respiratory origins has revealed itself one of new challenges to overcome in the most recent pulmonary breath acquisition/monitor devices.

Hitherto, multiple apparatus and methods are used for breath sampling and subsequent analysis of its chemical composition as non-invasive diagnostic instruments/tests for the diagnosis of the above mentioned diseases and others. Some of the problems related with the current breath tests can be summarized as follows:

- i. Incapacity of precisely select the fraction of exhaled air to collect or analyse;
- ii. Inability to collect/analyse only one fraction of exhaled air, since the great majority of systems uses capnography procedures. Capnography, defined as the method of monitoring the concentration or partial pressure of carbon dioxide (CO<sub>2</sub>) in the respiratory mixture of gases, has some limitations because it varies with (a) the inherent variation of breath composition and concentration of each constituent throughout the breathing cycle; (b) the speed of the breath, which affects the composition of the mixture between alveolar air and dead space air; (c) the depth and frequency of breathing, which control changes from autonomous to conscious breathing, when a person is asked to provide a sample of breath.
- iii. Some breath analysis procedures, such as those utilized in the analysis of VOCs, need special procedures for collecting and preparing the samples to prevent undesired sources of error. Such errors could arise from the presence of VOCs in the ambient gases and from the presence of undesired factors affecting the samples, such as the adsorption of breath components in the

conduits of the device. Subject inconvenience of being connected to a breath testing instrument for a long time;

- iv. Poor utilization of the breath test instrument, which is not cost-effective for a single subject to use a breath test instrument for several hours;

Several patent application documents discuss the state of the art in breath sampling for its analysis. For example, in WO 2014/110181 A1 and WO 2015/143384 A1 several methods and systems are described to automatically obtain and analyse a lung gas sample from the breath of a person for compositional analysis. WO 2015/143384 A1 introduces the imposition and control of the respiratory rate dependent on subject characteristics (sex and age). However, these systems and methods do not comprise an intelligent control software that 'learns' and adapts according with the respiratory characteristics of the subject, as the technology now developed contains. Furthermore, it enables a simultaneous analysis of multiple compounds of the exhaled air instead of analysing a single compound at a time as suggested by the mentioned documents. Although the referred documents disclose the possibility of measurement of the temperature of the air of the respiratory airways, the possibility to assess the degree of inflammation of the respiratory airways it is not provided, as it is disclosed in the present application.

US 2006/0200037 A1 and US 2015/065901 A1 disclose a physical process of acquisition of exhaled air, comprising a sensor (which measures a characteristic of the exhaled air), valves and a control module. These components provide a feedback mechanism to assess the state of the operation or a processor to measure the acceptability of the breath signal. In addition to similar components, the technology now developed comprises an intelligent control software that allows the definition of global variables of the process, imposes a respiratory rate to the subject (according to the characteristics of the subject), and synchronizes the breath cycle of the subject with a representative and modelled respiratory

cycle, which learns and adapts to the subject's breathing characteristics. Therefore, the precision in the prediction of the instants of exhaled air sampling is increased. Additionally, the technology now developed also allows the analysis of exhaled air compounds in real time, by coupling the device to an analytic analyser.

Additionally, the system developed includes a heating element of the exhaled air conducting tubes in order to prevent the adsorption of compounds to the walls of the device; and also includes the assessment to the degree of inflammation of the respiratory airways based on the measurement of the temperature of the exhaled air.

Therefore, there is an important need for a breath sampling apparatus which will overcome some of the above-mentioned disadvantages of present breath testing sample collection procedures. The problems remaining to be solved comprise the question of how to achieve accurate, selective and repeatable sampling, how to ensure easy and safe handling, and maybe most importantly, the issue of sample stability to allow a proper chemical analysis.

## **SUMMARY**

The present application describes a system for controlled and selective sampling of exhaled air comprising:

- A portable sampling device comprising at least one air sensor and a diverter valve;
- A hardware module connected to the portable sampling device, configured to receive, process and transmit data from the at least one air sensor, and to actuate the diverter valve;
- A processing device comprising interface means and processor means, said processing device being configured to operate the hardware module according to a machine learning algorithm based on the data sent by the hardware module.

In one embodiment of the system, the portable sampling device has a t-shaped internal cavity formed by:

- A longitudinal conduit comprising an air sensor conduit in its inlet port wherein the at least one air sensor is installed, and an elimination air conduit in its outlet port;
- A vertical conduit, connected to the longitudinal conduit, comprising an air sampling conduit wherein the diverter valve is installed, and wherein the outlet of the vertical conduit is connected to air collected means;

In another embodiment of the system, the portable sampling device comprises a heating component covering the internal surfaces of the air sensor conduit air, the elimination air conduit and the air sampling conduit.

Yet in another embodiment of the system, the air collected means are of a reservoir type or analyser type.

Yet in another embodiment of the system, a disposable non-rebreathable mouthpiece is attached to the longitudinal inlet port.

Yet in another embodiment of the system, the air sensor is a temperature sensor.

In another embodiment of the system, the hardware module comprises:

- A signal condition circuit, configured to receive and process the signal from the air sensor;
- A processing and communication unit, configured to manage the acquisition and the signal communication to the processing device;

- An automatic flow switching circuit (15) configured to operate the diverter valve of the portable sampling device.

The present application also describes a method of operating the system for controlling and selective sampling of exhaled air previously described, characterized by being independent of the subject's CO<sub>2</sub> metabolic production and comprising the following steps:

- a) Initialization of the interface means of the processing device;
- b) Configuration of subject-related variables in the processing device, namely age, genre and physiological conditions of the subject such as, but not limited to, seated, lying down or under effort trials;
- c) Configuration of global variables of the acquisition process in the processing device, including:
  - The fraction of interest of exhaled air to sample, according to the origin of the same;
  - The percentage of the valve opening which conducts the exhaled air inside a portable sampling device;
  - The number of respiratory cycles for the calculation of the average time of expiration by a machine learning algorithm.
- d) Acquisition of exhaled air through disposable and non-rebreathable mouthpiece, for at least one respiratory cycle and until it is regular, according with a rhythm previously defined by the said machine learning algorithm and demonstrated by a graphical interface, based on the said subject-related variables, collected in step b);
- e) Measuring the exhaled air flow, identifying the endogenous fraction of exhaled air independently of carbon dioxide metabolism of the subject, through the temperature variation measured by a

temperature sensor, for the calculation of the exhaled air flow by the said machine learning algorithm;

**f)** Measuring the breathing frequency and the average time of the respiratory cycle, comprising the inspiratory and expiratory phases, by the machine learning algorithm;

**g)** Synchronizing the acquired respiratory cycle with the respiratory cycle learned and modeled during the steps d) to f) by the machine learning algorithm;

**h)** Calculating the average time of expiration, by the said machine learning algorithm for the adjustment of the representative and modeled respiratory cycle;

**i)** Prediction of the instants of collection of exhaled air fraction of interest by said machine learning algorithm;

**j)** Heating the internal parts of the air sensor conduit, elimination air conduit and air sampling conduit of said portable sampling device, by means of the heating component;

**k)** Sending the instants for exhaled air acquisition predicted in i) to the processing and communication unit of the hardware module;

**l)** Said unit actuates on a valve of the device that when closed conducts the exhaled air fraction of interest to an elimination outlet of said portable sampling device, and when open conducts the exhaled air fraction of interest to a sampling outlet of said device;

**m)** Collection of exhaled air fraction of interest by said portable sampling device.

In one embodiment of the method, the exhaled air fraction of interest to be collected has several origins, namely mouth, nasal, esophageal and alveolar air.

In another embodiment of the method, the exhaled air fraction of interest is collected and derived from a single respiratory cycle being available for real time analysis by the analytical equipment.

Yet in another embodiment of the method, the exhaled air fraction of interested is collected and derived from multiple respiratory cycles being conducted to a sample reservoir.

The present application also describes the use of the system now developed for collecting the exhaled air fraction of interest for analysis of its chemical composition.

Besides that, the present application also describes the use of the system now developed for detection of the inflammatory state of the respiratory airways through the measurement of the temperature of the exhaled air by the temperature sensor during a respiratory cycle.

## GENERAL DESCRIPTION

The present application relates to a system and respective method of operation, for selectively and controllably collect exhaled air from different respiratory origins, namely, but not limited to, oral cavity, esophageal air and alveolar air, independently of the subject's metabolic production of CO<sub>2</sub>. The air fraction is available for real time analysis of its chemical composition or simply collected for future analysis. The system is comprised by two attachable modules: the portable sampling device and the hardware module, controlled by a machine learning software loaded on a processing device.

The portable sampling device is comprised by a T-shaped internal cavity which can be sized and shaped to enclose at least an air

sensor and a diverter valve. Moreover, the portable sampling device can enclose various air conduits, such as, but not limited to, an air sensor conduit, an elimination air conduit, and an air sampling conduit. A disposable non-rebreathable mouthpiece is attached to a longitudinal inlet of the portable sampling device.

The said air sensor of the portable sampling device is configured to directly or indirectly detect the different phases of the respiratory cycle of a subject, by using several types of sensors, such as, but not limited to, flow sensors, airway pressure sensors, capnometers, breath sound sensors and thermal sensors. Due to the possibility of correlating the variation of temperature of the exhaled air with the air flow of exhaled air and, since the temperature is a marker of pathological factors and important as a measure of physiological events, the portable sampling device can comprise a sensor of temperature. Depending on the variation of temperature of the exhaled air recorded in the sensor of temperature of the portable sampling device a different output will be produced. It is also configured to be capable of being connected to the portable sampling device in the air sensor conduit and its replacement is allowed after a significant number of utilizations, in order to maintain the full capacities of the system.

The valve of the portable sampling device can be configured to be responsive to a gate signal transmitted by the hardware module, indicated by the machine learning software, and to automatically change its position according to such gate signal. The type of automatic valve which can be used for this purpose may vary. Since the hardware module of the system is an electronic device, a solenoid valve can be electromechanically actuated by controlling an electric current flowing through a coil, which switches the output of the exhaled air flow between two valve ports. It can be appreciated that this technology is not limited in this regard and any suitable electrical or mechanical valve can be used to divert the exhaled air in the portable sampling device. By default, the flow is directed to the normally open port when the said valve is

not operated. When the intelligent software algorithm determines the change of position of said valve, from position **a** (closed) to position **b** (open), the said valve can selectively conduct a predetermined fraction of the flow of exhaled air passing through the longitudinal elimination air conduit to the respective elimination outlet of the portable sampling device, or through the air sampling conduit to the vertical outlet. When the valve is in position **a**, the flow of exhaled air which circulates through the sensor air conduit, is then directed through the longitudinal conduit and exits through the longitudinal elimination outlet of the portable sampling device. Also if the valve is in position **a**, the flow of exhaled air passing by the sampling air conduit, below the valve, is inexistent. However, when the valve is in position **b**, the flow of exhaled air circulates through the sensor air conduit and is then diverted through the sampling air conduit vertically disposed, where the fraction of the flow of exhaled air can either be collected in the air sample reservoir or directly and real-time analyzed in the analytical analyser coupled to the system. The analytical analyzer can be selected from the group of: chemical, electrical, optical and chromatographic analyzers. It can be noted that the system is not limited in this regard and any suitable analyzer can be used to precisely determine the chemical composition of exhaled air samples.

The portable sampling device also comprises a heating component covering its internal surface. The said heating component is configured to actuate during the overall process of acquisition of exhaled air in order to avoid particle condensation and the adsorption of exhaled air constituents to the internal walls of the air conduits of the portable sampling device.

The hardware module is configured to control the overall system by modeling the signal acquired by the air sensor and determining the actions to be taken in order to affect the direction of the exhaled air, controlled by the position of the valve. The said hardware module is, thus, responsive to the air sensor and to the machine learning software of the system since it receives, processes and

transmits signals between the remaining components of the system. This hardware module comprises:

- A signal conditioning circuit, configured to receive and process the signal from the air sensor of the said portable sampling device, in order to allow a better use of the analog digital converter (ADC) by obtaining an amplified signal;
- A processing and communication unit which manages the acquisition and the signal communication to the processing device where the machine learning software is loaded;
- And an automatic flow switching circuit that affects the steering flow of exhaled air by the valve.

The processing and communication unit is configured to create a gate signal when the digital output of the ADC transitions to a high logical level, becoming the transistor of the automatic flow switching circuit in saturation, allowing the passage of current to the valve and causing the flow of air to pass through the air sampling conduit. If the ADC digital output is at a low logical level, the transistor is cut and there is no current flow to the valve, which implies that the air flow exits through the elimination air conduit.

The system also includes a machine learning software which is responsive to the hardware module and comprises a graphical interface to interact with the subject/operator, allowing the definition of global features and assessment of the state of the operation. Said machine learning software also includes an internal algorithm to control the device functioning and to determine the precise moment for selectively sampling exhaled air, through a machine learning process.

The algorithm implemented in the machine learning software of the system comprises a digital filter in order to acquire the signal obtained from the air sensor with as minimal noise as possible, ensuring, at the same time, no loss of information. The algorithm is configured to:

- Measure the respiratory flow, and to identify the endogenous fraction of the exhaled air, independently of the carbon dioxide metabolism of the subject, through the air sensor's processed signal, thereby calculating the flow of exhaled air;
- Effectively detect the breathing frequency of the subject;
- Distinguish between inspiratory and expiratory breath phases, based on the detection of maxima and minima of the sensor-processed signal;
- Synchronize the breath cycle of the subject with a representative and modelled breath cycle through at least three complete respiratory cycles. The imposition of a breath pace rhythm to the subject, by the graphical interface and according with the global features of the subject, allows a fast synchronization of breath rhythms and, consequently, less time of acquisition of the predetermined portion of exhaled air.
- Determine the average time of expiration in order to select a predetermined fraction of the expiration interval, which is dependent of the respiratory origin of the exhaled air;
- Calculate the average time of expiration of the subject, defined by the time difference between a maximum and a subsequent minimum, according with a number of breath cycles that the operator selects in the graphical interface of the machine learning software.

The machine learning process related with the system is based on the continuous calculation and saving of the average time of expiration values, allowing the prediction of the time of occurrence of a new expiration and, consequently, the prediction of the precise time-frame for the acquisition of the fraction of exhaled air to sample. This ability, coupled with the synchronization mechanism, makes said system capable of interpreting different breathing rhythms from subject to subject

and allows a more precise and less time consuming acquisition of the predetermined portion of exhaled air.

After the prediction of the moments of breath sampling during exhalation, the machine learning software is configured to transmit that information to the hardware module which operates on the valve, through a gate signal, as described above.

The graphical interface of the machine learning software can be used to define the global operating variables such as, but not limited to, the fraction of exhaled air to collect/analyze, the percentage of aperture of the valve and the number of cycles used to determine the average time of expiration. Said graphical interface of the machine learning software (16) also allows defining subject-related variables, such as, but not limited to genre, age and physiological conditions (seated, lying down or under effort trial), to start and stop the acquisition process and to save data for later analysis. The graphical interface also provides simultaneously feedback indicators for communicating with the subject/operator. Said feedback indicators represent a central part of the present technology, since the breathing rhythm can be followed by the subject, according to the global subject-related variables previously defined, and the state of functioning of the valve (open or closed). This information can be displayed in an animated way (for the breath cycle synchronization) or graphically, such as the treated signal obtained by the air sensor, that can be used as a feedback indicator. However, this technology is not limited in this regard and other types of indicators can be used with this purpose.

After the connection of all components to the processing device the graphical interface is initiated. The operator first defines the global operating and the subject-related variables. The global operating variables include, but are not limited to, the selection of the fraction of exhaled air to collect/analyze (mouth, nasal, esophageal or alveolar air); the percentage of aperture of the valve; and the number of respiratory cycles for determining the

average time of expiration by the algorithm. The said subject-related variables include, but are not limited to, the genre, age and subject physiological conditions (seated, lying down or under effort trial). The subject is then asked to exhale into the non-rebreathable mouthpiece, which is already attached to the portable sampling device. During this step, and as the subject breathes into the portable sampling device through the mouthpiece, the operator must verify that the subject's breathing rhythm follows a regular behavior, according to the breathing pace, previously defined by the subject-related variables, and displayed in the graphical interface. Next, the electrical signal produced by the air sensor is then processed and transmitted by the hardware module to the machine learning algorithm.

Said algorithm then determines a set of parameters, through the analysis of the signal produced by the air sensor and transmitted by the hardware module. The said parameters are critical for the procedure of sampling the exhaled air fraction of interest and include (i) the respiratory flow, with identification of the endogenous fraction of exhaled air independently of carbon dioxide metabolism of the subject; (ii) the exhaled air flow; (iii) the breathing frequency and (iv) the average time of the respiratory cycle, which comprises the inspiratory and expiratory phases.

Subsequently, the synchronization between the breath cycle of the subject and a representative and modeled breath cycle of the algorithm is evaluated by the machine learning algorithm. If this synchronization does not occur during three completed respiratory cycles, the subject is informed by the graphical interface so that the subject corrects his breathing cycle, by imposing a breathing rhythm. As soon as the said synchronization occurs, the average time of expiration is calculated by the machine learning algorithm, for the previously predefined number of cycles, enabling the process of machine learning and the prediction of the exact moments for exhaled air fraction collection. The prediction of said exact moments for the collection of the fraction of interest of exhaled air is related with the region of interest, of the subject's

respiratory signal, during exhalation. These regions of interest for collection of the exhaled air fraction of interest are defined according with a percentage of the subject's exhalation during its respiratory cycle. After this prediction, the feedback indicator "state of aperture of the valve (closed or open)" is communicated to the operator. The machine learning algorithm then transmits the moments of exhaled air acquisition to the processing and communication unit of the hardware module, which actuates on the automatic flow switching circuit by generating and transmitting a gate signal to the valve, for a period of time dependent on the fraction of interest of exhaled air to collect. The valve can then selectively gate the fraction of interest of the exhaled air flow. The said fraction of interest of the exhaled air flow can be stored in an air collection reservoir or directly analyzed in the analytical analyzer. Lastly, the presence of chemical compounds in the fraction of interest of exhaled air can be detected, whether offline or in real time. Then, the operator can optionally write comments that have elapsed during the acquisition process and save them along with the acquisition data.

#### BRIEF DESCRIPTION OF THE FIGURES

For an easier understanding of the technology developed figures are attached, which represent preferred embodiments which, however, are not intended to limit the scope of the present application.

**FIGURES 1 and 2** illustrate a schematic view of the system for controlled and selective sampling of exhaled air, in which (1) represents the system, (2) the mouthpiece, (3) the portable sampling device which comprises: the inlet (4), the air sensor (5), the air sensor conduit (6), the elimination air conduit (7), the elimination outlet (8), the valve (9), the air sampling conduit (10) and the sampling outlet (11). The hardware module of the device (12) comprises: the signal conditioning circuit (13), the

processing and communication unit (14) and the automatic flow switching circuit (15). In both figures is also represented the machine learning software (16), the analytical analyzer (17), the collection reservoir (18) and the heating component (19).

**FIGURE 3** illustrates a schematic view of the method for selectively collecting exhaled air, wherein the reference signs represents the steps of:

20 - Definition of variables for the process and from the subject;

21 - Subject exhaling through the mouthpiece during multiple exhalations;

22 - Sensing the temperature of the exhaled air from the subject;

23 - Determination of respiratory parameters and phases (inspiration and expiration);

24 - Breath cycle of subject is synchronized with the mathematically simulated one;

25 - Communicate with the subject to impose a steady breath rhythm;

26 - Prediction of the moments for breath acquisition;

27 - Generate gate signal for predetermined period of time;

28 - Selectively gate a predetermined portion of flow of exhaled air;

29 - Initiate selectively acquisition of a predetermined portion of flow of exhaled air to the collection reservoir;

30 - Initiate selectively acquisition of a predetermined portion of flow of exhaled air to the analytical analyzer;

31 - Detect presence of chemical compounds in a predetermined portion of exhaled air.

**FIGURE 4** shows a representative graph of the synchronization between an acquired respiratory signal of a subject with a normal

breathing rhythm (32), with the signal of the representative and modeled respiratory cycle (33) by the machine learning software (16) algorithm, obtained by the subject's breathing pace imposition and the machine learning mechanism. In FIGURE 4, and as example, it is also represented the time-frame related with alveolar air collection (34).

#### DETAILED DESCRIPTION

The present application relates to a system (1) and respective method of operation, for selectively and controllably collect exhaled air coming from different respiratory origins, namely, but not limited to, oral and nasal cavities, esophageal air and alveolar air, independently of the metabolic production of CO<sub>2</sub>. The exhaled air fraction of interest is available for real time analysis of its chemical composition or simply collected for future analysis, without adapting the configuration of the system. In a preferred embodiment, the system (1) is comprised by two attachable modules: the portable sampling device (3) and the hardware module (12), controlled by a machine learning software (16) loaded on a processing device.

The portable sampling device (3) includes a T-shaped internal cavity which can be sized and shaped to enclose at least an air sensor (5) and a diverter valve (9). Moreover, the portable sampling device (3) can enclose various air conduits, such as, but not limited to, an air sensor conduit (6), an elimination air conduit (7), and an air sample conduit (10). A disposable non-rebreathable mouthpiece (2) is attached to a longitudinal inlet (4) of the portable sampling device (3).

In the present embodiment, the said air sensor (5) of the portable sampling device (3) is configured to indirectly detect a flow of exhaled air from a subject, through temperature. The said air sensor (5) can be, but is not limited to, a coated precision solid state

temperature sensor, able to read temperatures ranging from 0° to 70°C.

The valve (9) of the portable sampling device (3) can be configured to be responsive to a gate signal transmitted by the hardware module (12) by indication of the machine learning software (16) and to automatically change its position according to such gate signal. In this preferred embodiment, the portable sampling device (3) comprises a solenoid valve (9) which has a common input and two outputs: one normally closed and another normally open. By default, the flow is directed to the normally open port when the said valve (9) is not operated. When the intelligent software (16) algorithm determines the change of position of said valve (9), from the position **a** (closed) to the position **b** (open), the said valve (9) can selectively conduct a predetermined fraction of the flow of exhaled air passing through the longitudinal elimination air conduit (7) to the respective sampling outlet (8) of the portable sampling device (3) or through the air sampling conduit (10) to the vertical outlet (11). When the valve (9) is in position **a**, the flow of exhaled air which circulates through the sensor air conduit (6), is then directed through the longitudinal conduit (7) and exits through the longitudinal elimination outlet (8) of the portable sampling device (3). Also if the valve (9) is in position **a**, the flow of exhaled air passing by the sampling air conduit (10), bellow the valve (9), is inexistent. However, when the valve (9) is in position **b**, the flow of exhaled air circulates through the sensor air conduit (6) and is then diverted through the sampling air conduit (10) vertically disposed, where the fraction of the flow of exhaled air can either be collected in the air sample reservoir (18) or directly and real-time analyzed in the analytical analyser (17) coupled to the system (1).

The portable sampling device (3) also comprises a heating component (19) covering its internal surface. The said heating component (19) is configured to actuate during the overall process of acquisition of exhaled air.

The hardware module (12) is configured to control the overall system (1) by modeling the signal acquired by the temperature sensor (5) and determining the actions to be taken in order to affect the direction of the exhaled air, controlled by the position of the valve (9). The said hardware module (12) is, thus, responsive to the temperature sensor (5) and to the machine learning software (16) of the system (1) since it receives, processes and transmits signals between the remaining components of the system (1). This hardware module (12) comprises:

- A signal conditioning circuit (13), configured to receive and process the signal from the temperature sensor (5) of the said portable sampling device (3), in order to allow a better use of the analog digital converter (ADC) by obtaining an amplified signal;
- A processing and communication unit (14) which manages the acquisition and the signal communication to the processing device where is loaded the machine learning software (16);
- And an automatic flow switching circuit (15) that affects the direction of the flow of exhaled air by the valve (9).

The processing and communication unit (14) is configured to create a gate signal when the digital output of the ADC transitions to a high logical level, becoming the transistor of the automatic flow switching circuit (15) in saturation, allowing the passage of current to the valve (9) and causing the flow of air to pass through the air sampling conduit (10). If the ADC digital output is at a low logical level, the transistor is cut and there is no current flow to the valve (9), which implies that the air flow exits through the elimination air conduit (7). According to the preferred embodiment presented in Figure 1, the hardware module (12) also includes a connection with the portable sampling device (3) and with the processing device where the corresponded machine learning software (16) is loaded.

The system (1) also includes a machine learning software (16) which is responsive to the hardware module (12) and comprises a graphical

interface to interact with the subject/operator, allowing the definition of global features and assessment of the state of the operation, and an internal algorithm to control the system (1) functioning and to determine the precise moment for selectively sampling exhaled air.

The algorithm implemented in the machine learning software (16) of the system (1) comprises a digital filter in order to acquire the temperature signal with as minimal noise as possible, ensuring, at the same time, no loss of information. The algorithm is configured to:

- Measure the respiratory flow, and to identify the endogenous fraction of the exhaled air independently of the carbon dioxide metabolism of the subject, through the variation of temperature sensed by the temperature sensor (5), thereby calculating the flow of exhaled air;
- Effectively detect the breathing frequency of the subject;
- Distinguish between inspiratory and expiratory breath phases, based on the detection of maxima and minima of the temperature-processed signal;
- Synchronize the breath cycle of the subject with a representative and modeled respiratory cycle through at least three complete respiratory cycles. The imposition of a breath pace rhythm to the subject, by the graphical interface and according with the global features of the subject, allows a fast synchronization of breath rhythms and, consequently, less time of acquisition of the predetermined portion of exhaled air;
- Determine the average time of expiration in order to select a predetermined fraction of the expiration interval, which is dependent of the respiratory origin of the exhaled air;
- Calculate the average time of expiration of the subject, defined by the time difference between a maximum and a subsequent minimum, according with a number of breath cycles that the operator selects in the graphical interface of the machine learning software (16).

The machine learning process related with the system (1) is based on the continuous calculation and saving of the average time of expiration values, allowing the prediction of the time of occurrence of a new expiration and, consequently, the prediction of the precise time-frame for the acquisition of the fraction of exhaled air to sample.

After the prediction of the moments of breath sampling during exhalation, the machine learning software (16) is configured to transmit that information to the hardware module (12) which operates on the valve (9), through a gate signal, as described above.

The graphical interface of the machine learning software (16) can be used to define the global variables of the operation such as, but not limited to,

- The fraction of exhaled air to collect/analyze;
- The percentage of the aperture of the valve (9);
- And the number of cycles used to determine the average time of expiration.

The graphical interface of the machine learning software (16) also allows defining subject variables, such as, but not limited to genre, age and physiological conditions (seated, lying down or under effort trial), to start and stop the acquisition process and to keep data for later analysis. The graphical interface also provides simultaneously feedback indicators for communicating with the subject/operator, either showing the breath cycle synchronization animation or the treated signal obtained by the temperature sensor (5). In this preferred embodiment, the operation procedure starts by connecting all components to a processing device where the machine learning software (16) is loaded. The graphical interface of the machine learning software (16) must then be initiated. The operator first defines the global operating and subject-related variables (20). The global operating variables include the selection of the fraction of exhaled air to

collect/analyze (mouth, nasal, esophageal or alveolar air), the percentage of aperture of the valve (9) and the number of respiratory cycles for determining the average time of expiration by the algorithm. The subject-related variables include genre, age and subject physiological conditions (seated, lying down or under effort trial). The subject is then asked to exhale (21) into the non-rebreathable mouthpiece (2), which is already attached to the portable sampling device (3). During this step (21), and as the subject breathes into the portable sampling device (3) through the mouthpiece (2), the operator must verify that the subject's breathing rhythm follows a regular behavior, according to the breathing pace, previously defined by the subject-dependent variables, and displayed in the graphical interface of the machine learning software (16). Next, the temperature of the exhaled air is sensed by the temperature sensor (5) in the form of an electrical signal (22) which is then processed and transmitted by the hardware module (12) to the machine learning software (16).

The algorithm of the machine learning software (16) then determines a set of parameters (23), through the analysis of the signal produced by the sensor of temperature (5) and transmitted by the hardware module (12). The said parameters are critical for the procedure of sampling the exhaled air fraction of interest and include (i) the respiratory flow, with identification of the endogenous fraction of exhaled air independently of carbon dioxide metabolism of the individual; (ii) the exhaled air flow; (iii) the breathing frequency and (iv) the average time of the respiratory cycle which comprises the inspiratory and expiratory phases.

Subsequently, the synchronization between the breath cycle of the subject (32) and a representative and modeled breath cycle (33) of the algorithm is evaluated (24) by the machine learning software (16). If this synchronization does not occur during three completed respiratory cycles, the subject is informed by the graphical interface (25) so that the subject corrects his breathing cycle, by imposing a breath rhythm. As soon as the said synchronization occurs, the average time of expiration is calculated (26) by the

algorithm of the machine learning software (16) for three respiratory cycles enabling the process of machine learning and the prediction of the exact moments for exhaled air fraction acquisition (26). As example, the prediction of said exact moments for alveolar air collection is related with the region of interest (34) of the subject's respiratory signal (32), during exhalation. After this prediction, the feedback indicator "state of aperture of the valve" (close or open) is communicated to the operator. The machine learning software (16) then transmits the moments of exhaled air acquisition to the processing and communication unit (14) of the hardware module (12) which actuates on the automatic flow switching circuit (15) by generating and transmitting a gate signal to the valve (9) for a period of time dependent on the fraction of exhaled air to collect (27). The valve (9) can then selectively gate the fraction of interest of the exhaled air flow. The said fraction of interest of the exhaled air flow can then be stored in an air collection reservoir (29), or directly analyzed in the analytical analyzer (30). Lastly, the presence of chemical compounds in the fraction of interest of exhaled air can be detected (31) whether offline (29) or in real time (30). Then, the operator can optionally write comments that have elapsed during the acquisition process and save them along with the acquisition data.

Although the technology has been described with regard to its preferred embodiments, it should be understood that numerous modifications, changes, variations, substitutions and equivalents may be made by someone skilled in the art, without departing from the scope of the technology.

#### EXAMPLES OF APPLICATION

The ability to precisely sample a fraction of interest of the exhaled air according with its respiratory origin, allows real time or posterior (online or offline) analysis of composition of

said fraction of exhaled air. The knowledge of this composition allows to monitor and to help diagnose several diseases based on the abnormal concentration of already known biomarkers related to such diseases. The compositional analysis of exhaled air fraction samples maybe linked to a broad diversity of diseases that include: chronic inflammatory respiratory and lung diseases, cancer, diabetes, kidney dysfunction, liver impairment, intoxications, viral or bacterial infections, intestinal diseases among others.

Furthermore, the evaluation of temperature of the exhaled air during a single or multiple respiratory cycles allows the detection of the inflammatory state of the respiratory airways of the subject.

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## C L A I M S

1. A system for controlled and selective sampling of exhaled air comprising:

- A portable sampling device (3) comprising at least one air sensor (5) and a diverter valve (9);
- A hardware module (12) connected to the portable sampling device (3), configured to receive, process and transmit data from the at least one air sensor (5), and to actuate the diverter valve (9);
- A processing device comprising interface means and processor means, said processing device being configured to operate the hardware module (12) according to a machine learning algorithm based on the data sent by the hardware module (12).

2. System according to claim 1, wherein the portable sampling device (3) has a t-shaped internal cavity formed by:

- A longitudinal conduit comprising an air sensor conduit (6) in its inlet port (4) wherein the at least one air sensor (5) is installed, and an elimination air conduit (7) in its outlet port (8);
- A vertical conduit, connected to the longitudinal conduit, comprising an air sampling conduit (10) wherein the diverter valve (9) is installed, and wherein the outlet of the vertical conduit is connected to air collected means;

3. System according to claim 2, wherein the portable sampling device (3) comprises a heating component (19) covering the internal surfaces of the air sensor conduit (6), the elimination air conduit (7) and the air sampling conduit (10).

4. System according to claim 2, wherein in the air collected means are of a reservoir type (18) or analyser type (17).

5. System according to claim 2, wherein a disposable non-rebreathable mouthpiece is attached to the longitudinal inlet port.

6. System according to claim 2, wherein the air sensor is a temperature sensor.

7. System according to claims 1-6, wherein the hardware module comprises:

- A signal condition circuit (13), configured to receive and process the signal from the air sensor (5);
- A processing and communication unit (14), configured to manage the acquisition and the signal communication to the processing device;
- An automatic flow switching circuit (15) configured to operate the diverter valve (9) of the portable sampling device (3).

8. Method of operating the system for controlling and selective sampling of exhaled air executed of claims 1 to 7, characterized by being independent of the subject's CO<sub>2</sub> metabolic production and comprising the following steps:

- a) Initialization of the interface means of the processing device;
- b) Configuration of subject-related variables in the processing device, namely age, genre and physiological

conditions of the subject such as, but not limited to, seated, lying down or under effort trials;

**c)** Configuration of global variables of the acquisition process in the processing device, including:

- The fraction of interest of exhaled air to sample, according to the origin of the same;
- The percentage of the valve (9) opening which conducts the exhaled air inside a portable sampling device (3);
- The number of respiratory cycles for the calculation of the average time of expiration by a machine learning algorithm.

**d)** Acquisition of exhaled air through disposable and non-rebreathable mouthpiece (2), for at least one respiratory cycle and until it is regular, according with a rhythm previously defined by the said machine learning algorithm and demonstrated by a graphical interface, based on the said subject-related variables, collected in step b);

**e)** Measuring the exhaled air flow, identifying the endogenous fraction of exhaled air independently of carbon dioxide metabolism of the subject, through the temperature variation measured by a temperature sensor (5), for the calculation of the exhaled air flow by the said machine learning algorithm;

**f)** Measuring the breathing frequency and the average time of the respiratory cycle, comprising the inspiratory and expiratory phases, by the machine learning algorithm;

**g)** Synchronizing the acquired respiratory cycle with the respiratory cycle learned and modeled during the steps d) to f) by the machine learning algorithm;

**h)** Calculating the average time of expiration, by the said machine learning algorithm for the adjustment of the representative and modeled respiratory cycle;

- i) Prediction of the instants of collection of exhaled air fraction of interest by said machine learning algorithm;
- j) Heating the internal parts of the air sensor conduit (6), elimination air conduit (7) and air sampling conduit (10) of said portable sampling device (3), by means of the heating component (19);
- k) Sending the instants for exhaled air acquisition predicted in i) to the processing and communication unit (14) of the hardware module (12);
- l) Said unit (14) actuates on a valve (9) of the device (3) that when closed conducts the exhaled air fraction of interest to an elimination outlet (8) of said portable sampling device (3), and when open conducts the exhaled air fraction of interest to a sampling outlet (11) of said device (3);
- m) Collection of exhaled air fraction of interest by said portable sampling device (3).

9. Method, according to claim 8, characterized by the exhaled air fraction of interest to be collected has several origins, namely mouth, nasal, esophageal and alveolar air.

10. Method, according to claim 8, characterized by the exhaled air fraction of interest is collected and derived from a single respiratory cycle, being available for real time analysis by the analytical equipment (17).

11. Method, according to claim 8, characterized by the exhaled air fraction of interested is collected and derived from multiple respiratory cycles being conducted to a sample reservoir (18).

12. System, according to claims 1 to 7, used for collecting the exhaled air fraction of interest for analysis of its chemical composition.

13. System, according to claims 1-7, used for detection of the inflammatory state of the respiratory airways through the measurement of the temperature of the exhaled air by the temperature sensor (5) during a respiratory cycle.

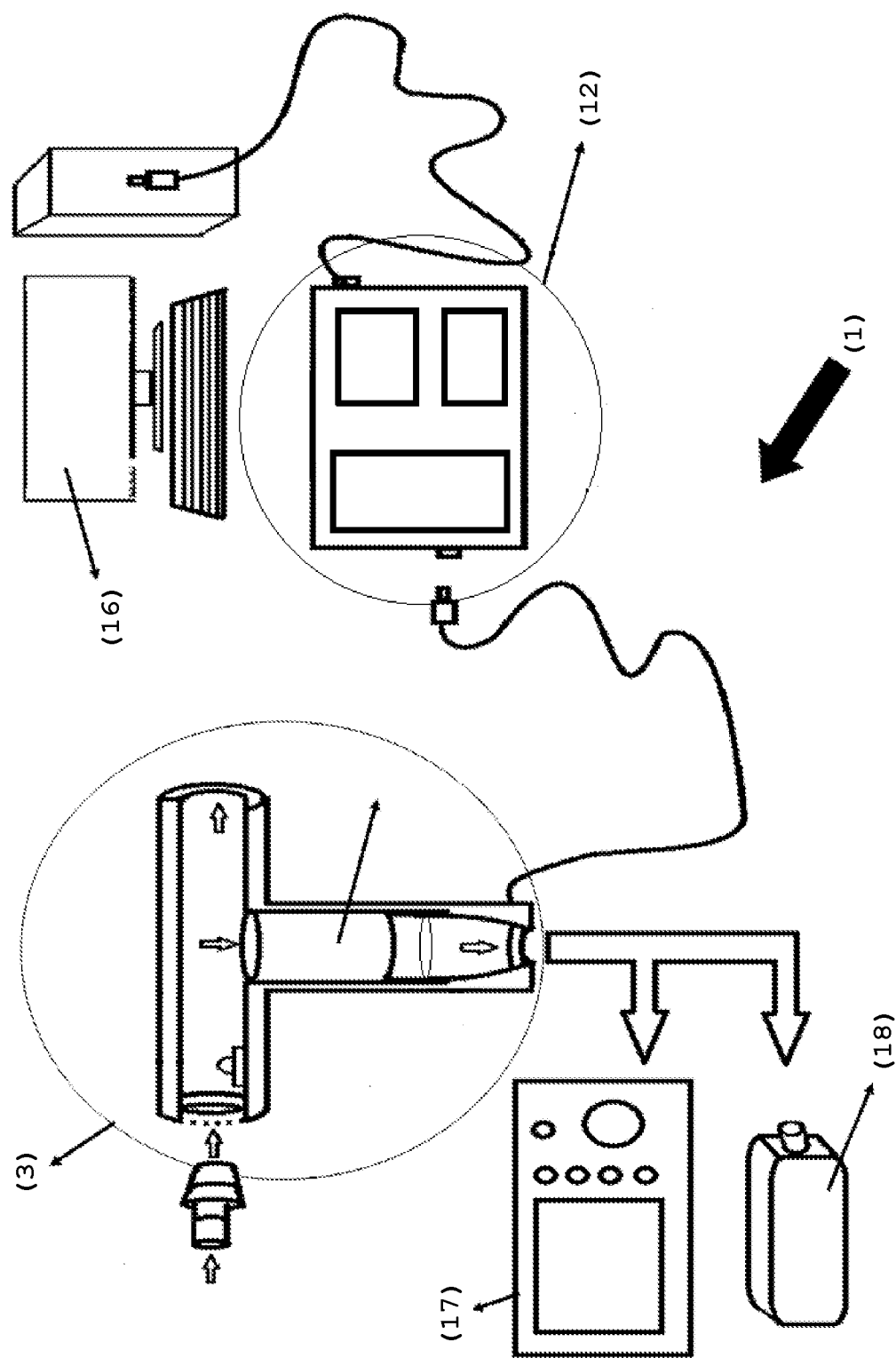


Figure 1

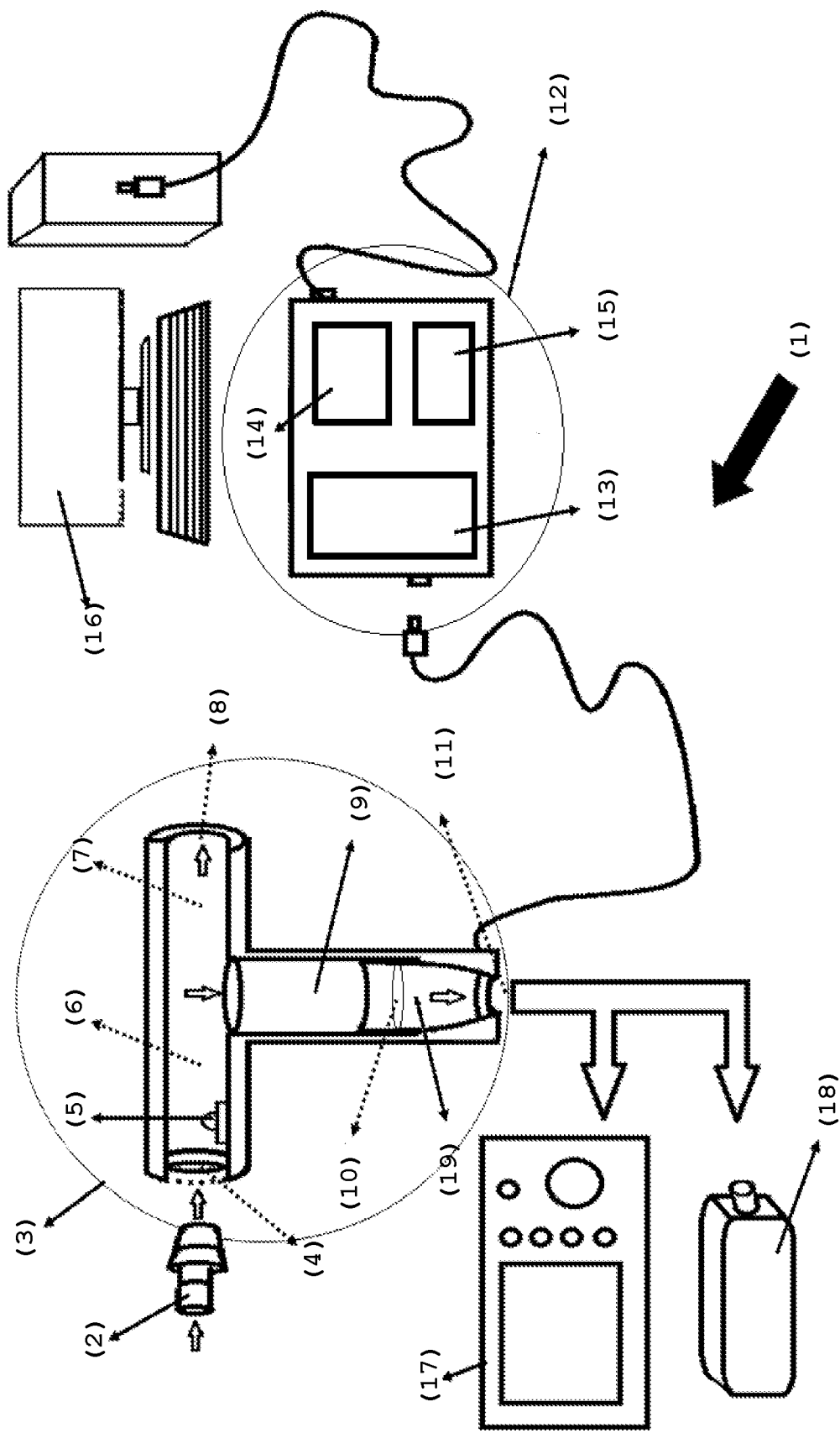


Figure 2

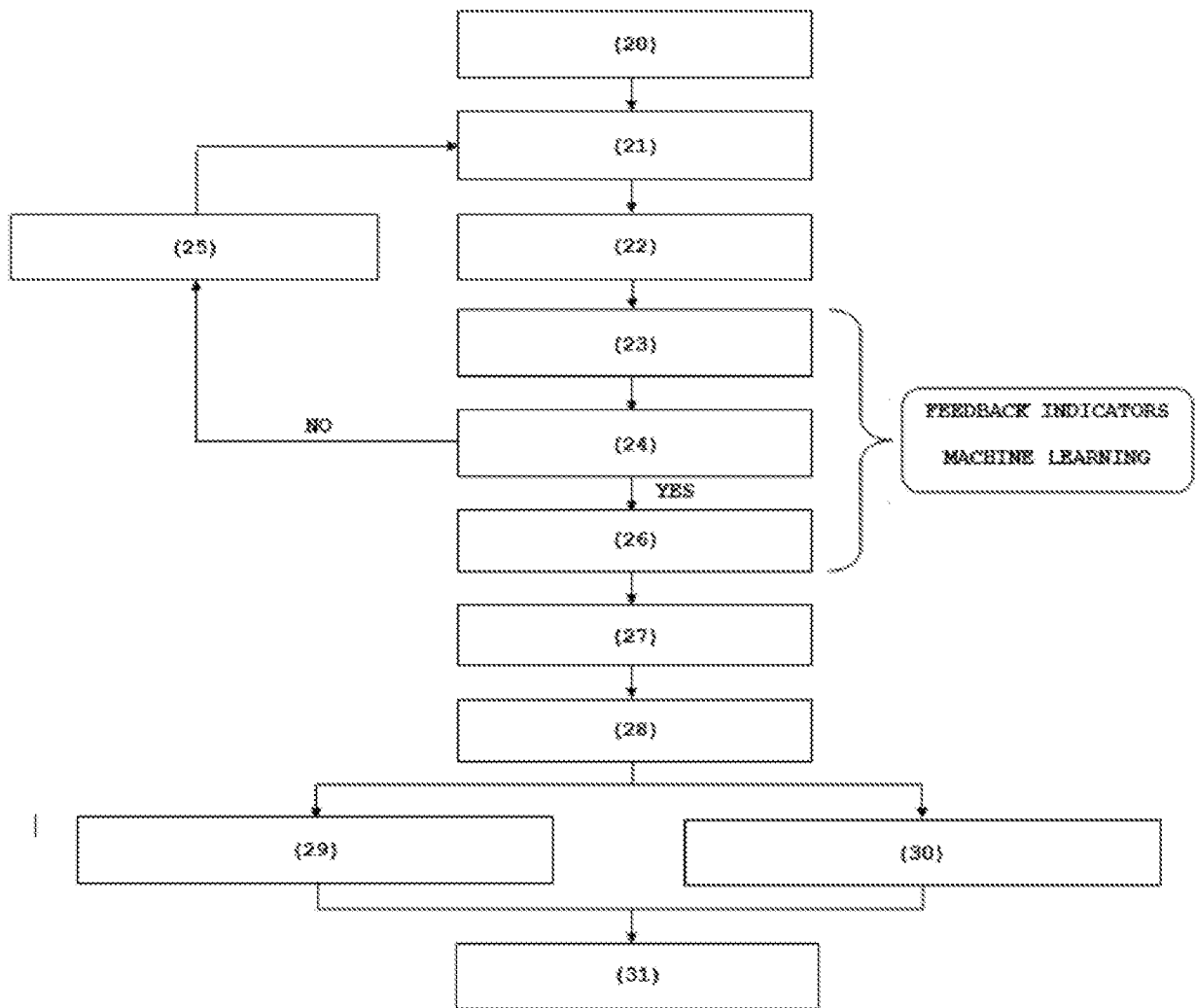


Figure 3

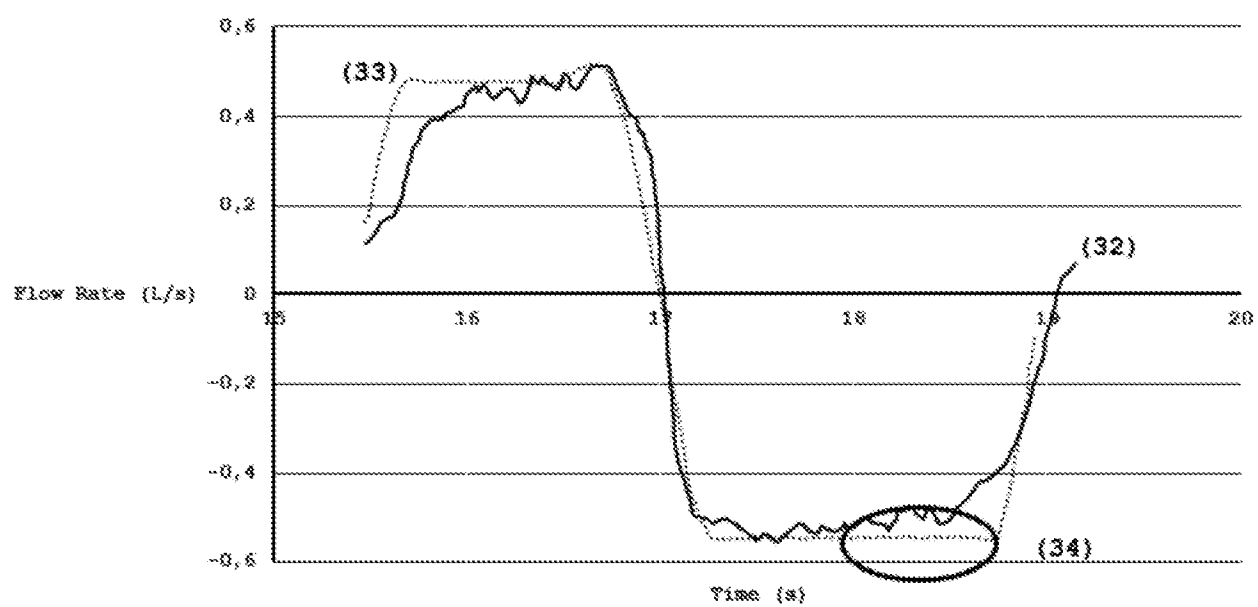


Figure 4

# INTERNATIONAL SEARCH REPORT

International application No  
PCT/IB2017/055322

| <b>A. CLASSIFICATION OF SUBJECT MATTER</b><br>INV. A61B5/097      A61B5/00      G06F19/00<br>ADD.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                              |                                                                                                                               |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------|
| According to International Patent Classification (IPC) or to both national classification and IPC                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                              |                                                                                                                               |
| <b>B. FIELDS SEARCHED</b><br>Minimum documentation searched (classification system followed by classification symbols)<br>A61B   G06F                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                              |                                                                                                                               |
| 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)<br>EPO-Internal, WPI Data                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                                                                                                                              |                                                                                                                               |
| <b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                                                                                                                                              |                                                                                                                               |
| Category*                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Citation of document, with indication, where appropriate, of the relevant passages                                                                           | Relevant to claim No.                                                                                                         |
| X                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | US 2003/079746 A1 (HICKLE RANDALL S [US])<br>1 May 2003 (2003-05-01)                                                                                         | 1                                                                                                                             |
| A                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | figures 1, 9A<br>paragraph [0120]<br>-----                                                                                                                   | 2-7                                                                                                                           |
| X                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | US 2001/041366 A1 (LEWIS NATHAN [US] ET AL) 15 November 2001 (2001-11-15)<br>figure 1<br>paragraphs [0035] - [0037], [0041], [0052], [0093], [0094]<br>----- | 1-7                                                                                                                           |
| X                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | US 2008/045825 A1 (MELKER RICHARD J [US] ET AL) 21 February 2008 (2008-02-21)<br>figures 5A, C<br>paragraphs [0089], [0093], [0102], [0157]<br>-----         | 1-7                                                                                                                           |
| <div style="display: flex; justify-content: space-between;"> <span><input type="checkbox"/> Further documents are listed in the continuation of Box C.</span> <span><input checked="" type="checkbox"/> See patent family annex.</span> </div>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                              |                                                                                                                               |
| <div style="display: flex;"> <div style="flex: 1;"> <p>* Special categories of cited documents :</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier application or patent but published on or after the international filing date</p> <p>"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)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="flex: 1;"> <p>"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</p> <p>"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</p> <p>"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</p> <p>"&amp;" document member of the same patent family</p> </div> </div> |                                                                                                                                                              |                                                                                                                               |
| Date of the actual completion of the international search<br><br><div style="text-align: center; font-size: 1.2em;">28 November 2017</div>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                                              | Date of mailing of the international search report<br><br><div style="text-align: center; font-size: 1.2em;">20/02/2018</div> |
| Name and mailing address of the ISA/<br>European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040,<br>Fax: (+31-70) 340-3016                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                                                                                                                                              | Authorized officer<br><br><div style="text-align: center; font-size: 1.2em;">Almeida, Mariana</div>                           |

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/IB2017/055322

| Patent document<br>cited in search report | Publication<br>date | Patent family<br>member(s)  | Publication<br>date      |
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# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/IB2017/055322

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

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

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

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

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

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

1-7

### Remark on Protest

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

**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

System for sampling of exhaled air.

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2. claims: 8-13

Method for predictive sampling of exhaled air.

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|                |                                                                         |         |            |
|----------------|-------------------------------------------------------------------------|---------|------------|
| 专利名称(译)        | 用于呼出空气的受控和选择性采样的系统和相应的操作程序                                              |         |            |
| 公开(公告)号        | <a href="#">EP3509488A1</a>                                             | 公开(公告)日 | 2019-07-17 |
| 申请号            | EP2017787616                                                            | 申请日     | 2017-09-05 |
| [标]申请(专利权)人(译) | NMT                                                                     |         |            |
| 申请(专利权)人(译)    | FACULDADE科学城DE TECNOLOGIA&DA里斯本新大学<br>NMT                               |         |            |
| 当前申请(专利权)人(译)  | FACULDADE科学城DE TECNOLOGIA&DA里斯本新大学<br>NMT                               |         |            |
| [标]发明人         | BORISSOVNA VASSILENKO VALENTINA<br>DA COSTA SANTOS PAULO HENRIQUE       |         |            |
| 发明人            | BORÍSSOVNA VASSILENKO, VALENTINA<br>DA COSTA SANTOS, PAULO HENRIQUE     |         |            |
| IPC分类号         | A61B5/097 A61B5/00 G06F19/00                                            |         |            |
| CPC分类号         | A61B5/097 A61B5/7267 A61B5/7475 G16H20/40 G16H40/63 G16H50/20 G16H50/30 |         |            |
| 优先权            | 2016109617 2016-09-12 PT                                                |         |            |
| 外部链接           | <a href="#">Espacenet</a>                                               |         |            |

#### 摘要(译)

本申请涉及用于对来自呼吸树的预定部分的呼出空气进行受控和选择性采样的系统 ( 1 ) 和相应的操作方法。系统 ( 1 ) 由两个可附接模块组成：便携式采样装置 ( 3 ) 和硬件模块 ( 12 )，由装载在处理装置上的机器学习软件 ( 16 ) 控制。开发的技术根据其特点 ( 年龄，流派和生理状况 ) 检测受试者的呼吸节奏，并使用机器学习过程 ( 16 ) 将受试者的呼吸周期与代表性的模拟呼吸周期同步。然后，预测打开/关闭阀 ( 9 ) 的时刻将选定的呼吸部分导入分析器 ( 17 ) 或收集器 ( 18 )。公开的系统 ( 1 ) 允许监测，诊断和评估患者的医疗状况，以及评估患者的呼吸道的炎症程度。