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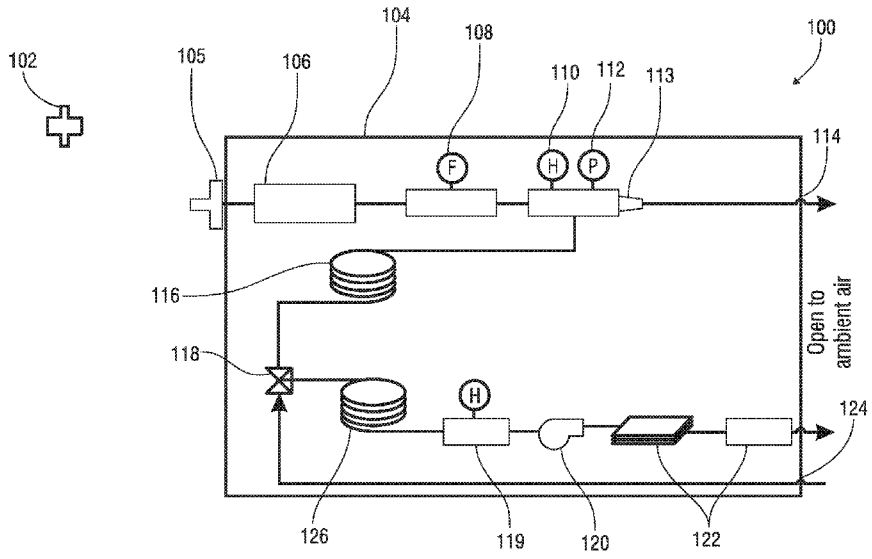


FIG. 1

(57) Abstract: A respiratory monitor is disclosed that includes features for conducting multiple pulmonary function tests in a single device and for detecting the presence of nitric oxide in exhaled breath. The respiratory monitor includes one or more reactor and sensor assemblies. Also described is a mouthpiece that allows for separate inhalation and exhalation pathways and for filtering inhaled and exhaled breath for predetermined species prior to exhalation into the respiratory monitor. The monitor further allows for wired, wireless and network connectivity and for cloud-based systems for communicating and correlating pulmonary data as well as relevant environmental data and displaying the data for use by patients and health care professionals.

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RESPIRATORY MONITOR FOR DETERMINING NO AND NO2

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application is a continuation-in-part of U.S. Patent Application Serial No. 14/495,853 filed on September 24, 2014, which claims priority from and is related to U.S. Provisional Application No. 61/949,871, filed March 7, 2014, and U.S. Provisional Application No. 61/955,192, filed March 18, 2014. These prior applications, including the entire written descriptions and drawing figures, are hereby incorporated into the present application by reference in their entirety.

FIELD OF THE INVENTION

[0002] The present invention relates generally to monitoring devices used to measure pulmonary functions, and more particularly to spirometry testing and testing for nitric oxide, as well as other markers, associated with monitoring respiratory medical conditions.

BACKGROUND

[0003] Respiratory diseases are some of the most common disorders in the world. Such respiratory diseases included conditions such as COPD, asthma, cystic fibrosis and pulmonary fibrosis. Chronic obstructive pulmonary disease (COPD), for example, affects millions of people and is responsible for extensive morbidity and mortality in the United States. COPD is a term used to describe chronic lung diseases characterized by progressive development of airflow limitation that is usually not fully reversible with medication. The common symptoms of COPD include breathlessness, wheezing and a chronic cough.

[0004] Asthma is another example of a chronic lung disease with symptoms similar to COPD, such as breathlessness and wheezing, but etiologically distinct from COPD. Asthma is a prevalent health care problem; it affects millions in the United States and around the world. About 40% of patients with asthma can be classified as having moderate to severe asthma and would benefit from more frequent monitoring of their airway inflammation. Although COPD and asthma require different treatments, test results for COPD and asthma often overlap.

[0005] Asthma in particular is characterized by an inflammatory reaction in hyper-reactive airways that restrict airflow into the lungs. In recent years, measurement of exhaled nitric

oxide (eNO) has been shown to be a non-invasive and complementary tool to other pulmonary function tests in assessing airway inflammation, specifically in subjects with asthma. Accordingly, the presence of eNO has become a well-known, globally accepted biomarker for airway inflammation.

[0006] Nitric oxide is produced endogenously in cells by NO synthase and secreted by eosinophils in the distal alveoli. Its production is increased in response to inflammatory cytokines (which is associated with asthmatic episodes), and exhaled NO is thought to be an indirect measurement of airway eosinophilic inflammation. Thus, nitric oxide exhaled from the lower airways (e.g. non-nasal airways) can be correlated with the degree of airway inflammation. Patients with asthma have high levels of NO in their exhaled breath. Nitric oxide levels increase prior to the presence of clinical symptoms and its levels decline in response to appropriate therapy as airway inflammation subsides. These two characteristics make this an ideal biomarker for managing asthma status. For this reason, in 2011, the American Thoracic Society (ATS) issued new guidelines recommending the measurement of exhaled nitric oxide for the diagnosis and management of asthma. A diagnosis of asthma can be made when the level of nitric oxide in exhaled breath exceeds 50 ppb. High eNO levels are also associated with other inflammatory respiratory conditions.

[0007] In diagnosing respiratory diseases, a series of tests are routinely conducted. A common pulmonary function test (PFT) is spirometry, which measures obstruction of an individual's airway. A decreased maximum/forced lung exhalation rate often suggests airway obstruction. Results from the spirometry test can be used to estimate lung function and aid in assessing respiratory diseases and conditions. In the spirometry test, the patient expels air forcefully into a device to measure the amount (volume) of air or the air speed (flow) exhaled in one complete breath. The commonly used techniques to measure eNO require a subject to exhale into a device containing an NO sensor (online) or into a reservoir that can be analyzed later (offline). Since the concentration of eNO is inversely related to flow rate where lower exhalation rates allow more time for eNO to enter from the airway, the eNO test requires a user to exhale at a steady flow rate, normally at 50ml/sec. As described above, the level of eNO, measured in parts per billion (ppb), is significantly higher among asthmatic patients compared to healthy individuals.

[0008] Although the spirometry test is a common method of measuring airflow obstruction and can facilitate the monitoring of pulmonary disorders, the overlapping results in some

conditions of COPD and asthma limit the use of the spirometry test alone for differentiating COPD from asthma. Additional investigations employing eNO tests, CT scans or pulse oximetry are also commonly employed to aid in assessing pulmonary diseases and conditions.

[0009] There are a number of challenges in current pulmonary function testing. Pulmonary function tests employ devices that are typically large and require the patient to be present in the physician's office or in the hospital for the tests. Moreover, the tests require separate devices, since in assessing respiratory disorders and conditions, separate measurement protocols are required for spirometry and for eNO testing. Typically, NO is measured in a clinical setting at a hospital or a physician's office for diagnostic purposes. The devices are expensive to purchase and maintain. Patients who have the most to gain from regular NO monitoring do not have regular access to accurate NO measuring equipment without frequent visits to their doctors. Thus, for at least the millions of people with moderate to severe asthma, there is a need for a cost-effective device that allows weekly or daily NO monitoring at home

[0010] Another challenge in current standard pulmonary function testing is the accuracy and efficiency of the testing. An effective eNO test would be complimentary to the standard tests, but there is a dearth of inexpensive sensors capable of detecting the minute amounts of NO (typically measured in parts per billion) present in exhaled air. Moreover, NO sensors need to provide an accurate NO measurement in the presence of other possibly interfering gas components, including water and carbon dioxide (CO2). A further challenge for NO measurement is the difficulty in distinguishing between nitric oxide (NO) and nitrogen dioxide (NO2) in a patient's breath. That is, the gas introduced from the patient's breath typically has concentrations of NO, NO2, carbon monoxide (CO), and oxygen (O2). Traditional sensors are often unselective or incapable of distinguishing between the two main NOx components of interest, NO and NO2, resulting in erroneous readings.

[0011] Thus, it would be desirable and advantageous to provide an accurate, efficient and portable respiratory monitor capable of conducting multiple pulmonary function tests, as well as other associated measurements, in a single device. In some applications, it would also be desirable and advantageous to provide a compact monitor with low power consumption. It would also be desirable and advantageous to provide such a device that further allows for the remote monitoring of testing data, thereby avoiding the necessity for patients to make trips to

doctor offices and hospitals. Additionally, it would be desirable and advantageous to provide such a respiratory monitor that allows for correlation of respiratory data to other relevant environmental data that can be presented in an efficient and easily understandable format.

SUMMARY

[0012] The present invention relates to respiratory monitors that incorporate nitric oxide detectors wherein exhaled breath from a user enters the detection device via a sample inlet that leads to a flow pathway within the detection device. In the flow pathway, one or more humidity equilibrators equilibrate the humidity of the breath sample in the flow pathway to the humidity of the ambient air to produce a humidity equilibrated breath sample. A catalytic filter in the flow pathway then receives the humidity equilibrated sample and generates a known equilibrium mixture of NO and NO2 from NOx. A NOx sensor positioned in the flow pathway then measures the NOx concentration in the sample. A controller thereafter calculates the total NO in the sample based on the measured NOx concentration and the known equilibrium.

[0013] In another aspect of the invention, one or more respiratory functions can be measured in a single device. The monitoring device comprises a housing that contains an inlet section positioned in the housing and configured to receive a gaseous sample, e.g., air expelled from a subject's lungs. A measuring section is located adjacent to the inlet section, along with a flow detection component positioned within the inlet section and configured to measure the flow rate of a gaseous sample entering the inlet section. An adjustable airflow restriction component is positioned upstream of the flow detection component. An adjustable partition can also be positioned downstream of the flow detection component for further directing and restricting air flow in the device. At least one gas detection sensor is positioned in the measuring section and configured to measure the presence of a predetermined gas contained in a gaseous sample received in the inlet section.

[0014] In another aspect of the invention, the gas detection sensor includes at least one electrochemical nitric oxide (NO) sensor configured to detect exhaled NO at aperture-directed flow rates.

[0015] The device can further include an optical sensor configured to perform blood flow measurements, and also include an accelerometer configured to perform respiratory measurements.

[0016] The device can also include at least one oxygen (O_2) sensor configured to detect O_2 levels in exhaled breath.

[0017] If desired, the device can further include an electronic controller integrated with the device and electronically coupled with the sensors. The controller can be configured to enter user information, execute programs, receive signals from the sensors and transmit data to a selected network or other remote locations.

[0018] In another aspect of the invention, a mouthpiece for users of monitoring devices permits fresh air to be inhaled through the mouthpiece via a dedicated pathway, and exhaled through the mouthpiece and into the monitoring device via a separate dedicated pathway. One or more filtering agents, filters or filtering media can be incorporated into one or both of the pathways to permit the screening of certain gaseous components, for example, NOx.

[0019] In another aspect of the invention, spirometry and nitric oxide measurements can be correlated with selected environmental factors and presented in an easily understandable format. The devices described herein can be adapted to communicate measurements by wired or wireless technology and maintain data in the cloud for remote monitoring, access, and predictive analytics.

[0020] In some embodiments, the invention provides a gas sensor comprising a reactor portion, a sensor portion, one or more connecting flow channels between the reactor and sensor portions, and separate heating elements attached to each of the reactor and sensors. In other embodiments, the invention provides a gas sensor comprising a reactor portion, a sensor portion, one or more connecting flow channels between the reactor and sensor portions, and a heating element with heat separation or conduction media disposed between the reactor and sensor.

[0021] The reactor and sensor assembly of the present invention may include a plurality of chambers. For example, a first chamber may comprises a catalytic filter adapted to catalyze the formation of an equilibrium mixture of NO and NO_2 from NO_x in an incoming gas stream. A second chamber located downstream from the first chamber comprises a sensor element adapted to contact the equilibrium mixture of NO and NO_2. The sensor element comprises a sensing potentiometric electrode and a reference potentiometric electrode. A gas conduit connects the first and second chambers. A heating element is disposed between the catalytic filter and sensor element. The heating element comprises a single heat source and is

adapted to distribute heat to the first and second chambers. The catalytic filter and sensor element are each maintained at different temperatures using the heating element. In some embodiments, the first gas chamber is disposed below the second gas chamber, and the gas conduit comprises external tubing connecting the first and second gas chambers. In other embodiments, the assembly includes a ceramic package and pins extending from a lower portion of the ceramic package. The ceramic package forms at least a portion of a housing around the first and second chambers, and the pins are adapted to electronically connect the sensor element to a printed circuit board.

[0022] In yet other embodiments, reactor and sensor assembly of the present invention provides a plurality of zones through which breath gas may flow. In some embodiments, the assembly comprises a base platform; a plurality of interlocking support structures disposed on the base platform to define a serpentine gas flow path. The support structures comprise a first surface; a second surface disposed below the first surface; and a third surface disposed below the second surface. The assembly further includes a catalytic filter disposed on an upper side of the third surface, the catalytic filter adapted to catalyze the formation of an equilibrium mixture of NO and NO_2 from an incoming gas stream; and a sensor element disposed on an underside of the third surface, the sensor element adapted to contact the equilibrium mixture of NO and NO_2. The sensor element comprises a sensing potentiometric electrode and a reference potentiometric electrode. The assembly also includes a heating element disposed between the catalytic filter and sensor element. The heating element comprises a single heat source adapted to distribute heat to the catalytic filter and sensor element. The catalytic filter and sensor element are each maintained at different temperatures using the heating element.

[0023] In other embodiments, the present invention provides an apparatus for determining total NO_x, including NO and NO_2 concentrations from a gas stream that comprises a housing; a substrate disposed within the housing; a catalytic filter disposed on the substrate; a sensor element disposed on the substrate downstream from the catalyst filter; and a heating element disposed within the substrate below the catalytic filter and sensor element. The catalytic filter is adapted to catalyze the formation of an equilibrium mixture of NO and NO_2 from an incoming gas stream. The sensor element is adapted to contact the equilibrium mixture of NO and NO_2 and comprises a sensing potentiometric electrode and a reference potentiometric electrode. The heating element comprises a single heat source and is adapted to distribute

heat to the catalyst filter and sensor element. Advantageously, the catalytic filter and sensor elements are each maintained at different temperatures using the heating element.

[0024] The present invention further provides for an apparatus for determining total NO_x concentration, including NO and NO_2 concentrations from a gas stream comprising a housing; a gas inlet positioned in the housing; and a measuring section. The gas inlet section comprises a flow detection component; an adjustable flow-restriction component positioned downstream of the flow detection component; and an adjustable partition positioned downstream of the flow detection component. The measuring section includes one or more of the reactor and sensor assemblies described below, located adjacent to the inlet section and in fluid communication with the inlet.

BRIEF DESCRIPTION OF THE DRAWINGS

[0025] Embodiments, which use the principles of the present invention, are illustrated with reference to the accompanying drawings.

[0026] Fig. 1 is a schematic illustrating one embodiment of an NO detection device.

[0027] Figs. 2-3 is a layout of one embodiment of an NO detection device.

[0028] Figs. 4 and 5A illustrate one embodiment of a sensor plate.

[0029] Fig. 5B illustrates one embodiment of a sensor.

[0030] Figs. 6A – 6C illustrates one embodiment of a microchannel reactor and sensor assembly.

[0031] Fig. 7 is a schematic illustrating one embodiment of a user interface.

[0032] Fig. 8 is an example of a calibration curve.

[0033] Fig. 9 illustrates a perspective view of one embodiment of the present monitoring device.

[0034] Fig. 10 illustrates a perspective view of one embodiment of the present monitoring device with one embodiment of a mouthpiece assembled onto the monitoring device.

[0035] Fig. 11 illustrates a plan view of the back of one embodiment of the monitoring device showing the device in the open partition position.

[0036] Fig. 12 illustrates a plan view of the back of one embodiment of the monitoring device as illustrated in Fig. 11 showing the device in the closed partition position.

[0037] Fig. 13 illustrates a plan view of one embodiment of the impeller-shutter assembly of the present monitoring device.

[0038] Fig. 14 illustrates a perspective view of one embodiment of the impeller-shutter assembly as shown in Fig. 13.

[0039] Fig. 15 illustrates a perspective view of one embodiment of the impeller shell.

[0040] Fig. 16 illustrates a plan view of one embodiment of the retainer ring assembly of the present monitoring device.

[0041] Fig. 17 illustrates a perspective view of one embodiment of the retainer ring assembly as shown in Fig. 15.

[0042] Fig. 18 is a sample chart illustrating flow rates against time for spirometry (PEF) and FeNO measurements.

[0043] Fig. 19 is a perspective view illustrating one embodiment of a multi-pathway mouthpiece.

[0044] Fig. 20 is a perspective view illustrating the user side of one embodiment of a multi-pathway mouthpiece.

[0045] Fig. 21 is a perspective view of the device side of one embodiment of a multi-pathway mouthpiece.

[0046] Fig. 22 is a perspective view of the airflow of one embodiment of a multi-pathway mouthpiece.

[0047] Fig. 23 is a side view of one embodiment of a multi-pathway mouthpiece.

[0048] Fig. 24 is an exploded view of one embodiment of a multi-pathway mouthpiece.

[0049] Fig. 25 is a schematic illustrating the connecting of an NO detection device to a network.

[0050] Figure 26 is a pneumatic diagram of an NO detection device, according to one embodiment of the present invention.

[0051] Figure 27 is a perspective view of a reactor-sensor assembly, in accordance with one embodiment of the present invention.

[0052] Figure 28 is a cross-sectional view of a side of a reactor-sensor assembly, in accordance with one embodiment of the present invention.

[0053] Figures 29A through 29D illustrate a sensor plate in accordance with one embodiment of the present invention. Figure 29A is a plan view of the sensor plate from the sensor side. Figure 29B is an enlarged plan view of a portion of the sensor plate from the sensor side. Figure 29C is a bottom plan view of the sensor plate from the heater side. Figure 29D is an enlarged plan view of a portion of the sensor plate from the heater side.

[0054] Figures 30A through 30D illustrate a sensor plate with thru-holes between the sensor and heater sides in accordance with one embodiment of the present invention. Figure 30A is a plan view of the sensor plate from the sensor side. Figure 30B is an enlarged plan view of a portion of the sensor plate from the sensor side. Figure 30C is a bottom plan view of the sensor plate from the heater side. Figure 30D is an enlarged plan view of a portion of the sensor plate from the heater side.

[0055] Figure 31 is an angled top view of a sensor plate with thru-holes between the sensor and heater sides in accordance with one embodiment of the present invention.

[0056] Figures 32A through 32C show a reactor-sensor assembly using ceramic packaging. In this embodiment, the sensor is fixed and electrically connected in the package. Figure 32A illustrates exploded views of the reactor-sensor assembly. Figure 32B illustrates a perspective view of an upper portion of the assembly. Figure 32C illustrates a perspective view of the assembled device.

[0057] Figure 33 is a cross-sectional view of a side of a reactor-sensor assembly using ceramic packaging.

[0058] Figure 34A illustrates schematically side and top plan views of disassembled components of a reactor-sensor assembly. Figure 34B illustrates a side-cross sectional view of assembled components of the reactor-sensor assembly shown in Figure 34A.

[0059] Figure 35 is a cross-sectional view of a side of a reactor-sensor assembly according to another embodiment of the present invention.

DETAILED DESCRIPTION

[0060] As used herein, the terms "comprises," "comprising," "includes," "including," "has," "having," or any other variation thereof, are intended to cover a non-exclusive inclusion. For example, processes, methods, articles, or apparatuses that comprise a list of elements are not necessarily limited to only those elements but may include other elements not expressly listed or inherent to such processes, methods, articles, or apparatuses. Further, unless expressly stated to the contrary, "or" refers to an inclusive "or" but not to an exclusive "or." For example, a condition A or B is satisfied by any one of the following: A is true (or present) and B is false (or not present), A is false (or not present) and B is true (or present), and both A and B are true (or present).

[0061] Also, use of "a" or "an" are employed to describe the elements and components of the invention. This is done merely for convenience and to give a general sense of the invention. This description includes one or at least one and the singular also includes the plural unless it is obvious that it is meant otherwise.

[0062] Unless otherwise defined, technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although methods that are similar or equivalent to those described herein can be used in the practice or testing of the present invention, suitable methods and materials are described herein. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety. In case of conflict, the present specification, including definitions, will control. In addition, materials, methods, and examples are illustrative only and not intended to be limiting.

[0063] In the following description, numerous specific details, such as the identification of various system components, are provided to understand the embodiments of the invention. One skilled in the art will recognize, however, that embodiments of the invention can be

practiced without one or more of the specific details, ordinary methods, components, materials, etc. In still other instances, well-known structures, materials, or operations are not shown or described in detail to avoid obscuring aspects of various embodiments of the invention.

[0064] Reference throughout this specification to "one embodiment" or "an embodiment" means that a particular feature, structure, or characteristic described in connection with the embodiment is included in at least one embodiment of the present invention. Thus, the appearance of the phrases "in one embodiment" or "in an embodiment" in various places throughout this specification are not necessarily all referring to the same embodiment. Furthermore, the particular features, structures, or work characteristics may be combined in any suitable manner in one or more embodiments.

[0065] In one aspect, the present respiratory monitor allows for the detection of nitric oxide in exhaled breath, taking into account variables such as humidity, temperature, pressure, and flow rate. In general, an exhaled breath sample is received in the monitor through a sample inlet. The sample proceeds along a flow pathway and is equilibrated for humidity. The humidity-equilibrated sample proceeds along the pathway to a catalytic filter adapted to generate a known equilibrium mixture of NO and NO2 from NOx. Thereafter, the sample flows to an NO sensor configured to measure the NOx concentration in the humidity-equilibrated sample. A controller thereafter calculates the total NO in the sample. A detailed description is set out below of various embodiments of the present monitor that further illustrate the present invention.

[0066] Referring to Figure 1, an NO detection device 100 is shown with a disposable mouthpiece 102 connected to a detection box 104 directly or by way of flexible hose. The detection box 104 is illustrated showing (in direction of air flow): an inlet 105 for receiving a breath sample, a desiccant 106, such as activated alumina, a flow sensor 108, humidity sensor 110 and pressure sensor 112, and a flow restrictor 113. Following the flow restrictor 113, a first portion of the sample can exit the system at an outlet 114. In this embodiment, a second portion of the sample can branch off from the first portion, before flow restrictor 113, and continue through the detection box 104 for analysis. The second portion can thus pass through a humidity equilibrator 116, such as nafion tubing, a 3-way control valve 118, another humidity equilibrator 126, such has nafion tubing, a humidity sensor 119, a pump 120, and a microchannel reactor/sensor assembly 122. Further, ambient air is brought into

the system through an inlet 124 (through the 3-way control valve 118). Ambient air then passes through the humidity equilibrator 126, humidity sensor 119, pump 120, and the microchannel reactor/sensor assembly 122.

[0067] The flow restrictor 113 can advantageously be used to further partition the sample (as the remainder is sent through the outlet 114). That is, the flow restrictor 113 can act to create back pressure at the inlet 105 and in the user's airways that closes the user's velum (soft palate), thereby preventing nasal breath from entering the mouth and subsequently being passed through the mouthpiece. Pulling the sample portion off of the main breath can advantageously maintain the volume and flow rate of gas analyzed at a constant level. Further, siphoning off a sample of breath can reduce the power consumption and size of the device 100, enabling the device to be battery operated. That is, the smaller gas volume can be filtered, heated, and analyzed using lower amounts of power and/or smaller components than a higher gas volume would take to analyze.

[0068] The humidity equilibrators 116, 126 can include a selectively permeable membrane, such as nafion tubes (polymer-based tubes), that selectively allow water molecules to pass through the wall of said tubing, thereby equilibrating the moisture content within the tube to the moisture content external to the tube while concurrently not affecting the concentration of NO, NO2, or NOx within the tube as it passes along the length of the tube. The humidity equilibrators 116, 126 can thus be used to equilibrate humidity of the breath sample to ambient conditions. The humidity equilibrators can also be used in combination with the desiccant 106.

[0069] To enhance the accuracy of the NO detection by the microchannel reactor/sensor assembly 122, it is generally desirable to maintain a substantially constant humidity in the system. In the embodiment illustrated, ambient air is drawn into the system through the inlet 124. Further, the humidity equilibrators 116, 126 equilibrate the humidity of the breath sample to ensure that the breath sample has substantially the same humidity as the ambient air. The first humidity equilibrator 116 reduces the humidity of the sample breath only while the second humidity equilibrator 126 ensures that both the breath sample and the ambient air have a substantially equivalent controlled amount of humidity.

[0070] In some embodiments, the NO detection device also may include additional desiccant located with the mouthpiece or other areas outside of the detection box. The desiccant may

be useful in helping to condition the breath gas and to avoid removing NO from the breath gas when the humidity is above acceptable limits. For example, when a specific amount of water is added to the breath gas—for example, when the atmospheric moisture of the sample increases—it may react with and thus reduce the amount of NO in the breath gas. Additional desiccant may be included to help condition the breath sample and avoid the removal of excessive NO from the sample. A pneumatic diagram of one embodiment of the NO detection device is shown in Figure 26. Desiccant 500 is incorporated into the external mouthpiece to help remove NO from the breath gas before it enters the detection box.

[0071] In some embodiments, an NO_x filter may be incorporated into the detection box. As shown in Figure 26, NO_x filter 501 may be positioned downstream from the inlet to help filter NO from the ambient air entering the detection box. The inclusion of the NOx filter allows the NO to be removed or at least partially removed from the incoming air to allow for no or minimal fluctuations in the NO levels of the incoming ambient air.

[0072] In some embodiments, one or more valves may be included to balance flow from the intake and ambient air. For example, needle valves can be employed to help maintain a substantially continuous gas flow when switching from ambient to breath flow. For instance, a needle valve 502 may be located before the humidity equilibrator, as shown in Figure 26. Thus, breath gas contacting the intake ambient air may pass through this needle valve to balance the flow. Another needle valve 503 may be located along the inlet for ambient air, for example after the air passes through the NOx filter.

[0073] In some embodiments, the NO detection device may include one or more check valves to address changes in humidity in the reactor and sensor assembly. The valves can help avoid error readings when ambient air is not being admitted into the device; for example, when the device is turned on and off. Referring to Figure 26, check valves 504 and 505 may be located at the entrance and exits of the reactor-sensor housing, respectively. An oxygen sensor 506 may also be incorporated into the detection box to expand the measurement capabilities of the device.

[0074] The microchannel reactor and sensor assembly 122 are configured to determine the total NO concentration from the breath sample gas, as shown in Figure 1. A patient's breath sample can include NOx, which includes pure NO, pure NO2, and mixtures thereof. The gas introduced from the patient's breath typically has concentrations of NO, NO2 and carbon

monoxide (CO) in the range of 0 to 1000 ppb. Further, the gas typically contains 14-18% oxygen (O2). As illustrated, the microchannel reactor and sensor assembly 122 includes a catalyst filter comprising platinum and zeolite within the flow pathway. The gas flowing through the flow pathway interacts with the catalyst filter at a particular temperature to form an equilibrium mixture of NO and NO2. The microchannel reactor and sensor assembly 122 further includes a sensor element configured to sense the amount of NOx flowing therethrough. In the embodiment shown, the sensor element includes two electrodes on a solid electrolyte yttria-stabilized zirconia as follows: (1) a sensing potentiometric electrode disposed downstream of the catalytic filter device so as to contact the equilibrium mixture of NO and NO2, and (2) a reference potentiometric electrode. Because the relative amounts of NO and NO2 are known due to the equilibrium reaction through the filter, the NOx reading of the sensor can be used to determine the amount of NO in the sample.

[0075] The sensor and the microchannel reactor are maintained at different temperatures to provide a driving force for the NOx equilibration reactions. That is, the reactor equilibrates the NO to NO2 mixture based principally on the temperature of the reactor (which includes platinum-zeolite (PtY), and then the potential develops on the sensor element based on this equilibration of NO and NO2 changing when reacting with reference electrode (PtY) and the sensing electrode at a temperature different than the temperature of the reactor. The sensor works by measuring the potential difference between the two electrodes, and a total NOx concentration (and then NO concentration) can be calculated by comparing the potential to a calibration curve. An example of such a calibration curve is illustrated in Figure 8, which is generated by passing gas mixtures of known concentrations through the detection box 104. The sensor response may be dependent on the duration of the exposure to the sensing element, and thus the exposure duration is included in the example calibration curve of Figure 8. The flow rate of the gas over the sensing element may also affect the sensor response, but flow rate is well controlled in this embodiment such that flow is not a factor for calibration.

[0076] Details regarding a reactor and sensor is described in U.S. Patent No. 6,764,591, titled "Potentiometric sensors comprising yttria-stabilized zirconia and measurement method of total NOx sensing without CO interference," the entirety of which is incorporated by reference herein.

[0077] Suitable catalytic materials include, without limitation, Zeolite-Y or ZSM-5 (*e.g.*, Zeolite Socony Mobil–5) with a surface area per mass of 425 m^2/g as received. In ZSM-5, the zeolite compound is loaded with platinum ions in an ion-exchange process before being applied to the reactor portion of the reactor-sensor assembly. The structure enables increased loading of platinum clusters onto the zeolite material. In one embodiment using ZSM-5, the catalytic material may contain approximately 1-4% μm platinum in zeolite. Although platinum is described as an example, alternative catalysts could be used and dispersed in a zeolite or other high surface area structures.

[0078] Referring to Figures 6A-6C, in one embodiment, the microchannel reactor/sensor assembly 122 can include a stack of thin plates adhered together. As shown in Figure 6B, the stack can include (in order of air flow) an inlet adaptor 202, a heater and resistance temperature detector (RTD) plate 204, a spacer 206, a PtY plate 208, another spacer 210, another heater and RTD plate 212, a sensor plate 214 that suspends a sensor 215, a sensor spacer 216, and an outlet adaptor 218. The plates can include spaces there between configured to control the flow of air. Thus, as shown in Figure 6C, the breath sample can flow in through the inlet adaptor 202, down in the space provided between the plates that are coated with a catalytic material (here, PtY) along the gas path. The breath sample then passes up in a space provided between plates coated with a catalytic material before passing into yet another space provided between plates of the microchannel reactor/sensor assembly 122 where the sensor resides and the breath sample can interact with the electrode materials on the surface of the sensor 215, and ultimately through the outlet adaptor 218. In this embodiment, PtY plate 208 has an area of PtY located on both sides of the plate corresponding to the apertures in spacer plates 206 and 210. Similarly, heater/RTD plates 204 and 212 each have an area of PtY located on one side of the plate corresponding to the apertures in spacer plates 206 and 210.

[0079] As shown in Figure 4, sensor 215 is suspended within an aperture in the sensor plate 214. Sensor 215 can include a substrate and a plurality of sensors 303, each sensor 303 including two electrodes (the sensing potentiometric electrode and the reference potentiometric electrode). In this embodiment, there are nine sensors 303 connected in series. In some embodiments, the range of ratios of electrode material surface areas can be between 1:1 and 5:1, such as approximately 3:1. A ratio within this range can advantageously ensure that the sensor is configured to measure NO in the parts-per-billion

(ppb) range as well as minimize the level of signal conditioning required to get the NO result in the ppb range of interest (3-500ppb).

[0080] Referring to Figures 5A-5B, the sensor 215 can also have a heating element and RTD element formed on the back side of the sensor substrate (or within the substrate), opposite from sensor elements 303. The heating element and RTD element may be formed into serpentine shapes and built into the sensor substrate (e.g., the substrate can be a co-fired ceramic). The heater and RTD plates 204, 212 can also have their heating elements and RTD elements formed into serpentine shapes as shown in Figure 6B. In this embodiment, plates 204 and 212 are identical, each have a heating element and RTD element on one side (as seen on plate 212 in Figure 6B) and PtY deposited on the opposite side (as seen on plate 204). The imbedded serpentine heater and RTD elements can advantageously provide preferred heat distribution through the plates of the microchannel reactor sensor assembly and provide precise detection and control of the heat differences on the plates of the microchannel reactor sensor assembly.

[0081] As shown in Figures 4-5B, the sensor and integrated heater can be suspended within microchannel frames to keep the heat conduction down. When the paths of heat conduction are minimized, the sensor with integrated heater can maintain a preferred heat distribution across the sensor array. The temperature of the sensor array is important for sensor performance and accuracy. The suspended architecture with high resistance to heat conduction means that only the sensor substrate is heated, thus reducing the amount of power required to bring the sensor to target temperature. Controlling the power budget is important for maintaining battery operation and thus portability of the device.

[0082] Advantageously, by having the microchannel reactor and sensor 122 assembly set up as a series of plates as describe herein, the ratio of surface area of PtY exposed to the volume of air sample is maximized. Further, using plates can allow the microchannel reactor/sensor assembly 122 to be relatively small, allowing the device 100 to be more easily portable, and reducing the energy needed to heat the air sample. In other embodiments (not shown), the microchannel reactor and sensor 122 assembly can be fabricated using other techniques to further miniaturize the assembly. For example, various material deposition (additive) and removal (subtractive) processes may be employed to create microchannel reactor and sensor assemblies having even smaller dimensions. The assemblies can be built up layer by layer using chemical vapor deposition (CVD), physical vapor deposition (PVD), electrodeposition,

electroless deposition, or the like. In some embodiments, voids for air flow, such as those shown in Figure 6C, can be formed by creating sacrificial layers which are later dissolved after they have served as a substrate for layers added on top of the sacrificial layers.

[0083] Referring to Figures 2-3, the layout of the device 100 can be compact to ensure portability. For example, in one embodiment, the detection box 104 can be 8" by 2" by 6.5". The relatively flat design can allow for the maximization of distance between the heated components (microchannel reactor/sensor) and the non-heated but heat sensitive components (battery and PCB board). Since the components in the "flat layout" are not stacked on top of each other, this reduces the volume of the device, which allows for efficient heat dissipation.

[0084] The device 100 can be configured to precisely control the important variables, such as humidity, temperature, pressure, and flow rate. For example, the humidity can be controlled using the first and second humidity sensors 110, 119. The first humidity sensor 110 can detect the amount of humidity that is coming into the device 100 from the patient's breath through the mouthpiece 102. The second humidity sensor 119 can detect the amount of humidity once the breath transverses the humidity control system into the microchannel reactor/sensor 122. If the humidity level at the second sensor 119 is equal to or greater than that at the first sensor 110, this may be indicative of a fault in the system. Accordingly, a controller can signal an error. The humidity at the second sensor 119 should be substantially equal to ambient conditions and controlled tightly to the ambient humidity level, such as to have a humidity within 2% of ambient. This control ensures that the humidity level that is going into the microchannel reactor sensor assembly is substantially constant during the duration of a measurement.

[0085] Further, the temperature difference of the catalytic converter and the sensor can be controlled by the RTD or RTDs to be within about 100-300 degrees Celsius, such as about 200 degrees Celsius. Precise control of this temperature difference is important in some embodiments, as the higher the temperature difference, the greater the signal. In use, the catalytic converter should operate above 200 degrees Celsius in order to maintain reaction efficiency while the sensor should operate in excess of 350 degrees Celsius to activate oxygen conduction within the sensor electrolyte material. Further, in some embodiments, temperatures above 950 degrees Celsius at the NO sensor could be too high for the device to function properly while temperatures below 200 degrees Celsius at the reactive filter could be too low for the catalytic reactive filter to function efficiently. In one embodiment, the desired

temperature difference is achieved by ensuring that the electronics keep the temperature of the reactive filter and the temperature of the sensor nominally at 250 degrees Celsius and 550 degrees Celsius, respectively.

[0086] The flow sensor 108 and pressure sensor 112 can be used to trigger the 3-way control valve 118 to toggle and pull from the breath sample line rather than the ambient line, thereby feeding the breath sample over the microchannel reactor/sensor assembly to perform the NOx measurement. In some embodiments, the target flow rate is 3L/min (+/-10%). Likewise, pressure sensors can look for a pressure of 5 to 20 cm of H2O. If either of the flow rate or the pressure range is not met, the 3-way control valve 118 can be configured not to toggle, and as such, the NO sensor will not measure NO in the patient's breath. In some embodiments, the pressure and flow sensors 108, 112 can also be used to provide feedback to the user regarding the pressure and/or flow so as to help the user provide the necessary pressure and/or flow for activation of the NO measurement. Further, in some embodiments, the user is required to meet both the pressure and flow rate goals continuously for a total of less than 15 seconds, such as approximately 10 seconds, in order to obtain the NO reading.

[0087] In some embodiments, by controlling all of these variables, the accuracy of the resulting NO reading can be within +/- 10 ppb, such as within +/-7 ppb or within +/-3 ppb.

[0088] Referring to Figure 7, in some embodiments, a user interface can be provided to give the patient visual, audible, and/or tactile feedback as to the variables and/or results of the system.

[0089] In some embodiments, the device 100 is calibrated using electronics coupled to the microchannel reactor and sensor. To do so, the heating parameters for each reactive filter and sensor assembly can be uploaded to the device when the micro-channel reactive filter and sensor assembly is plugged into the device. The microchannel reactive filter and sensor assembly (MCRS) can also provide the calibration curve parameters to the device. This is how the device interprets whether a measured potential from the sensor is equal to a specific NO concentration. A sample calibration curve is shown in Figure 8.

[0090] The detection system 100 can be a flow-through device in that air (either from the ambient through inlet 124 or from the breath at mouthpiece 102) can continuously flow into and out of the system. That is, the amount of air into and out of the system at any one time can be controlled. Having a controlled and continuous flow of ambient air through the device

before and after the user's breath can advantageously set a reliable baseline for NO measurement. Further, by providing analysis of the breath via continuous airflow (i.e., without storing the breath), the NO reading can be provided quickly and efficiently. For example, the system can provide the NO reading in less than 15 seconds from when the user begins to breath into the device.

[0091] The flow rate through the mouthpiece can be regulated to 3 L/min (+/- 10%). The flow through the catalytic converter and NO sensor can be in the 0.01 to 1 L/min range, such as 0.2 L/min. The power needed to heat the MCR can be 2-9 Watts. The mass of the reactive filter (catalytic converter) can be within 2-200 grams. The external dimensions of the microchannel reactive filter and sensor assembly in this embodiment are nominally 0.75 inch x 1.25 inch x 0.5 inch. The variation for the temperate at the converter can be less than +/-2 degrees Celsius. The efficiency of the converter can be >90% to ensure proper performance of the sensor.

[0092] As described above, pulmonary function tests typically require different machines for conducting different tests. For example, the large delta between the breath flow rates for spirometry and FeNO measurements has previously prevented use of a single mechanism to make the measurements. In the embodiment illustrated below, multiple markers, such as spirometry and eNO tests, can be measured and tracked in a single device mediated by airflow-restriction mechanism. Other pulmonary function tests or gas sensors may be employed in the device illustrated.

[0093] In one embodiment, a monitoring device is contained in a housing that contains an inlet section, a measuring section and a flow detection component. In addition, the device contains an adjustable airflow restriction component and at least one gas detection sensor. The inlet section receives a gaseous sample from a subject, e.g., a subject, or source, that expels air into the inlet section, which then proceeds downstream into the device according to variable restrictions that alter the speed and path of the gaseous sample expelled from a subject into the device. In the embodiment illustrated, an inlet section is positioned in the housing and configured to receive a gaseous sample. A measuring section is positioned adjacent to the inlet section and connected via a hole in the inlet section. A flow detection component is positioned in the inlet section and configured to measure the flow rate of a gaseous sample entering the inlet section. Positioned upstream of the flow detection component is an airflow restriction component. An adjustable partition can also be

positioned downstream of the flow detection component, which can be adjusted to further direct and restrict airflow. At least one gas detection sensor is positioned in the measuring section.

[0094] As indicated above, the lung-function monitoring device comprises two sections for collecting and sensing a gaseous sample from subjects. An inlet section is composed of an inlet port or channel having an orifice at one end that extends axially along an airflow path to the opposite end, which incorporates an airflow restriction component, such as a shutter-controlled aperture. A disposable or easy-to-sterilize mouthpiece can be adapted to the orifice opening to allow for directing airflow into the inlet section. When performing a spirometry test, for example, a user blows air into the device via a mouthpiece to an inlet port where a gaseous sample can flow through a flow detection component, such as an impeller-based flow meter, and exit the inlet section via an opposite opening that exits the device. Conversely, when performing eNO test, a user steadily exhales breath into the inlet section with the airflow restriction component in a restricted position, which consequently re-routes the gaseous sample to the eNO detector contained in the sensing section. To further close off an airflow out of the device, a movable partition on the back of the housing can be moved to a closed position during this test to further retain and re-route the gaseous sample through the hole and into the measuring section. At least one gas sensor, e.g., such as the NO sensor described above, is placed along a sensing compartment.

[0095] To further illustrate the invention, reference is made to the drawings that are directed to one embodiment of the present invention. Referring to Fig. 9, an example of the monitoring device housing 305 is shown. The housing is preferably designed such that it can be hand-held and portable. The housing further contains an inlet section containing an impeller assembly 309. A mouthpiece 307 is shown which can be attached to the device for directing airflow into the inlet section containing the impeller assembly 309. The mouthpiece can be of any suitable shape and made of any suitable material as long as it allows for the exhaled breath of a user to be directed into the inlet section of the device. The mouthpiece may be disposable, or made of a material that is easily sterilized.

[0096] Referring more specifically to Fig. 10, the mouthpiece 307 is shown attached to the monitoring device 305. By way of example and depending on the desired test, a subject expels a gaseous sample, e.g., air from the lungs, into the inlet port via the mouthpiece. A flow detection meter positioned in the inlet and situated along the flow path measures the

gaseous sample. In a preferred embodiment, the flow detection meter is an optical-impeller based flow meter that optically counts impeller revolutions.

[0097] Referring to Figs. 11 & 12, the monitoring device is illustrated showing a movable partition 311 positioned on the back of the monitoring device housing. In this embodiment, the movable partition can be adjusted to further alter the airflow path in the device to enable the device to be employed for different tests. For example, the movable partition can be adjusted to a fully open position, as shown in Fig. 11. In this position, expelled breath from a subject can pass directly through the device, allowing, for example, a spirometry test that requires a subject to expel breath forcefully into the device. In another example, the movable partition can be adjusted to a fully closed position, as shown in Fig. 12. In this position, air expelled by a subject into the device will be routed along an alternate path, for example, to a sensing area. In such a closed position, the device can be employed in measuring eNO where a user expels breath at a slow and steady rate into the device. In addition, the movable partition can be adjusted to any position between fully open and fully closed to accommodate other test requirements.

[0098] Referring to Figs. 13 & 14, one embodiment of an impeller-shutter assembly 313 is illustrated. The impeller assembly 309 is shown housed in an impeller-shutter assembly 313 and forms part of the flow meter, which includes the impeller assembly, sensing elements, such as one or more optical sensors, and an impeller shell 315. Referring more specifically to Fig. 15, the impeller shell 315 is illustrated with hole 317, which allows for airflow communication between the inlet section and the measuring section.

[0099] In the embodiment illustrated, the impeller assembly of the flow meter requires a certain amount of air flowing into the device to cause the impeller assembly to spin. At a very low flow rate, the impeller will not spin, or will spin erratically. When a subject forcefully expels air into the device for certain measurements, e.g., a pulmonary function spirometry test, a gaseous sample flows through the impeller, causing it to rotate. In a typical spirometry test, the airflow can range from 100 to 700 LPM. The air then exits at the opening end of the shutter-controlled aperture. The amount and speed of air passing through the impeller can then be detected by sensing means along the impeller assembly. In one embodiment of the present invention, the measured lung function parameters from the flow meter can be converted to signals and transmitted to a microcontroller integrated with the monitoring device.

[0100] Again referring to Figs. 13 & 14, the impeller-shutter assembly 313 is shown with an airflow restrictor/shutter disposed upstream of the impeller assembly 309 along the airflow path extending from the inlet section. As shown in the embodiment depicted, the flow shutter comprises a multi-blade diaphragm comprising shutter blades 319. The aperture of the flow shutter can be adjusted to fully opened, closed or partially-opened positions to a desired degree to control the amount of the gaseous sample exiting the inlet section, allowing for different tests requiring different air flow speeds.

[0101] Referring more specifically to Figs. 16 & 17, the opening dimensions of the flow shutter can be fine-tuned by an outer retainer ring assembly 321, which forms part of the impeller-shutter assembly 313. The dimension of the shutter opening is adjusted by rotating the ring 321 back and forth in the direction 323. The shutter opening can be controlled mechanically through manual manipulation or controlled electronically through, for example, integrating the rotation of the ring with a microcontroller integrated with the device.

[0102] When the flow shutter is fully open in response to manual control or to an electrical signal during a spirometry test, which requires a user to exhale forcefully, the open shutter allows the free flow of air entering the inlet section. Meanwhile, a flow rate can be measured by a flow meter.

[0103] As described, the shutter-controlled mechanism of the present lung-function monitoring device allows measurement of gaseous samples requiring selected flow rates. For example, measurement of eNO concentration requires a steady flow of air, for example, of 3 to 5 LPM over a period of about 10 seconds. To conduct this test, the aperture of the shutter assembly is adjusted manually or electronically to achieve a predetermined flow rate. The closed exit of the inlet section results in redirecting the inflow of exhaled breath to the contiguous sensing section coupled with at least one NO sensor contained in the sensing section to measure the level of NO in exhaled breath. As illustrated in Fig. 18, the adjustability of flow rates into the device allows for multiple tests in one device that require vastly different flow-rate conditions. For example, spirometry flow rates reach into the hundreds of liters per minute and return to zero within five seconds. FeNO measurements require a constant flow rate of three liters per minute for ten consecutive seconds.

[0104] By way of illustration, in one embodiment of the invention, the device can be constructed to make three respiratory measurements, e.g., (1) a spirometry test, which

includes common tests such as PEF and FEV1 wherein the user exhales forcefully into the device during a short time at rates ranging from 100 to 700 LPM, (2) a fractional exhaled nitric oxide test (FeNO) wherein the user exhales at a controlled rate of approximately 3 LPM over a period of approximately 10 seconds, and (3) a respiratory rate test. A large diaphragm shutter upstream of an optical-impeller based flow meter allows for the measurement of large, short duration flows of up to about 700 LPM when the leaf shutter is in the open position and air flow is substantially unrestricted through the device, e.g., the adjustable partition is in the open position, allowing for the free flow of the spirometry test to be exhausted out of the device. When the shutter is in its restricted position, air flow through the device is limited to no more than about 5 LPM, allowing for the NO test that requires the slow, steady exhalation of breath. In the restricted position, the air flows to the nitric oxide sensor, such as a solid-state nitric oxide sensor. In one embodiment, the restricted flow can be siphoned off, for example by a pump that siphons off the sample through the impeller shell hole, and delivered to the NO sensor. The pump can also be used to purge the device. The respiratory rate can be measured using an accelerometer that measures chest wall movements that correlate to breaths. In one embodiment, an accelerometer for measuring respirations (e.g., breaths per minute) can be coupled to the user's torso. Measurements from the accelerometer can be transmitted to the monitoring device of the present invention by wire, or wirelessly.

[0105] In addition to the above, in one embodiment the device is constructed to perform two other peripheral measurements: (1) pulse, and (2) pulse oximetry. These blood flow measurements can be made using optical sensors per standard methods.

[0106] With the above-described capabilities, the device can measure at least four markers that are of importance to asthma patients and doctors. Additional features and embodiments are described below.

[0107] As illustrated, a user generally exhales into the device through a mouthpiece. Any suitable mouthpiece may be employed in the practice of the invention described herein. However, it is advantageous to employ a mouthpiece that allows a user to inhale outside air through the mouthpiece, and exhale through the mouthpiece and into the device through a path separate from the path of inhaled air. It is further advantageous to filter the inhaled or exhaled air with one or more filtering media. One embodiment of such a mouthpiece is illustrated below.

[0108] Referring to Figs. 19 to 22, a mouthpiece 401 is illustrated having a user side 403 and a device side 405. As a user inhales through the mouthpiece, fresh, outside air 409 enters the mouthpiece via one-way valve 407 and flows through a dedicated inhalation pathway 411 to the user. When the user exhales breath into the mouthpiece, the exhaled breath proceeds through a second dedicated pathway 413 through a second one-way valve 415 and then into the device.

[0109] As described above, the illustrated mouthpiece can contain one or more filters or filtering media. For example, referring more specifically to Fig. 23, a filtering media 417 for scrubbing NOx can be situated inside the mouthpiece adjacent to the one-way entry valve 407. In addition, an additional filter, such as a paper filter 419 can be incorporated into the device for filtering out microorganisms, such as bacteria or fungi. In addition, a desiccant, for example, can be included in the device for removing water vapor from exhaled breath that might otherwise enter the device and promote the growth of microorganisms or harm sensitive electronic components.

[0110] The filters or filtering media may be of any appropriate kind. By way of illustration, filters and filtering media can be adopted for screening out gases of interest, including NOx, CO, CO2, NH3, O2, H2O, etc. Examples of filtering media include activated alumina, Sofno-Fil, Sofno-Lime, silica, activated zeolite structures, and the like. Paper filters may be of any appropriate type for the intended function, for example, polypropylene, paper, cotton, or other fabric depending on the desired function.

[0111] The mouthpiece housing can be composed of any suitable materials. For example, the materials chosen should not interfere with the flow of the gases through the device or the filter materials. One such suitable material is polyethylene terephthalate (PET). The mouthpiece can be a single use, disposable component that can be sanitized prior to use or packaging, or easily sanitizable and reusable.

[0112] The described mouthpiece has numerous advantages. It can reduce the maintenance of monitors by moving the consumable filter media to a single use, disposable component. Or, in another embodiment, where the mouthpiece is reusable, filter media may be replaced or recharged as needed. This can reduce the need for monitor servicing, e.g., for the purpose of changing filter media or valves. This improves the cost efficiency of the monitors. Safety is increased because some breathing devices require the user to inhale through the device,

potentially allowing bacteria or fungi from the device to enter the user. The described mouthpiece can also filter species that are detrimental to breath analyses.

[0113] In a particularly preferred device, the mouthpiece will operate with greater than fifty percent efficiency in the removal of specific species. For example, removal of moisture should reduce exhaled breath relative humidity to between 5 to 70%. Ingress and egress flow rates of between 25 to 300 sccm are desirable. Operating conditions should be ambient temperatures between 10 degrees Celsius to 45 degrees Celsius and relative humidity of between 5% to 99%.

[0114] In another embodiment of the present invention, pulmonary function, and other related tests, can be enhanced by incorporating a microcontroller. For example, a user can enter his or her data into the microcontroller, execute programs and receive the transmitted signals from integrated flow meter and NO sensor. The microcontroller can further include information storage means for storing entered parameters and received data.

[0115] In another embodiment, one or more gas sensors can be configured to measure clinically relevant-biomarkers, e.g., H2, CO, or O2 can be integrated with the present lung-function measuring device. Other sensing methods, e.g., electrochemical, acoustic, calorimetric, optical, or biological sensing methods can be incorporated for detecting gas molecules. For example, as described above, optical sensors (e.g., pulse oximetry) can be incorporated for measuring blood flow characteristics.

[0116] In another embodiment, the portable microcontroller can integrate with selected wired or wireless networks, e.g., Wi-Fi, Bluetooth, or USB to transmit and store data at remote locations. GPS can also be integrated to provide user location. For example, testing data can be automatically forwarded to a physician for monitoring and analysis.

[0117] In another embodiment, the device can obtain the user's location and local weather conditions, including air quality, and subsequently record and transmit this data. In a particularly preferred embodiment, fractionally exhaled nitric oxide concentration (FENO score) can be tracked and presented alongside tracking for other spirometry values such as FEV1, FEV6, PEV, FVC, TLC, and SVC, and alongside other environmental factors such as outside air temperature, weather conditions, wind speed, wind direction, barometer values, barometer trends, pollen count, air quality, ground level ozone, dew point, and humidity.

[0118] As a further illustration, the device 100 can be used with a data storage and information system to provide users and caregivers with asthma-related information. For example, referring to Figure 23, the device 100 can be configured to connect via the Internet to a cloud server. The device 100 can thus include a Wi-Fi, blue tooth, cellular, Ethernet or other connection to the Internet. The cloud can include, for example, stored environmental data, such as air quality, air particle count, and other conditions, clinical guidelines, patient historical data, etc., which can then be relayed back to the user and or physician based upon the user's reading by way of the device 100, a web-based application, mobile device application, or local computer.

[0119] In some embodiments, the device can be configured to gather environmental data using a sensor built into the device. In other embodiments, the device's location can be determined by GPS or cellular triangulation, or Wi-Fi signal triangulation or other system sensor or a combination in whole or part of such systems and then querying a national and accepted data source for the above mentioned environmental parameters.

[0120] In other embodiments, the devices described herein can be used with a subscription service. For example, a physician can buy a subscription for so many uses of the device, then the physician will be granted access to the "ecosystem" database that can provide specific user results including but not limited to historical trends, local trends, regional trends, notifications may be such things as appointment reminders, or a notice of high pollen count within a nearby region that mayor may not correspond to particular NO reading, etc. The subscription service would also provide the user or physician the ability to record and or maintain a symptom diary that would be tracked along with exhaled nitric oxide measurements, and or any additional clinical or non-clinical data of interest to the user, physician, or other party.

[0121] As described above, there is an abundance of relevant medical and environmental parameters that bear on monitoring and evaluating an individual's respiratory functions. Relevant parameters also include an individual's activity and behavior parameters. The ability to collect, store, and analyze such parameters can be of tremendous benefit to patients, caregivers and healthcare professionals. With devices, such as those described herein, relevant parameters can be communicated to a secure computer network data system that collects, stores and analyzes such data. Moreover, once such data is collected and analyzed, it can be tracked and can be accessed via a customizable computer graphic interface.

Consequently, the ability to simultaneously view such data in a customizable graphical user interface allows the plethora of available data to quicken the evaluation by healthcare professionals and individuals, such as patients.

[0122] Relevant medical parameters include, in addition to exhaled nitric oxide measurements, values obtained for other medical parameters of interest, such as nasal nitric oxide, exhaled CO and CO2 levels, exhaled acetone, exhaled ketones, interleukin counts PEF, FEV1, FEV6, PEV, FVC, TLC, and SVC, blood eosinophil counts, blood oxidation levels, pulse oximetry, weight, height, BMI, and the like.

[0123] Environmental parameters include values such as ambient NO, air quality, airborne particle count temperature, dew point, wind speed, wind direction, pollen count, pollen blooms, smog, and the like. An individual's activity and behavior patterns include exercise and medication therapy adherence and the like.

[0124] As indicated, relevant medical and environmental data can be communicated, such as by uploading, to a computer network data system. Programs for analyzing, tracking and displaying the data can be computer based, cloud based or a combination. Access can be accomplished by any suitable computerized device that can display the information desired, such as desktops, laptops, tablets, mobile devices, and an appropriate respiratory monitor, such as those described herein, having a suitable microcontroller and graphical user interface display with access to the network that enable data communication between the device and the network such that data can be displayed on the accessing device,

[0125] A computer implemented method for collection, storage, analysis, and facilitating access to the medical data and medically relevant data such as environmental parameters or patient behavioral data can be presented by a number of methods including but not limited to: graphs, plots, maps, pictures and tables for the purpose of providing environmental and behavioral context (potential correlation) to medical parameters of interest.

[0126] Networked diagnostic devices, such as those described herein, can send data to the networked system that includes date, time, location, user identification number, and clinical parameters such as exhaled nitric oxide concentration, and device specific information regarding device performance, etc. Networked diagnostic devices can also receive data from the networked system that includes active user identification numbers, and software update information, etc.

[0127] In a preferred embodiment, a network accessed graphical user interface is employed that will be displayed during access to the network that is capable of displaying queried data in the form of graphs, charts, maps, pictures, and tables in a specific format based on the user's preference and access level. Further the user interface will be capable of determining and maintaining security based on the user's level of access, but always transmitting data in such a manner that it uses appropriate security measures, such as encoding, encryption, pass-key access, etc.

[0128] The network accessed graphical user interface may be primarily used to display a single patient profile that would include that specific patient's specified medical parameter historical data shown on a trend chart. Such trend charts can display a single, or a plurality of medical parameters using the equivalent time based scale and such that the axis are consistent or matching orientations of goodness. For example FEV1 can be displayed as a percentage of 100 where 100% is good. FeNO can be shown on scale of 5-300 where low numbers are good. The FeNO score can be oriented such that the lowest score (5ppb) is oriented at the top (up). Additional parameters selected by the user for display can be presented in similar fashion

[0129] In addition, at the preference of a user, medical parameter trends can be simultaneously displayed with environmental data trended by the location preference chosen by the user. For example, a patient and their doctor's office are often not co-located, thus when a health care professional (HCP) is reviewing a patient's profile, the HCP may elect to view FeNO scores simultaneously with the air quality historical data for the HCP's office, or it maybe displayed with the air quality historical data from the patient's home address, city, zip code, or other means of geo-locating. Moreover, the graphical user interface can display historical data trends that may include special notes regarding specific data points. For example, in the context of FeNO measurements and geo-location, it can be noted where a particular patient may have traveled in between or during a particular evaluation. As such, an environment not typically listed (HCP office, home, work, etc.) can be noted and taken into account.

Reactor and Sensor Assemblies

[0130] The NO detection device of the present invention may include different elements sized and configured to allow for further manufacturing efficiencies and enhanced portability.

Exhaled breath from a user enters the detection device via a sample inlet and through a flow pathway within the detection device. In some embodiments, the flow pathway includes a reactor and sensor assembly that comprises a reactor portion with a catalytic filter, a sensor portion with a plurality of sensor pads, and a unitary heating element with a resistive temperature device. The reactor portion receives the humidity equilibrated breath sample and generates a known equilibrium mixture of NO and NO_2 from NO_x. The sensor portion includes a sensor that measures the NO_x concentration in the sample, and a controller calculates the total NO in the sample based on the measured NO_x concentration and the known equilibrium.

[0131] In one embodiment, the reactor and sensor portions of the assembly may be placed in separate gas chambers that are connected by one or more gas channels. The heating element is placed between the reactor and sensor portions. The heating element distributes heat to both portions of the assembly. In a preferred embodiment, the heating element includes a single heater with heat separation or conduction media between the reactor and sensor portions. The configuration allows the reactor and sensor portions of the assembly to be maintained at different temperatures using a single heater and resistive temperature device.

[0132] Advantageously, the inclusion of a unitary heating element may reduce the power consumption required to achieve the desired operating temperatures and remain stable. Such a reduction of power may be beneficial from a usability perspective because the device may manage the current power remaining and allocate appropriately. The design may further reduce the overall size of the NO detection device. This architecture may also allow for an enhanced sensing device with a compact body that is suitable for a variety of uses, including without limitation, a compact hand-held device. As will be described below, some features of the heater and resistive-temperature device may also allow for manufacturing efficiencies and reduce the number of electrical connections required for the device.

[0133] The reactor-sensor architecture may be well suited for use in a personal portable device monitor that performs gas measurements for NO, for which compact size, fast warm-up times, and fast stabilization times are particularly important. The device may allow the measurement of NO content of a gas using a compact reactor and sensor assembly in a compact, portable, battery powered package that can be used or breath or other gas analysis. Given the efficiency of the device, the design may also increase the resolution of breath sampling. The assembly is well suited for performing exhaled nitric oxide measurements and

analysis that are beneficial for asthmatics to perform on a frequent basis to monitor airway inflammation. In addition, the reactor-sensor assembly may be used for a personal portable device that performs gas measurements for air born molecules when adapted with additional or alternative sensors, such as those used to detect CO, acetone, NO_2, NO_x, CO_2, ammonia, and others substances.

[0134] In some embodiments, the reactor portion of the reactor-sensor assembly is coated with a catalytic material that is used to precondition the gas fluidly transferred to the sensor portion of the reactor-sensor assembly. The catalytic material should have a high surface area that promotes the chemi-adsorption of the gas molecules so that the gas molecules can be reacted with high efficiency before continuing in the fluid flow path. Suitable catalytic materials include, without limitation, Zeolite-Y or ZSM-5 (*e.g.*, Zeolite Socony Mobil–5) with a surface area per mass of 425 m^2/g as received. In one embodiment using ZSM-5, the catalytic material may contain approximately 1-4% μm platinum in zeolite. Although platinum is described as an example, alternative catalysts could be used and dispersed in a zeolite or other high surface area structures.

[0135] The reactor portion is maintained at a condition that provides a consistent catalytic efficiency. The conversion efficiency is dependent on variables such as the flow rate, the nominal surface area of catalyst, the depth of the catalytic coating on the surface, the temperature of the catalyst, and humidity. In one embodiment, the reactor-sensor assembly may operate with a given flow rate range from 5 to 8 mL/min through the assembly, and the reactor portion is maintained at a constant temperature within the temperature range of 250 to 700°C, typically 280 to 350°C. In another embodiment, the reactor-sensor assembly uses a flow rate range of 7 to 50 mL/min and a temperature range from 275 to 350°C. In a preferred embodiment, the reactor portion operates at a well-maintained temperature of nominally 280 +/- 50°C. In an alternative embodiment, the reactor portion may have an additional heater and resistive thermal device (RTD) to monitor temperature that will be controlled and monitored by a central computing controller chip that will control the components to target temperatures.

[0136] The reactor portion of the reactor-sensor assembly will be heated to a different temperature than the sensor portion to provide a driving force for the NO_x equilibration reaction. In some embodiments, the sensor portion will be maintained at a temperature between 300 and 900°C. In other embodiments, the sensor portion is heated to a target

temperature of between 350 and 500°C. In a preferred embodiment, the sensor portion operates at a well-controlled temperature of nominally 450 +/- 50°C.

[0137] Referring to Figures 27 and 28, an exemplary reactor-sensor assembly 600 is shown. A reactor-sensor enclosure 601 with a plurality of layers disposed on a sensor carrier or substrate or embedded within the sensor substrate. The enclosure contains a sensor layer 602, a catalyst layer 603 located below the sensor, and a heating element 604 positioned within the substrate, between the sensor and catalyst layers. An insulator 605 may be placed on the sensor substrate, below the heating layer. As a non-limiting example, the insulator may be constructed of aluminum oxide (Al_2O). Other suitable insulators include any dielectric material that exhibit a high melting point with low thermal expansion coefficients, mechanical strength, and resilience at high temperatures, such as, without limitation, mullite ($Al_6Si_2O_{13}$) or its composites. The insulating material should be capable of withstanding high temperatures while maintaining structural integrity. One or more gaskets 606 may be used to help to seal the space between the sensor substrate and inner surface of the detection box. As will be discussed in further detail below, the sensor layer may include a plurality of sensors, each having two electrodes (a sensing potentiometric electrode and a reference potentiometric electrode) that are electrically connected to a controller. The controller may be electrically connected to both the reactor portion of the assembly (with the catalytic filter) and the sensor portion.

[0138] The housing defines two chambers divided by the sensor substrate. One chamber includes the catalyst layer, and the other chamber includes the sensor layer. Each of the chambers has an inlet and outlet, and air is forced through and then outside of the unit after exiting the sensor chamber. In some embodiments, the catalyst (reactor) chamber and the sensor chamber are connected by one or more fluid conduits. Here, one or more intermediate cooling tubes (not shown), such as a Viton tube, may be used to connect to the catalyst and sensor chambers. The cooling tube may be placed outside the unit to connect the outlet of the catalyst chamber to the inlet of the sensor chamber. Other structures (e.g., pipes, tubing, or connecting structures) that are capable of fluidly delivering gas may be used.

[0139] Figure 28 shows a path for airflow through the chambers, according to one embodiment of the present invention. An exhaled breath sample flows from the inlet of the catalyst chamber and contacts the catalyst layer, where it interacts with the catalyst at a particular temperature to form an equilibrium mixture of NO and NO_2. Exhaled breath gas

then exits through the outlet of that chamber. The sample then flows through the intermediate tube to the inlet of the downstream sensor chamber, where it is allowed to contact the sensor surface. The sensor is configured to sense the amount of NO_x flowing through the sample. A controller calculates the total NO in the sample based on the measured NO_x concentration and the known equilibrium of NO and NO_2. After passing through the sensor chamber, the exhaled breath sample leaves the reactor-sensor assembly through the outlet of the sensor chamber.

[0140] The heating element can 605 advantageously provide preferred heat distribution to the sensor and catalyst layers. The reactor and sensor portions of the assembly are maintained at different temperatures, and advantageously, the reactor-sensor assembly can be designed to allow for precise detection and control of the heat differences in the catalyst and sensor layers of the assembly. In addition, the device can be configured to control other important variables such as humidity, pressure, and flow rate. It will be appreciated that a number of variables, such as the temperatures and temperature differences in the catalyst and sensor chambers, may be controlled by adjusting the materials or the amount of materials applied to the assembly. As a non-limiting example, the heat distribution to the different chambers may be modified by the use of an insulator material with different heat transfer properties. The heat distribution can also be affected by changes in the amount of catalyst mass present, relative to the mass of the sensor. In addition to material selection and amounts, heat distribution from the heating element may also be affected by the dimensions of the chambers. For example, increasing the available volume of one of the chambers through which a gas sample flows may increase the temperature difference between the chambers. The temperatures may also be adjusted by modifying the heat supplied to the assembly through a heat trace, for example.

[0141] The sensor may be secured to the sensor substrate in any suitable way. As an example, the sensor may be placed on the sensor substrate above the thermal insulator, which helps to support the sensor. In this embodiment, the insulator may have a thermal conductivity of approximately 0.1 W/mK, a thickness of approximately 0.3 mm, and thermal resistance of approximately 3 m^2K/W. The sensor and catalyst may be heated to temperatures of approximately 400°C and 200°C, respectively, using a power consumption of approximately 4W.

[0142] In yet other embodiments, the sensor may be suspended from an upper surface of the sensor substrate using welding wires. In this example, the sensor and catalyst may be heated to temperatures of over 400°C and slightly under 200°C, respectively, using a power consumption of approximately 4W.

[0143] Alternatively, the sensor may be secured to the sensor substrate using bonding wires. That is, the thermal insulator is secured to the sensor substrate using inorganic adhesive. The heating layer is placed above the insulator. The sensor is positioned above the heating layer and secured to the substrate using bonding wires. Optimally, the space separating the inner surface of the upper metal housing and the sensor substrate should be sealed using an elastic material, as should the space separating the inner surface of the lower metal housing and the catalyst.

[0144] In a preferred embodiment, the housing (*e.g.*, a main resin enclosure) may measure approximately 45 mm in length, 25 mm in width, and 20 mm in height with a catalyst measuring approximately 11 mm x 7 mm x 3 mm. In another embodiment, the size of the enclosure may be increased to approximately 30 mm x 50 mm x 100 mm, depending on assembling and operation variables such as: ease of assembly, requirements for the surface temperature of the enclosure, desired heat exchange parameters, and size of the catalyst and its conversion efficiency.

Electrical Connections for the Reactor-Sensor Assembly

[0145] A further advantage of the present invention is a reduction in the number of electrical connections between the reactor-sensor assembly and the controller. The sensor used in the reactor-sensor assemblies described in the present invention may be constructed to include different types of electrical connections on either side of the sensor/heater assembly. In some embodiments, the reactor-sensor assembly has a minimum of six electrical connections to the controller for: the reactor-sensor heater (+), reactor-sensor heater (-), reactor-sensor resistive temperature device (+), reactor-sensor resistive temperature device (-), sensor signal (+), and sensor signal (-). These electrical connections are made to minimize electrical interference and to reduce the amount of heat transferred out of the reactor-sensor assembly.

[0146] Referring to Figures 29A through 29D, in one embodiment, a heating element and resistive temperature device are formed on or within the backside of the sensor substrate. A sensor is positioned above a heating element on a carrier board. The sensor has a plurality of

sensor pads. The sensor may be electrically connected to the substrate board, for example, by wire bonding (as illustrated schematically in Figure 31). On the sensor-facing side, electrical connections for the sensor signals are created by weldments 608 and 609 positioned at opposite corners. On the heater-facing side, electrical connections for the heater and resistive temperature device 610, 611, 612, and 613 are created by additional weldments positioned at the four corners. In a preferred embodiment, the weldments may be formed by electric resistance welding with Pt/Au ribbon, or other welding methods known in the art for joining metal components.

[0147] In an alternative embodiment of the present invention, the electrical connections are located on a single face of a sensor substrate. Referring to Figures 30A through 30D, a sensor is positioned above a heating element and placed on a carrier board or substrate. On the sensor-facing side, a set of electrical connections for the sensor signal 614 and 615 are located at opposite corners. Thru holes 616, 617, 618, and 618 corresponding to the electrical connections on the heater-facing side are also located on opposite edges of the sensor-side face to allow connections between the sensor and heater sides of the assembly. The thru holes create recesses through which electrical conduits may be printed, and they create a pathway for electrical signals to pass by using pins, for example.

[0148] Because this structure uses weldments on only the sensor-side face, it reduces the strain that might otherwise change the electrical signals in the assembly. The use of thru-holes and pins may also simply manufacturing in that it requires electrical connections and weldments on only one side of the heating element. The electrical connections may be created by wire bonding with Au wire or other welding methods known in the art for joining metal components.

Ceramic Packaging

[0149] In another embodiment, the reactor-sensor assembly may be housed, at least in part, within a ceramic package and positioned on a printed circuit board. The sensor is fixed and electronically connected to the package, with a muffler-like catalyst unit placed below the sensor via one or more insulation layers. In this embodiment, the reactor-sensor assembly utilizes the ceramic package and related technologies to save mass and power consumption, particularly in situations of low temperature around the device.

[0150] Referring to Figure 32A, ceramic package 700 includes a ceramic lid 701 with an upper metal tube 702, and a base housing 703. Pins 704 extend past the bottom of the housing, as also shown in the Figure 32B. The use of the pins allow for electrical connections between the sensor 705 and the printed circuit board (not shown), thus minimizing or eliminating the need for wire bonding during manufacture.

[0151] A catalyst unit 706 is placed below the sensor via the insulator 707. The catalyst unit may be sized and constructed to fit within the inner surfaces of the base housing (as shown in Figure 32A). It includes side covers 708 and 709 and tubing positioned on each side of the unit. The catalyst unit rests above a ceramic lid 710. As shown in expanded view, the catalyst unit also includes a metal lid 711 with a catalyst 712 and a sealing element 713 surrounded by a metal body 714. In some embodiments, the parts may be stacked or bonded using compression stress.

[0152] Referring to the assembled unit shown in Figure 32C, breath gas enters the reactor-sensor assembly through side tubing 715 positioned through the side cover. The gas is allowed to contact the catalyst in the catalyst unit, after which the gas flows out of the catalyst unit through tubing 716 on the other side. External tubing (not shown) allows the breath gas to flow through the upper metal tube and into the sensor unit. The configuration creates separate chambers for gas flow through the catalyst and sensor portions of the assembly.

[0153] A cross-section of an assembled reactor-sensor assembly integrated with a ceramic package is illustrated in Figure 33. Gas flows through side tubing 717 through the catalyst unit and exits through side tubing on the opposite side. An external tube allows for gas flow from the catalyst unit to the sensor unit through the top of the assembly. Electrical pins are formed on the base of the assembly 718 and allows the formation of an electrical connection between the sensor and a printed circuit board (not shown).

[0154] In a preferred embodiment, the reactor-sensor assembly may measure approximately 25 mm in length, 34 mm in width, and 20 mm in height with a catalyst measuring approximately 5 mm x 3 mm x 2 mm. The enclosure may be sized to be larger or smaller, however, depending on assembling and operation variables such as, without limitation, ease of assembly, requirements for the surface temperature of the enclosure, internal heat exchange parameters, and size of the catalyst and its conversion efficiency.

Thermal Zones within the Reactor-Sensor Assembly

[0155] Figures 34A and 34B illustrate another embodiment of a reactor-sensor assembly using a single heater and a single resistive temperature device. This configuration has the benefit of allowing for breath gas flow through compartments without requiring the use of external tubing to connect the chambers. The reactor-sensor assembly also may allow for conditioning of the gas, as well as gas flow through different zones in the assembly, including, as will be further discussed below, flow through a pre-heating zone before a gas sample interacts with the catalyst and a cooling zone before the sample contacts the sensor. Each of the zones in the assembly may have different geometries and be maintained at different temperatures.

[0156] In one embodiment, a housing includes a series of internal surfaces formed by lid-shaped surfaces, for example, nested within another and placed over the bottom of the housing. The internal surfaces create an elongated flow path and zones through which breath gas may flow. As illustrated in Figure 34A, an upper lid 800 is made of a material of low heat conductivity, such as stainless steel (SUS). An intermediate lid 801 is made of a material with moderate heat conductivity, such as aluminum (Al). A lower lid 802 is made of a material with moderate thermal and chemical stability, such as SUS or a thin alumina substrate. The catalyst 803, for example Pt-Y or other platinum loaded zeolite catalyst, is positioned on the surface of the lower lid (and above a heating element). In some embodiments, a catalyst maybe placed onto the substrate by positioning it on a recess on the lower lid. The sensor is positioned below the heating element. All of the surfaces are above the same sensor bottom housing 804. The lids and housing may be tightened, and the chambers substantially sealed, using Teflon packing and screws or other methods known in the art for maintaining a gas seal.

[0157] Referring to Figure 34B, at least a portion of each of the lid surfaces is positioned to fit under at least a portion of the successive lid surface. One or more gaps between the lid surfaces allow for gas flow between the surfaces and through the reactor and sensor assembly. When stacked above the bottom of the housing, each lid surface fits within the successive lid surface to create a continuous flow path 805 through the reactor-sensor assembly. The flow path can include resulting zones of varying temperatures. For instance, breath gas enters through an upper portion of the housing, where it may be preheated in a pre-

heating or pre-treatment zone. In this zone, the gas is initially warmed to facilitate reaction before it reaches the catalyst.

[0158] The breath gas then flows through a catalyst zone where it is allowed to react with the catalyst. It is then cooled as the gas flows through a cooling zone, after which the breath gas contacts the sensor in sensor zone. In a preferred embodiment, the sensor may be heated to approximately 400°C, while the temperature of a Pt-Y catalyst may be maintained at approximately 300°C with the aid of the heat exchange occurring in the cooling zone.

[0159] It is contemplated that the temperature differences in the zones of the reactor-sensor assembly, including the particular temperatures at which the sensor and catalyst zones are maintained, may be adjusted in one or more ways to optimize and/or control heat flow within the system. For example, the materials used, including the material selected for the insulator, may be modified to change the heat transfer properties within the system. The dimensions of the metal housing, such as the length, width, and height, may be modified to adjust the surface area of the internal surfaces and the volumes of the zones or chambers through which breath gas flows. The distances of the layers from the heating element may also be adjusted; for example, by changing one or more thicknesses of the layers or the distances from the heater location. The amount of catalyst material applied relative to the amount of sensor material present may also be adjusted to change the temperatures (or the temperature differentials) in the system. The distances of the flow paths may also affect the heat exchange properties within the assembly.

[0160] In another embodiment, a reactor-sensor assembly may include yet other configurations to allow for additional treatment of the gas flowing through the assembly. In one embodiment, a reactor-sensor assembly may include a reactor chamber, sensor chamber, a heating element between the reactor and sensor chambers, and one or more external gas conduits connecting the two chambers. A sensor substrate, for example, an alumina substrate, divides the chambers. A catalyst filter (PtY, for example) is positioned near the inlet of the reactor chamber to allow an extended flow-path for the gas sample after it has contacted the catalyst filter. The flow path of the gas sample after it has contacted the catalyst filter in this example is extended, as compared with an assembly where the catalyst filter is placed in or near the center of the reactor chamber. The extended flow path allows for cooling of the inlet gas sample before it reaches the sensor chamber.

[0161] Similarly, in some embodiments, a sensor layer may be positioned in the sensor chamber near the outlet area of the gas sample. The flow path of the gas samples before it contacts the sensor layer is also extended, as compared with an assembly where the sensor layer is positioned at or near the center of the sensor chamber. This extended flow path allows for additional cooling of the as sample in the reactor chamber.

[0162] In yet another embodiment of the present invention, the reactor-sensor assembly may be configured to allow for substantially linear gas flow through the assembly. Referring to Figure 35, a reactor-sensor assembly 900 may include a catalyst 901 and sensor 902 located on the same face of a substrate 903. A heating element, including a heating coil 904, is located below the catalyst and sensor, and embedded within the substrate.

[0163] A breath gas sample flows substantially linearly across the substrate, as shown in flow path 905. Breath gas flowing into the reactor-sensor assembly is passed through an initial pre-treatment area where it is heated before it is allowed to react with the catalyst. The breath gas then flows through a catalyst zone where it may interact with the catalyst. A segment of the substrate then provides a cooling zone where the breath gas is allowed to cool. The breath gas then flows through the sensor zone where it contacts the sensor.

[0164] A housing (not shown) surrounds the assembly. The housing may be made of various materials known in the art that allow for mechanical strength, ease of use, and effective maintenance of target temperatures within the reactor-sensor assembly. Suitable materials include, without limitation, stainless steel, alumina, plastic polyphenyline sulfide (PPS), ceramic, and beryllium oxide.

[0165] The reactor-sensor assemblies described above are designed to allow the maintenance of different temperatures in each of the zones. To that end, the heating element may be designed to distribute different amounts of heat to each of the zones. Moreover, the heating element may be modified to achieve target temperatures within the different assembly zones. For example, the temperatures or the temperature differentials in each of the zones may be further modified by changing the number of coils or loops in the heater trace. The temperatures may also be changed by varying the thickness or the width of the trace. The location of the catalyst and sensor on the substrate may also affect the temperatures in the various zones. For example, placing the catalyst and sensor farther away from each other

allows for additional cooling of breath gas after it reacts with the catalyst and before it contacts the sensor.

[0166] The component shapes, dimensions, and geometries described above for the reactor-sensor assemblies are provided as examples. The particular flow paths, shapes, forms, dimensions, and geometries described above may be modified to achieve the desired heat transfer properties or other performance properties within the reactor-sensor assemblies or as desired to improve manufacturing and operation. The heat transfer properties may be changed by modifying factors known in the art to affect heat transfer, including without limitation: the materials selected for use; the shape and dimensions of the path through which the gas sample flows; the shape and/or size of the of the metal housing; the shape and/or size of chambers through which gas flows; the surface areas of the internal surfaces contacting the gas sample; the volumes of the zones or chambers through which breath gas flows; the flow rate of gas entering the device; and the distances of the layers from the heating element.

[0167] As for additional details pertinent to the present invention, materials and manufacturing techniques may be employed as within the level of those with skill in the relevant art. The same may hold true with respect to method-based aspects of the invention in terms of additional acts commonly or logically employed. Also, it is contemplated that any optional feature of the inventive variations described may be set forth and claimed independently, or in combination with anyone or more of the features described herein. The breadth of the present invention is not to be limited by the subject specification, but rather only by the plain meaning of the claim terms employed.

[0168] This disclosure is sufficient to enable one of ordinary skill in the art to practice the invention, and provides the best mode of practicing the invention presently contemplated by the inventors. While a full and complete disclosure is made of specific embodiments of this invention, the invention is not limited by the exact construction, dimensional relationships, and operation shown and described. Various modifications, alternative constructions, design options, changes and equivalents will be readily apparent to those skilled in the art and may be employed, as suitable, without departing from the spirit and scope of the invention. Such changes might involve alternative materials, components, structural arrangements, sizes, shapes, forms, functions, operational features and the like.

CLAIMS

What is claimed is:

1. An apparatus for determining total NO_x, including NO and NO_2 concentrations from a gas stream comprising:
   (a) a first chamber comprising a catalytic filter; the catalytic filter adapted to catalyze the formation of an equilibrium mixture of NO and NO_2 from an incoming gas stream;
   (b) a second chamber downstream from the first chamber, the second chamber comprising a sensor element adapted to contact said equilibrium mixture of NO and NO_2, wherein the sensor element comprises a sensing potentiometric electrode and a reference potentiometric electrode;
   (c) a gas conduit connecting the first and second chambers; and
   (d) a heating element disposed between the catalytic filter and sensor element, the heating element comprising a single heat source adapted to distribute heat to the first and second chambers; wherein the catalytic filter and sensor element are each maintained at different temperatures using the heating element.

2. The apparatus of Claim 1, further comprising conduction media disposed between the catalytic filter and sensor element.

3. The apparatus of Claim 1, further comprising one or more heat separation elements disposed between the catalytic filter and sensor element.

4. The apparatus of Claim 1, wherein the sensor element is disposed on a sensor substrate separating the first and second chambers, and the heating element is embedded within the substrate.

5. The apparatus of Claim 1, wherein the first chamber is disposed below the second chamber, and the gas conduit comprises external tubing connecting the first and second chambers.

6. The apparatus of Claim 1, further comprising a ceramic package and pins extending from a lower portion of the ceramic package; wherein the ceramic package forms at least a portion of a housing around the first and second chambers; and further wherein

the pins are adapted to electronically connect the sensor element to a printed circuit board.

7. An apparatus for determining total NO_x, including NO and NO_2 concentrations from a gas stream comprising:

(a) a housing;

(b) a gas inlet positioned in said housing;

(c) a breath-flow pathway that proceeds downstream from said inlet;

(d) a humidity equilibrator positioned in said pathway;

(e) a reactor-sensor assembly positioned in said pathway, downstream of said humidity equilibrator; the reactor-sensor assembly comprising:

(i) a first chamber comprising a catalytic filter; the catalytic filter adapted to catalyze the formation of an equilibrium mixture of NO and NO_2 from a gas stream;

(ii) a second chamber downstream from the first chamber, the second chamber comprising a sensor element adapted to contact said equilibrium mixture of NO and NO_2, wherein the sensor element comprises a sensing potentiometric electrode and a reference potentiometric electrode;

(iii) a gas conduit connecting the first and second chambers;

(iv) a heating element disposed between the catalytic filter and sensor element, the heating element comprising a single heat source adapted to distribute heat to the first and second chambers, wherein the catalytic filter is heated to a temperature different from that of the sensor element using the heating element; and

(v) a controller in electrical communication with said sensor element.

8. The apparatus of Claim 7, further comprising conduction media disposed between the catalytic filter and sensor element.

9. The apparatus of Claim 7, further comprising one or more heat separation elements disposed between the catalytic filter and sensor element.

10. The apparatus of Claim 7, wherein the sensor element is disposed on a sensor substrate separating the first and second chambers, and the heating element is embedded within the substrate.

11. The apparatus of Claim 7, wherein the first chamber is disposed below the second chamber, and the gas conduit comprises external tubing connecting the first and second chambers.

12. The apparatus of Claim 7, further comprising a ceramic package and pins extending from a lower portion of the ceramic package; wherein the ceramic package forms at least a portion of an enclosure around the first and second chambers; and further wherein the pins are adapted to electronically connect the sensor element to a printed circuit board.

13. An apparatus for determining total NO_x, including NO and NO_2 concentrations from a gas stream comprising:

(a) a housing;

(b) a gas inlet section positioned in said housing and comprising:

(i) a flow detection component;

(ii) an adjustable flow-restriction component positioned downstream of said flow detection component; and

(iii) an adjustable partition positioned downstream of said flow detection component; and

(c) a measuring section located adjacent to said inlet section and in fluid communication with said inlet, comprising:

(i) a first chamber comprising a catalytic filter; the catalytic filter adapted to catalyze the formation of an equilibrium mixture of NO and NO_2 from a gas stream;

(ii) a second chamber downstream from the first chamber, the second chamber comprising a sensor element adapted to contact said equilibrium mixture of NO and NO_2, wherein the sensor element comprises a sensing potentiometric electrode and a reference potentiometric electrode;

(iii) a gas conduit connecting the first and second chambers; and

(iv) a heating element disposed between the catalytic filter and sensor

element; wherein the heating element comprises a single heat source adapted to distribute heat to the first and second chambers; and further wherein the catalytic filter is heated to a temperature different from that of the sensor element using the heating element.

14. The apparatus of Claim 13, further comprising conduction media disposed between the catalytic filter and sensor element.

15. The apparatus of Claim 13, further comprising one or more heat separation elements disposed between the catalytic filter and sensor element.

16. The apparatus of Claim 13, wherein the sensor element is disposed on a sensor substrate separating the first and second chambers, and the heating element is embedded within the substrate.

17. The apparatus of Claim 13, wherein the first chamber is disposed below the second chamber, and the gas conduit comprises external tubing connecting the first and second chambers.

18. The apparatus of Claim 13, further comprising a ceramic package and pins extending from a lower portion of the ceramic package; wherein the ceramic package forms at least a portion of an enclosure around the first and second chambers; and further wherein the pins are adapted to electronically connect the sensor element to a printed circuit board.

19. An apparatus for determining total NO_x, including NO and NO_2 concentrations from a gas stream comprising:

(a) a base platform;

(b) a plurality of interlocking support structures disposed on the base platform to define a serpentine gas flow path, the support structures comprising: a first surface, a second surface disposed below the first surface, and a third surface disposed below the second surface;

(c) a catalytic filter disposed on an upper side of the third surface, the catalytic filter adapted to catalyze the formation of an equilibrium mixture of NO and NO_2 from an incoming gas stream;

(d) a sensor element disposed on an underside of the third surface, the sensor

element adapted to contact said equilibrium mixture of NO and NO_2, wherein the sensor element comprises a sensing potentiometric electrode and a reference potentiometric electrode; and

(e) a heating element disposed between the catalytic filter and sensor element; wherein the heating element comprises a single heat source adapted to distribute heat to the catalytic filter and sensor element; and further wherein the catalytic filter and sensor element are each maintained at different temperatures using the heating element.

20. The apparatus of Claim 19, wherein the first and second surfaces form an area adapted to heat incoming breath gas before it contacts the catalytic filter.

21. The apparatus of Claim 19, wherein the second and third surfaces form an area adapted to decrease the temperature of breath gas after it contacts the catalytic filter and before it contacts the sensor element.

22. The apparatus of Claim 19, further comprising conduction media disposed between the catalytic filter and sensor element.

23. The apparatus of Claim 19, further comprising one or more heat separation elements disposed between the catalytic filter and sensor element.

24. The apparatus of Claim 19, wherein the support structures comprise a plurality of stacked lids.

25. An apparatus for determining total NO_x, including NO and NO_2 concentrations from a gas stream comprising:

(a) a housing;

(b) a substrate disposed within the housing;

(c) a catalytic filter disposed on the substrate, the catalytic filter adapted to catalyze the formation of an equilibrium mixture of NO and NO_2 from an incoming gas stream;

(d) a sensor element disposed on the substrate downstream from the catalytic filter, the sensor element adapted to contact said equilibrium mixture of NO and NO_2, wherein the sensor element comprises a sensing potentiometric electrode and a reference potentiometric electrode; and

(e) a heating element disposed within the substrate below the catalytic filter and sensor element; wherein the heating element comprises a single heat source adapted to distribute heat to the catalytic filter and sensor element; and further wherein the catalytic filter and sensor elements are each maintained at different temperatures using the heating element.

26. The apparatus of Claim 25, further comprising conduction media disposed between the catalytic filter and sensor element.

27. The apparatus of Claim 25, further comprising one or more heat separation elements disposed between the catalytic filter and sensor element.

28. A method, comprising:

(a) flowing a breath gas stream through an assembly comprising:

(i) a first chamber comprising a catalytic filter; the catalytic filter adapted to catalyze the formation of an equilibrium mixture of NO and NO_2 from an incoming gas stream;

(ii) a second chamber downstream from the first chamber, the second chamber comprising a sensor element adapted to contact said equilibrium mixture of NO and NO_2, wherein the sensor element comprises a sensing potentiometric electrode and a reference potentiometric electrode;

(iii) a gas conduit connecting the first and second chambers; and

(iv) a heating element disposed between the catalytic filter and sensor element; wherein the heating element comprises a single heat source adapted to distribute heat to the first and second chambers; and further wherein the catalytic filter and sensor elements are each maintained at different temperatures using a single heating element;

(b) generating a known equilibrium mixture of NO and NO_2 from NOx in the first chamber;

(c) measuring the NOx concentration in the breath gas stream in the second chamber; and

(d) determining the total NO in the breath gas stream based on the measured NOx concentration and the known equilibrium mixture using a controller.

29. The method of Claim 28, wherein the step of flowing a breath gas stream through an assembly comprises flowing a humidity-equilibrated breath gas stream.

30. The method of Claim 28, further comprising conduction media disposed between the catalytic filter and sensor element.

31. The method of Claim 28, further comprising one or more heat separation elements disposed between the catalytic filter and sensor element.

32. The method of Claim 28, wherein the sensor element is disposed on a sensor substrate separating the first and second chambers, and the heating element is embedded within the substrate.

33. The method of Claim 28, wherein the first chamber is disposed below the second chamber, and the step of flowing a breath gas stream through an assembly comprises flowing the breath gas stream through external tubing connecting the first and second chambers.

34. The method of Claim 28, wherein the assembly further comprises a ceramic package and pins extending from a lower portion of the ceramic package, and further wherein the ceramic package forms at least a portion of a housing around the first and second chambers; and further wherein the pins are adapted to electronically connect the sensor element to a printed circuit board.

35. A method, comprising:

(a) flowing a breath gas stream through an assembly comprising:

(i) a base platform;

(ii) a plurality of interlocking support structures disposed on the base platform to define a serpentine gas flow path, the support structures comprising: a first surface, a second surface disposed below the first surface, and a third surface disposed below the second surface;

(iii) a catalytic filter disposed on an upper side of the third surface, the catalytic filter adapted to catalyze the formation of an equilibrium mixture of NO and NO_2 from an incoming gas stream;

(iv) a sensor element disposed on an underside of the third surface, wherein the sensor element comprises a sensing potentiometric electrode and a

reference potentiometric electrode, and the sensor element is adapted to contact said equilibrium mixture of NO and NO_2; and

(v) a heating element disposed between the catalytic filter and sensor element; wherein the heating element comprises a single heat source adapted to distribute heat to the catalytic filter and sensor element; and further wherein the catalytic filter and sensor elements are each maintained at different temperatures using the heating element;

(b) generating a known equilibrium mixture of NO and NO_2 from NO_x using the catalytic filter;

(c) measuring the NO_x concentration in the breath gas stream using the sensor element; and

(d) determining the total NO in the breath gas stream based on the measured NOx concentration and the known equilibrium mixture using a controller.

36. The method of Claim 35, wherein the first and second surfaces form an area adapted to heat incoming breath gas before it contacts the catalytic filter.

37. The method of Claim 35, wherein the second and third surfaces form an area adapted to cool breath gas after it contacts the catalytic filter and before it contacts the sensor element.

38. The method of Claim 35, further comprising conduction media disposed between the catalytic filter and sensor element.

39. The method of Claim 35, further comprising one or more heat separation elements disposed between the catalytic filter and sensor element.

40. The method of Claim 35, wherein the support structures comprise a plurality of stacked lids.

41. A method, comprising:

(a) flowing a breath gas stream through an assembly comprising:

(i) a housing;

(ii) a substrate disposed within the housing;

(iii) a catalytic filter disposed on the substrate, the catalytic filter adapted to catalyze the formation of an equilibrium mixture of NO and NO_2 from

an incoming gas stream;

(iv) a sensor element disposed on the substrate downstream from the catalytic filter, wherein the sensor element comprises a sensing potentiometric electrode and a reference potentiometric electrode, and the sensor element is adapted to contact said equilibrium mixture of NO and NO_2; and

(v) a heating element disposed within the substrate below the catalytic filter and sensor element; wherein the heating element comprises a single heat source adapted to distribute heat to the catalytic filter and sensor element; and further wherein the catalytic filter and sensor elements are each maintained at different temperatures using the heating element;

(b) generating a known equilibrium mixture of NO and NO_2 from NO_x using the catalytic filter;

(c) measuring the NO_x concentration in the breath gas stream using the sensor element; and

(d) determining the total NO in the breath gas stream based on the measured NO_x concentration and the known equilibrium mixture using a controller.

42. The method of Claim 41, further comprising conduction media disposed between the catalytic filter and sensor element.

43. The method of Claim 41, further comprising one or more heat separation elements disposed between the catalytic filter and sensor element.

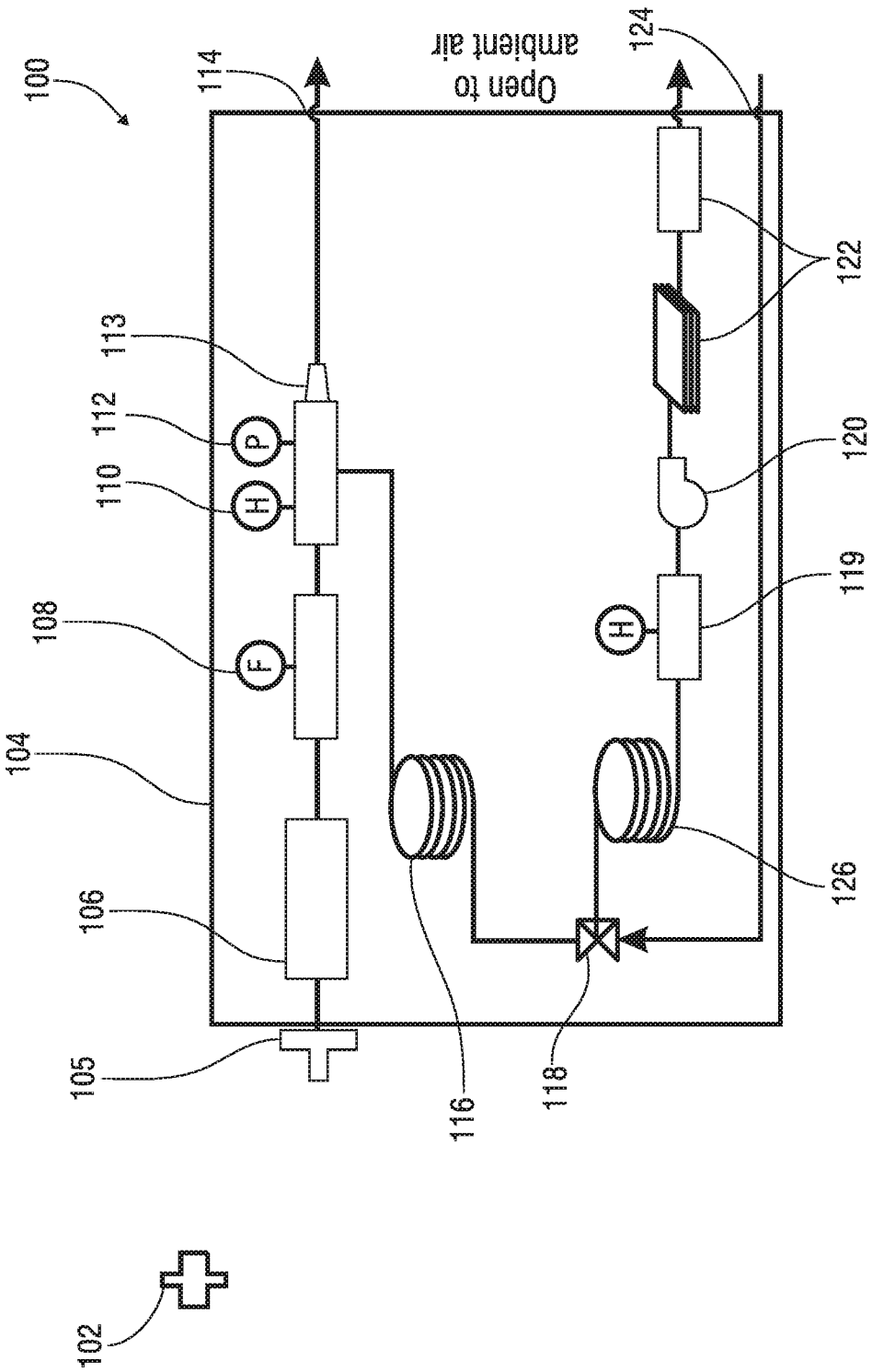

100
114
Open to ambient air
124
122
113
112
P
110
H
120
108
F
119
H
104
106
126
105
116
118
102

FIG. 1

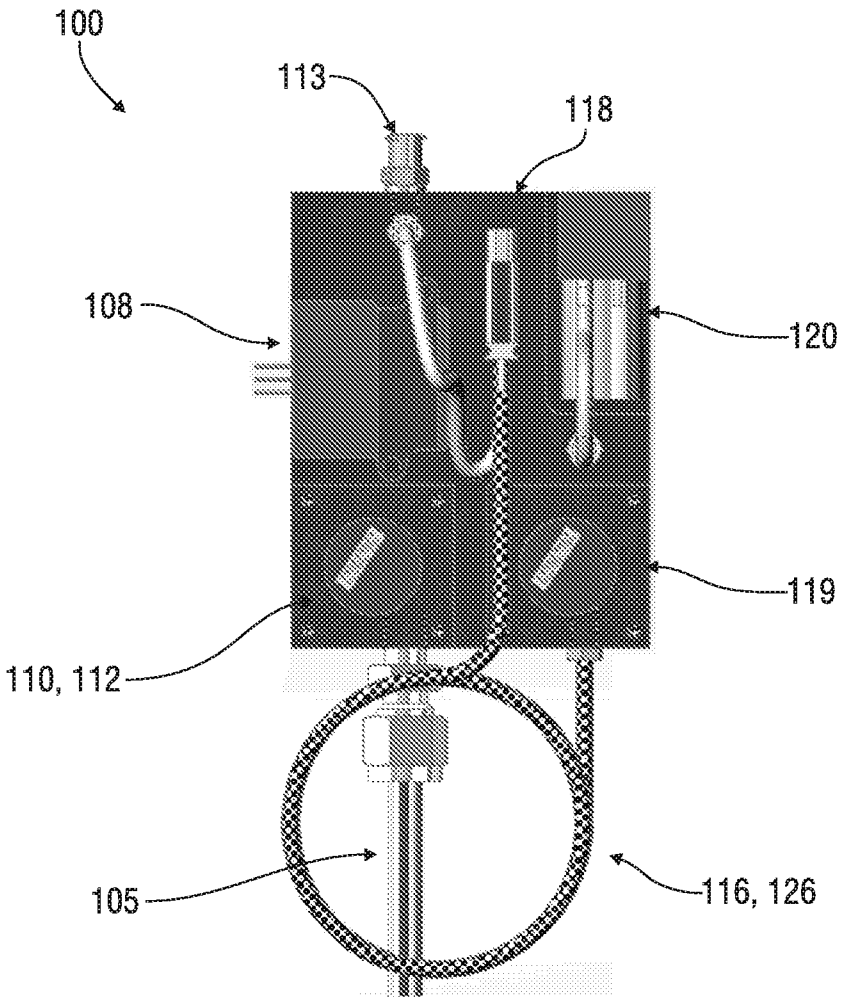


FIG. 2

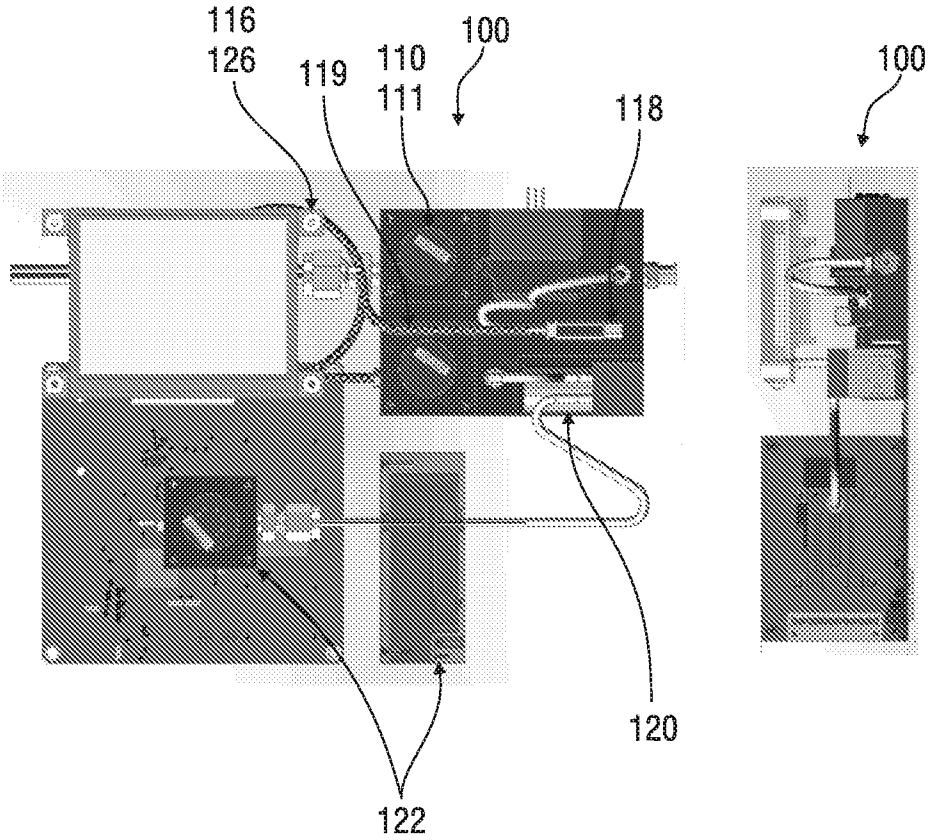


FIG. 3

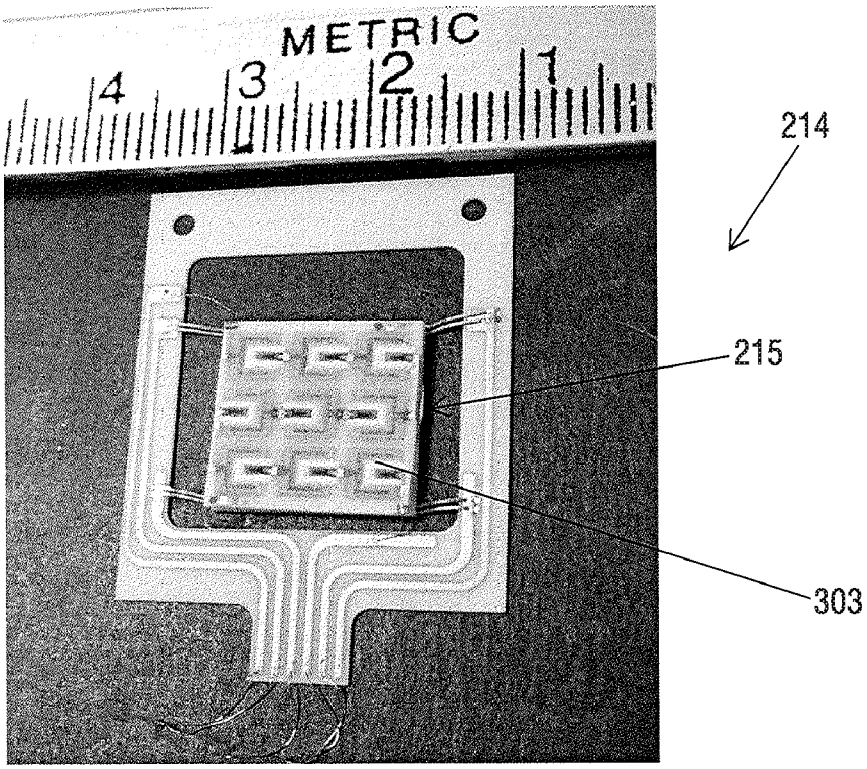


FIG. 4

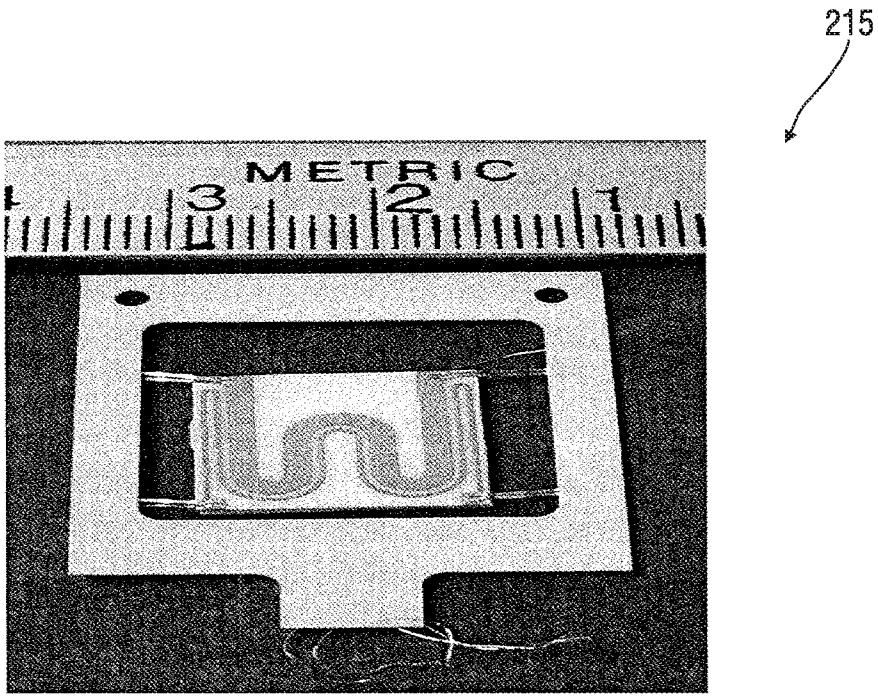


FIG. 5A

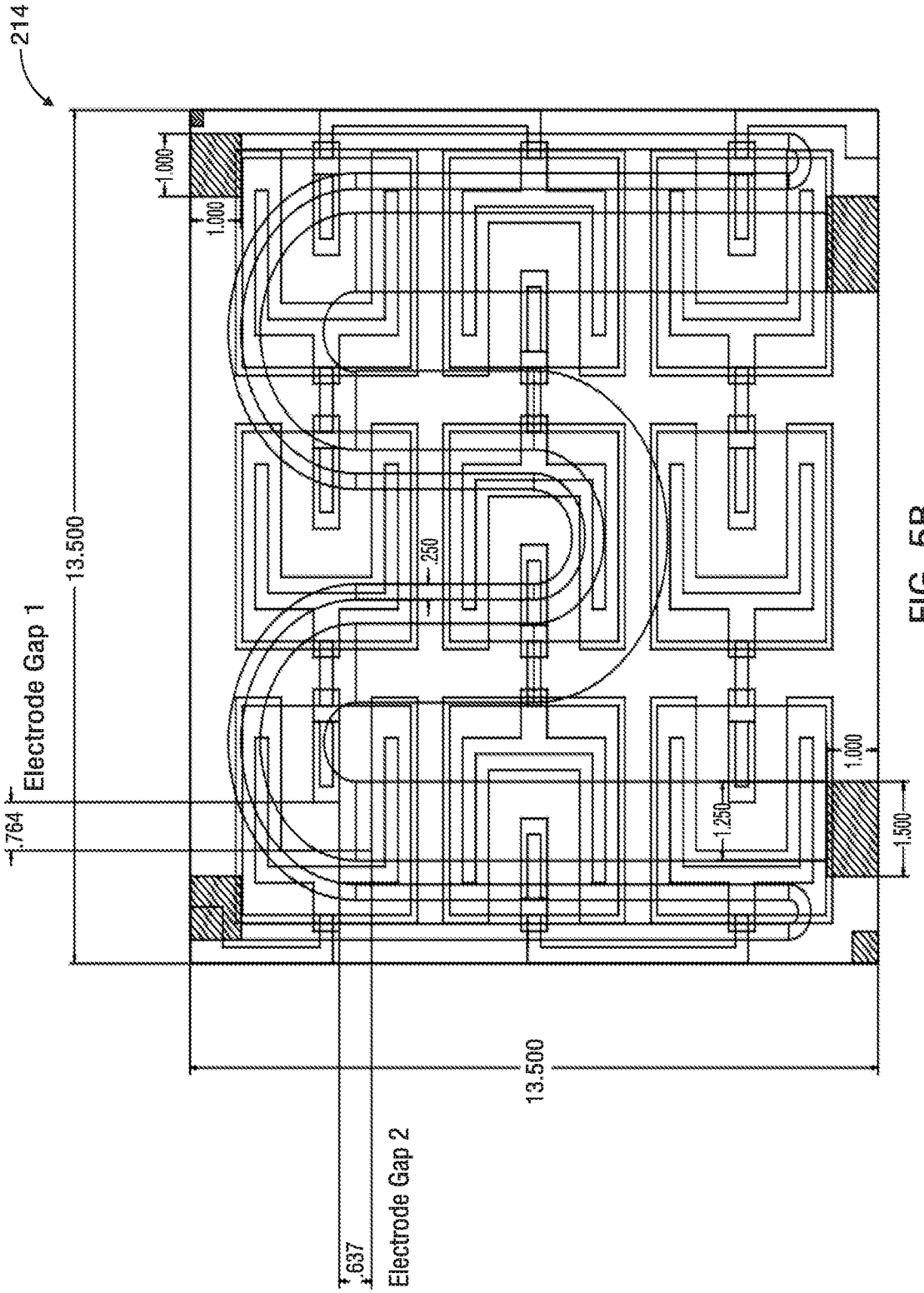

214
1.000
1.000
13.500
.250
Electrode Gap 1
.764
1.000
1.250
1.500
13.500
.637
Electrode Gap 2

FIG. 5B

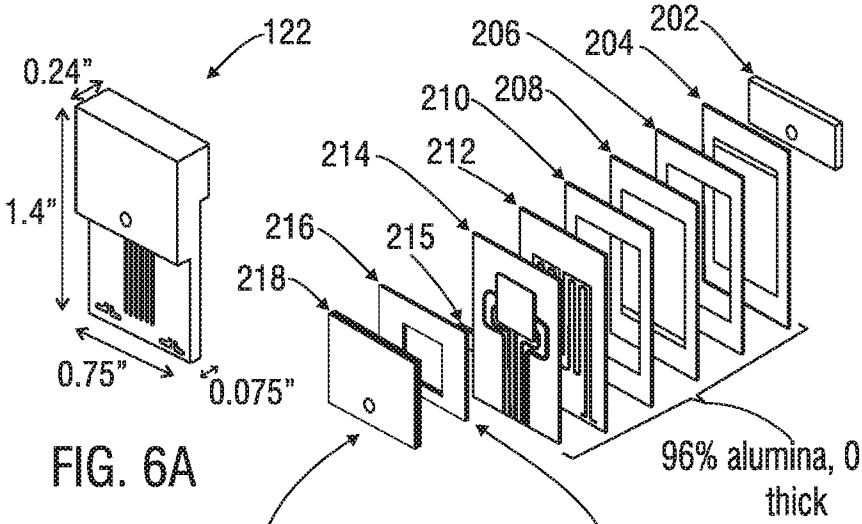


FIG. 6A

FIG. 6B

FIG. 6C

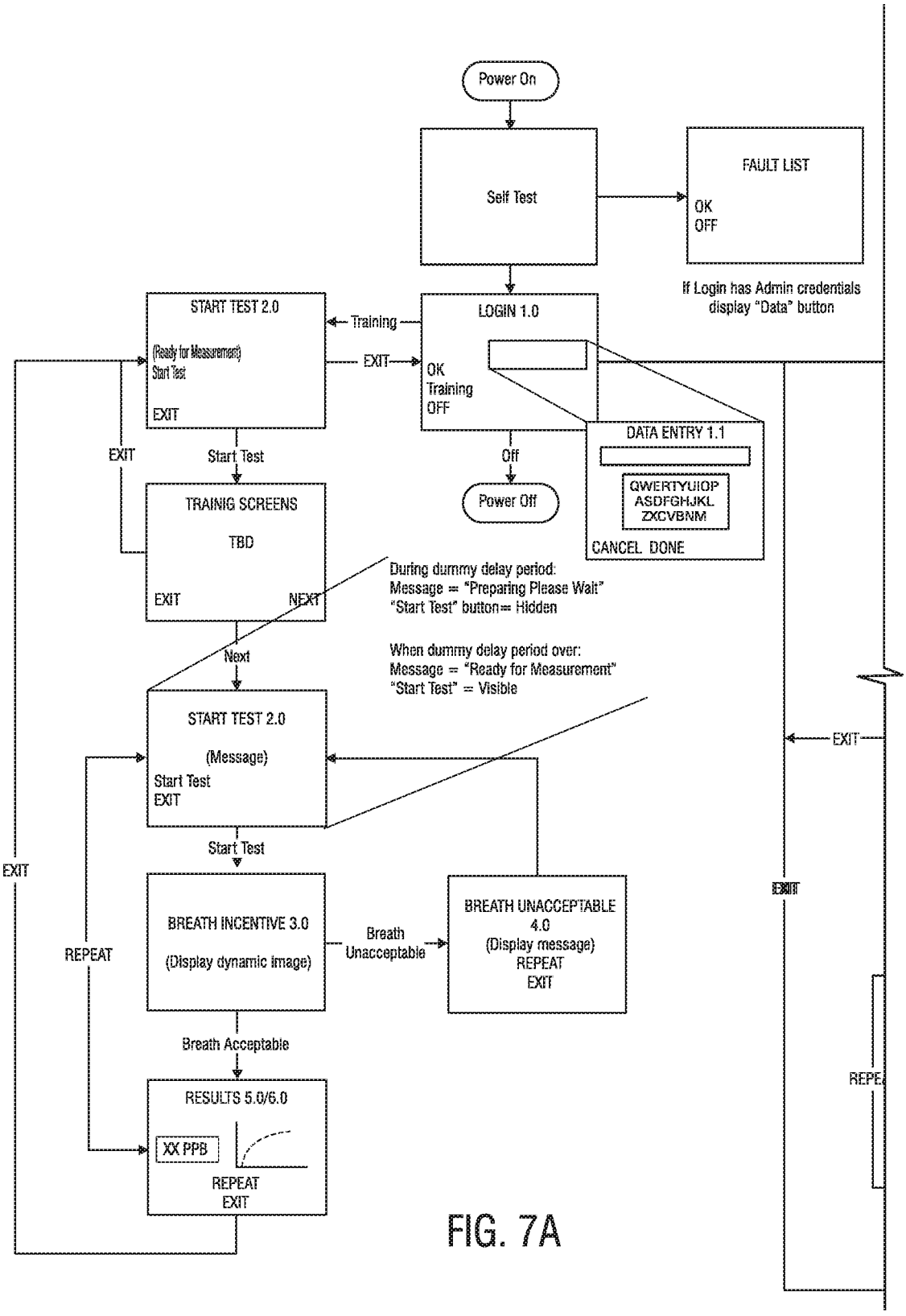

Power On
Self Test
FAULT LIST
OK
OFF
If Login has Admin credentials display "Data" button
START TEST 2.0
(Ready for Measurement)
Start Test
EXIT
Training
EXIT
LOGIN 1.0
OK
Training
OFF
DATA ENTRY 1.1
QWERTYUIOP
ASDFGHJKL
ZXCVBNM
CANCEL DONE
Off
Power Off
EXIT
Start Test
TRAINIG SCREENS
TBD
EXIT
NEXT
During dummy delay period:
Message = "Preparing Please Wait"
"Start Test" button= Hidden
When dummy delay period over:
Message = "Ready for Measurement"
"Start Test" = Visible
Next
START TEST 2.0
(Message)
Start Test
EXIT
EXIT
Start Test
EXIT
BREATH INCENTIVE 3.0
(Display dynamic image)
REPEAT
Breath Unacceptable
BREATH UNACCEPTABLE 4.0
(Display message)
REPEAT
EXIT
Breath Acceptable
RESULTS 5.0/6.0
XX PPB
REPEAT
EXIT
EXIT
REPE

FIG. 7A

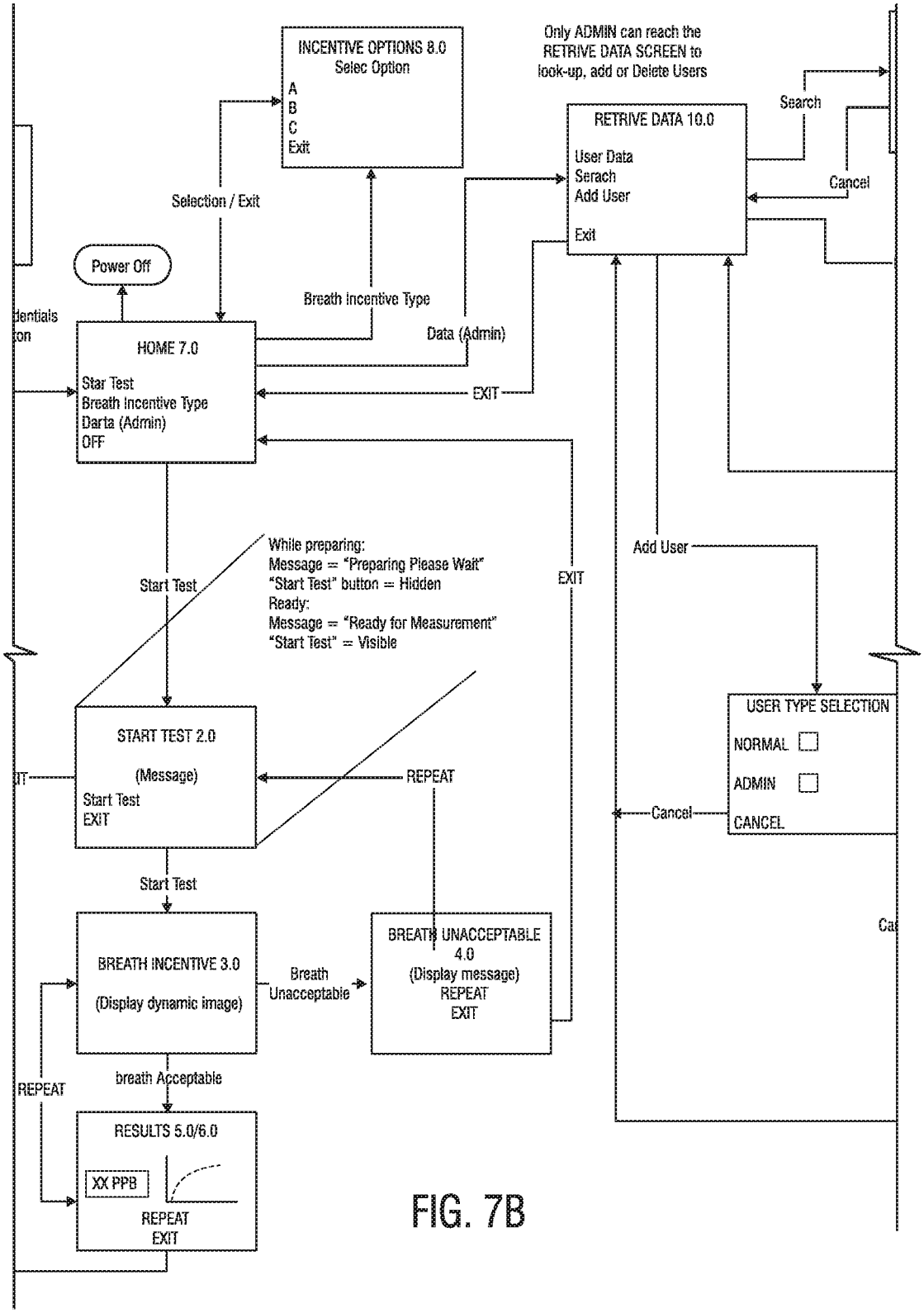

INCENTIVE OPTIONS 8.0
Selec Option
A
B
C
Exit
Only ADMIN can reach the RETRIVE DATA SCREEN to look-up, add or Delete Users
RETRIVE DATA 10.0
User Data
Serach
Add User
Exit
Search
Cancel
Selection / Exit
Power Off
Breath Incentive Type
Data (Admin)
HOME 7.0
Star Test
Breath Incentive Type
Darta (Admin)
OFF
EXIT
While preparing:
Message = "Preparing Please Wait"
"Start Test" button = Hidden
Ready:
Message = "Ready for Measurement"
"Start Test" = Visible
Start Test
Add User
USER TYPE SELECTION
NORMAL
ADMIN
CANCEL
START TEST 2.0
(Message)
Start Test
EXIT
REPEAT
Cancel
Start Test
BREATH INCENTIVE 3.0
(Display dynamic image)
Breath Unacceptable
BREATH UNACCEPTABLE 4.0
(Display message)
REPEAT
EXIT
REPEAT
breath Acceptable
RESULTS 5.0/6.0
XX PPB
REPEAT
EXIT

FIG. 7B

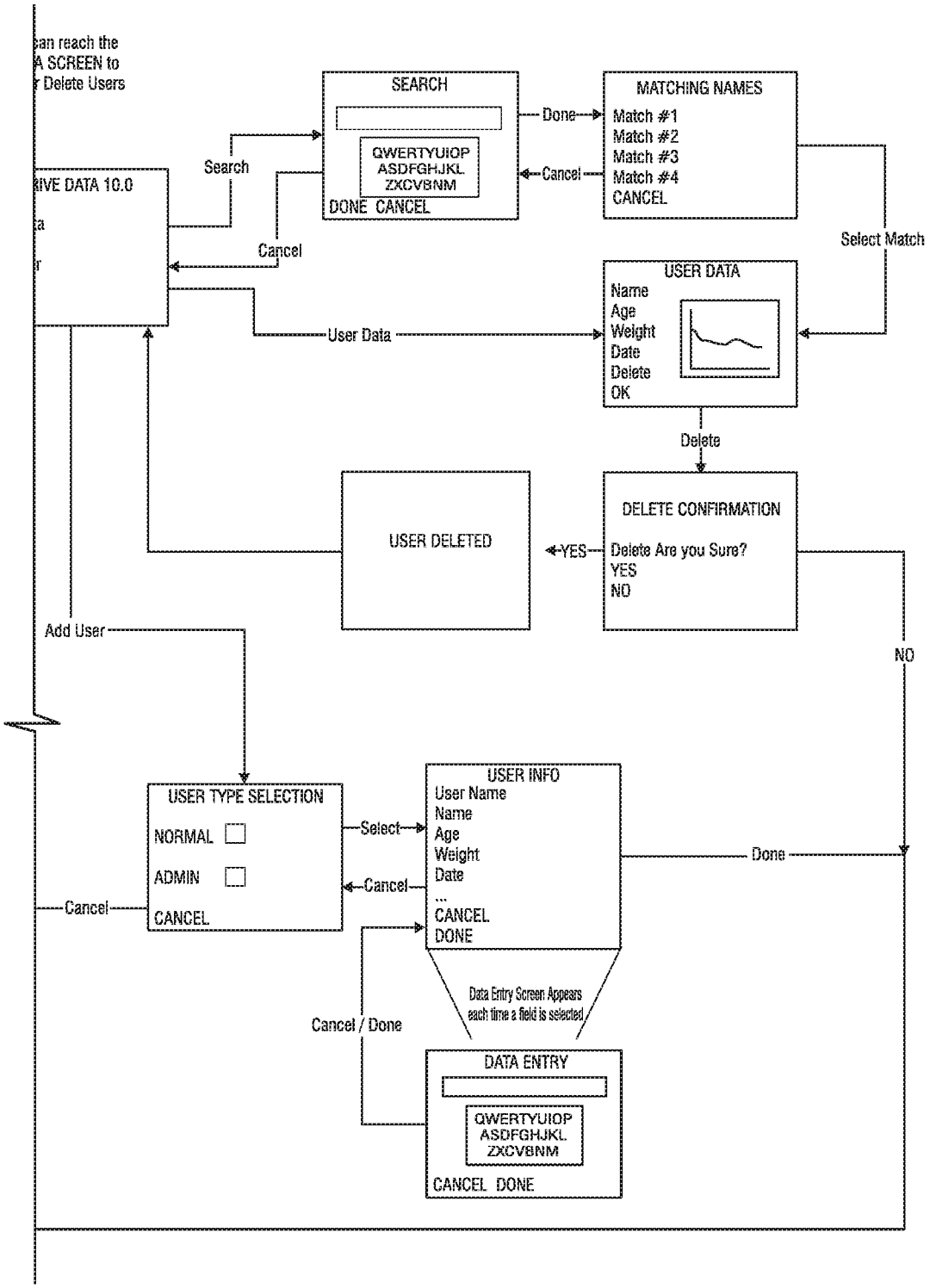

an reach the
A SCREEN to
Delete Users
IVE DATA 10.0
Search
Cancel
SEARCH
QWERTYUIOP
ASDFGHJKL
ZXCVBNM
DONE CANCEL
Done
Cancel
MATCHING NAMES
Match #1
Match #2
Match #3
Match #4
CANCEL
Select Match
USER DATA
Name
Age
Weight
Date
Delete
OK
User Data
Delete
DELETE CONFIRMATION
Delete Are you Sure?
YES
NO
YES
USER DELETED
Add User
NO
USER TYPE SELECTION
NORMAL
ADMIN
CANCEL
Select
Cancel
Cancel
USER INFO
User Name
Name
Age
Weight
Date
...
CANCEL
DONE
Done
Data Entry Screen Appears
each time a field is selected
Cancel / Done
DATA ENTRY
QWERTYUIOP
ASDFGHJKL
ZXCVBNM
CANCEL DONE

FIG. 7C

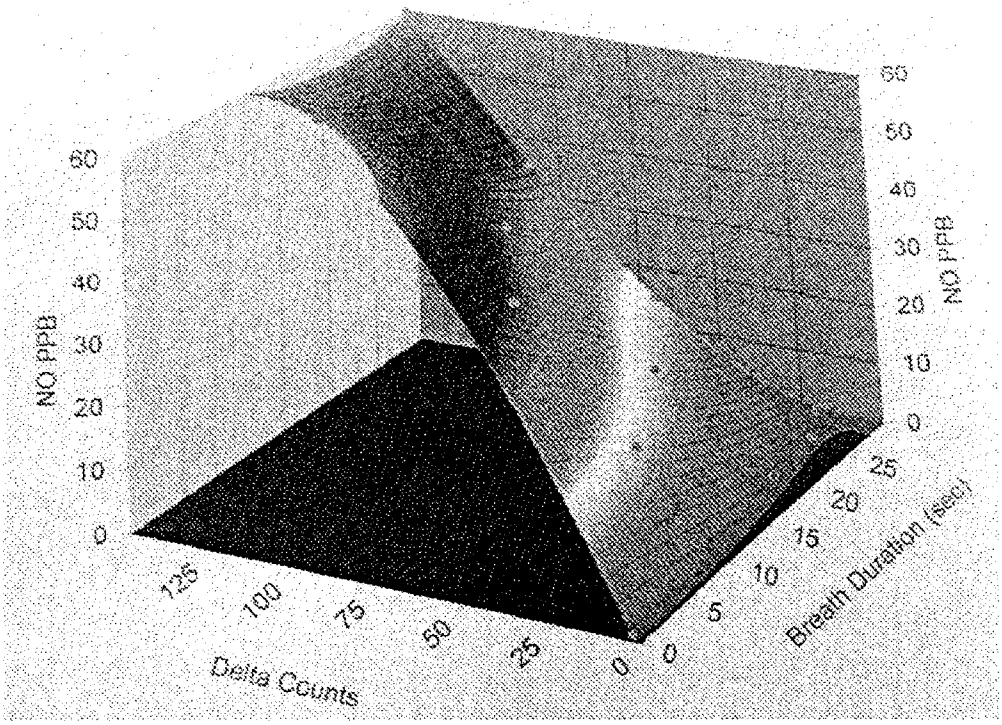

NO ppb
60
50
40
30
20
10
0
125
100
75
50
25
0
Delta Counts
0
5
10
15
20
25
Breath Duration (sec)
60
50
40
30
20
10
0
NO ppb

FIG. 8

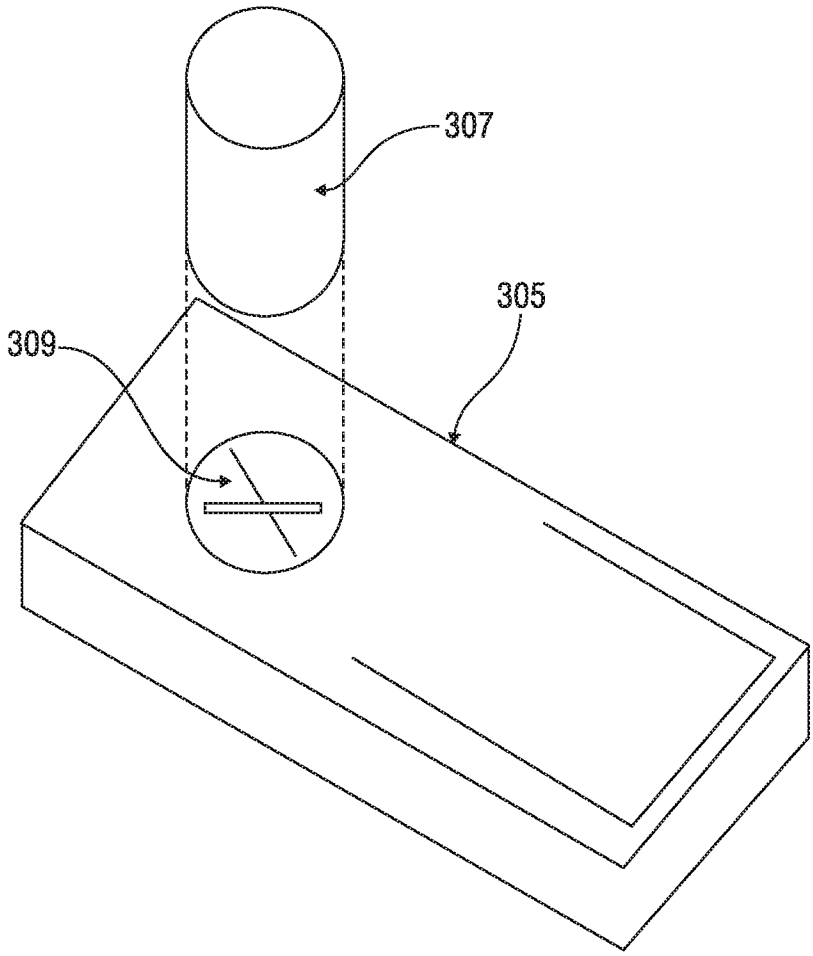


FIG. 9

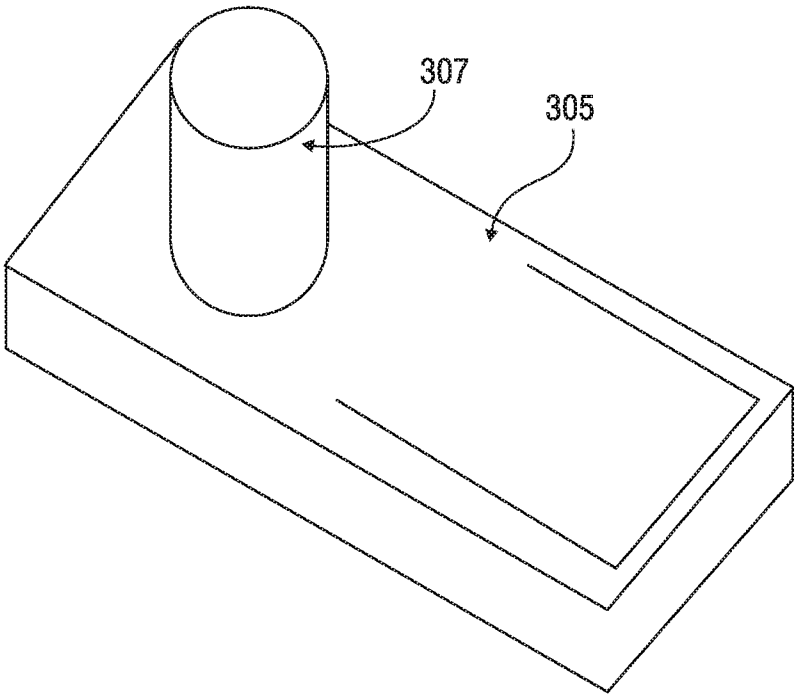


FIG. 10

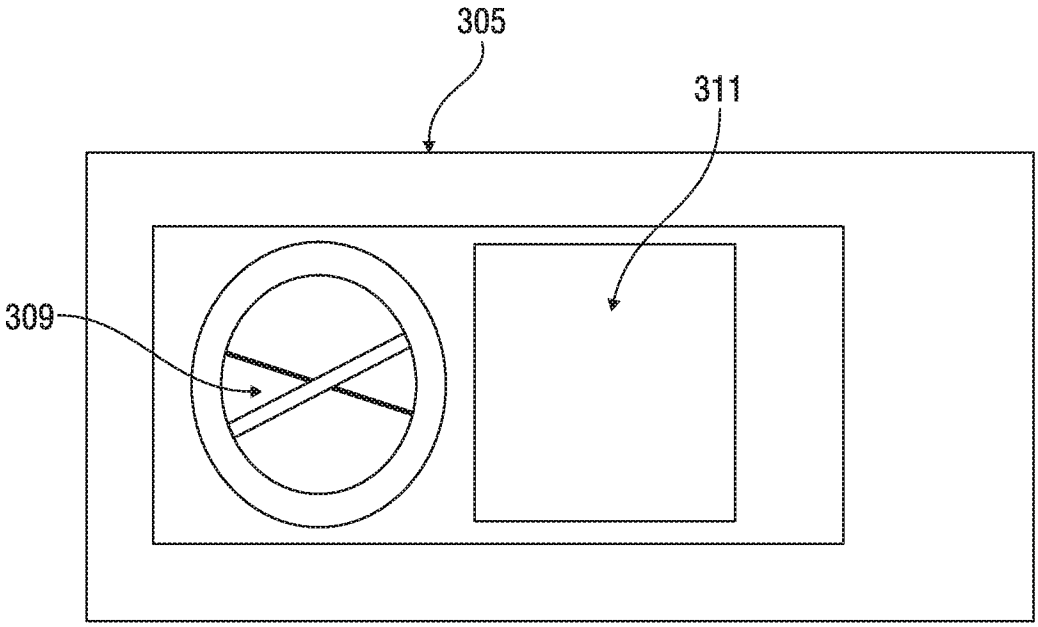


FIG. 11

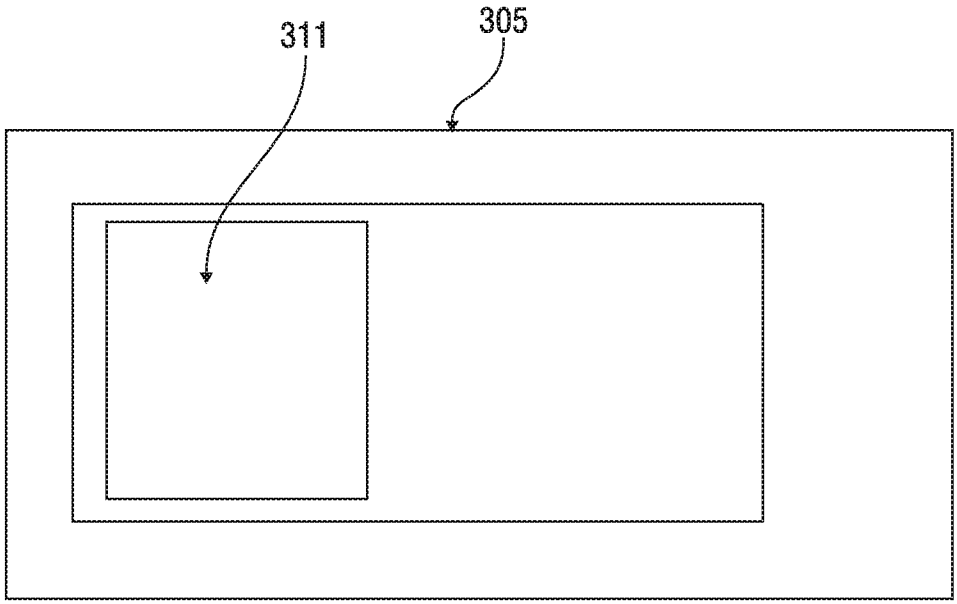


FIG. 12

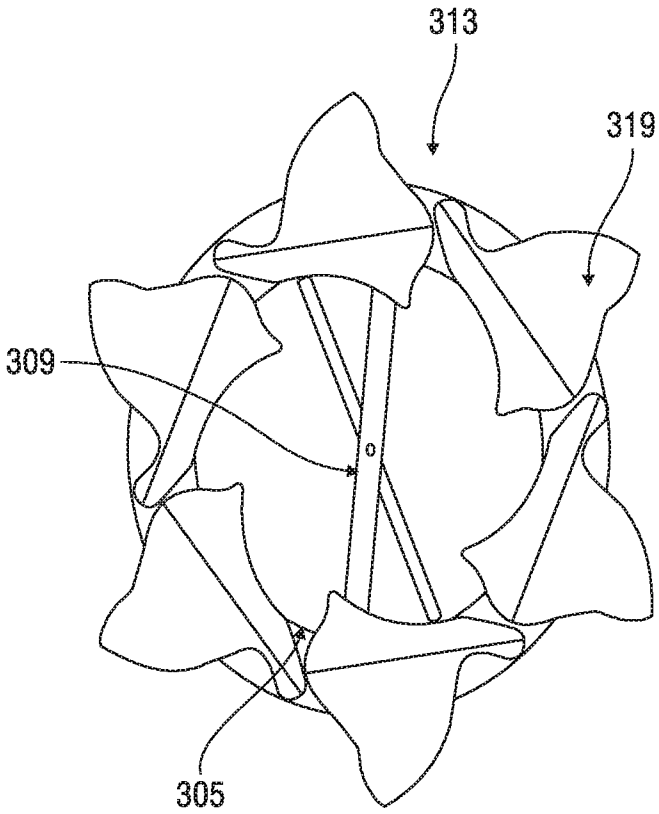


FIG. 13

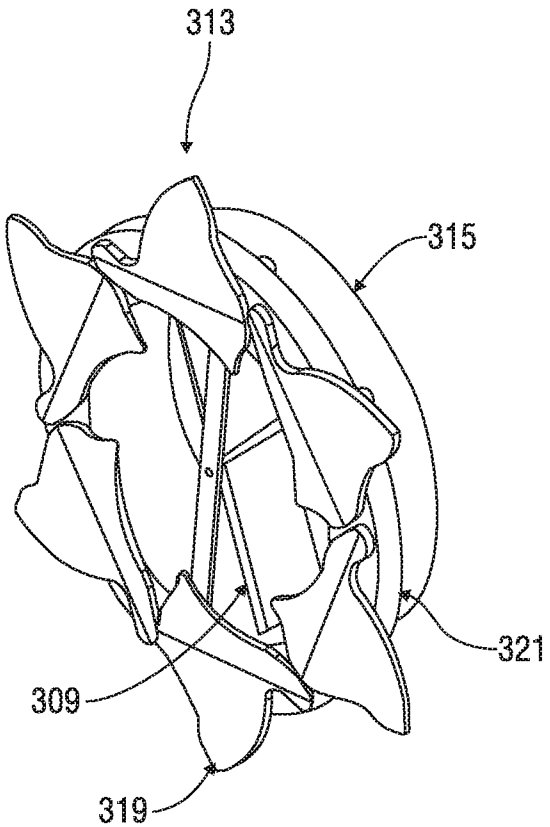


FIG. 14

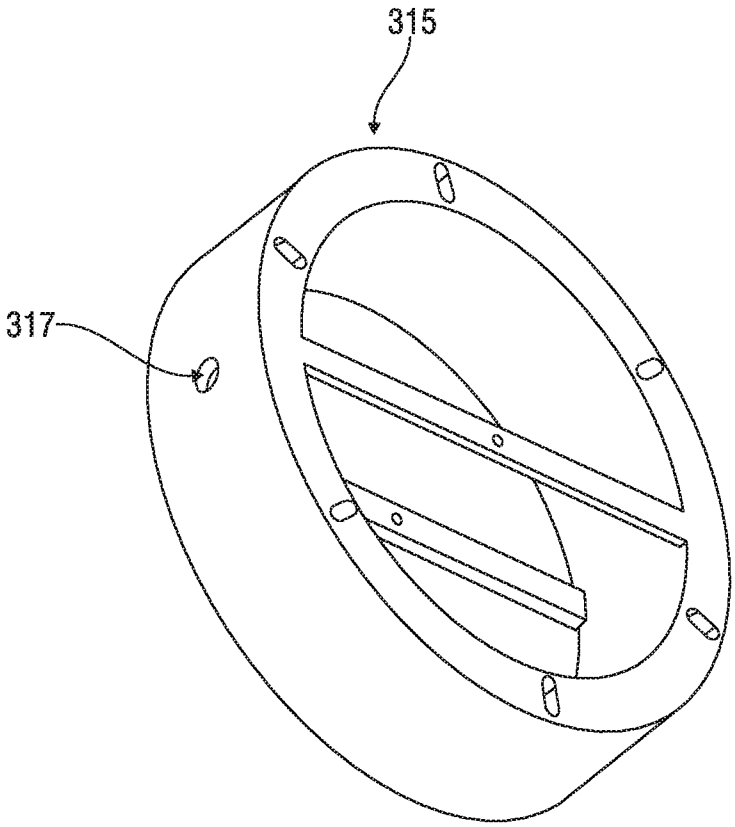


FIG. 15

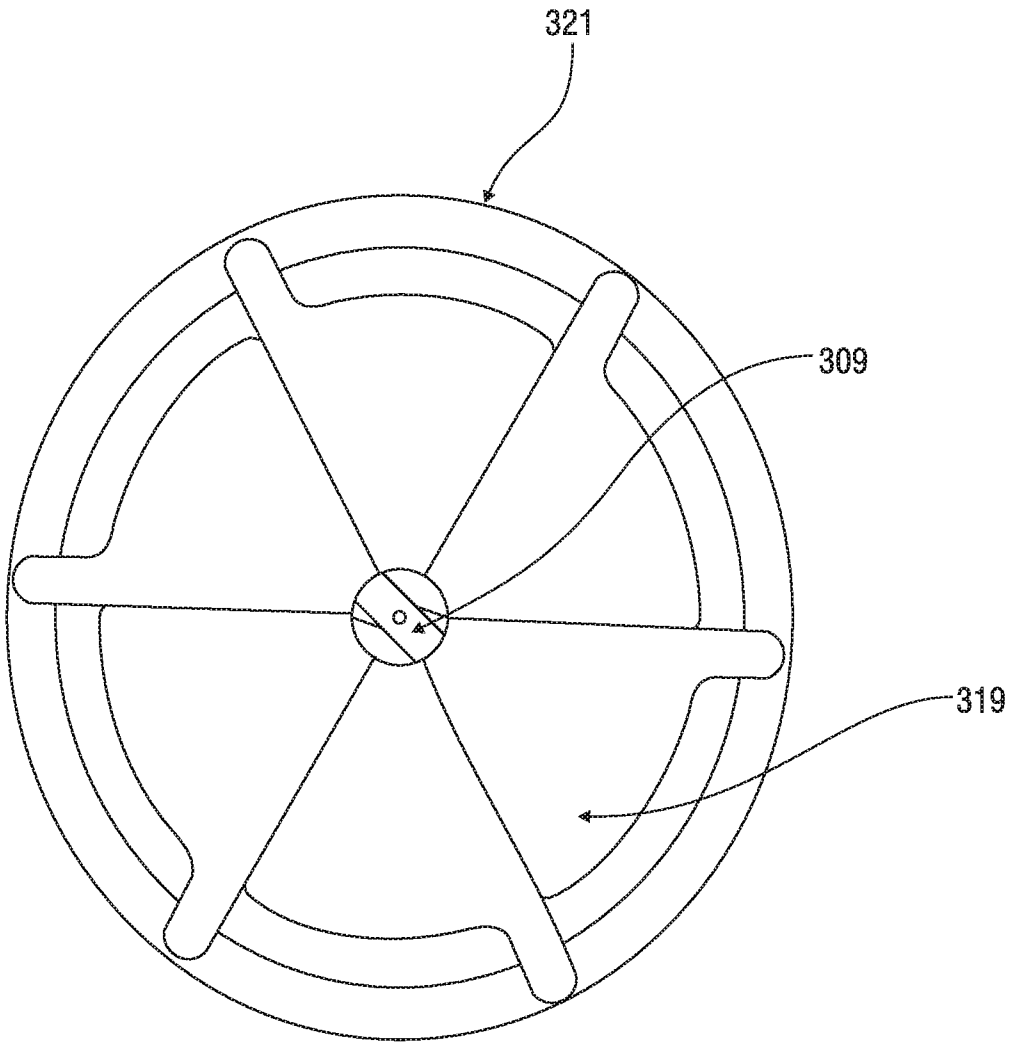


FIG. 16

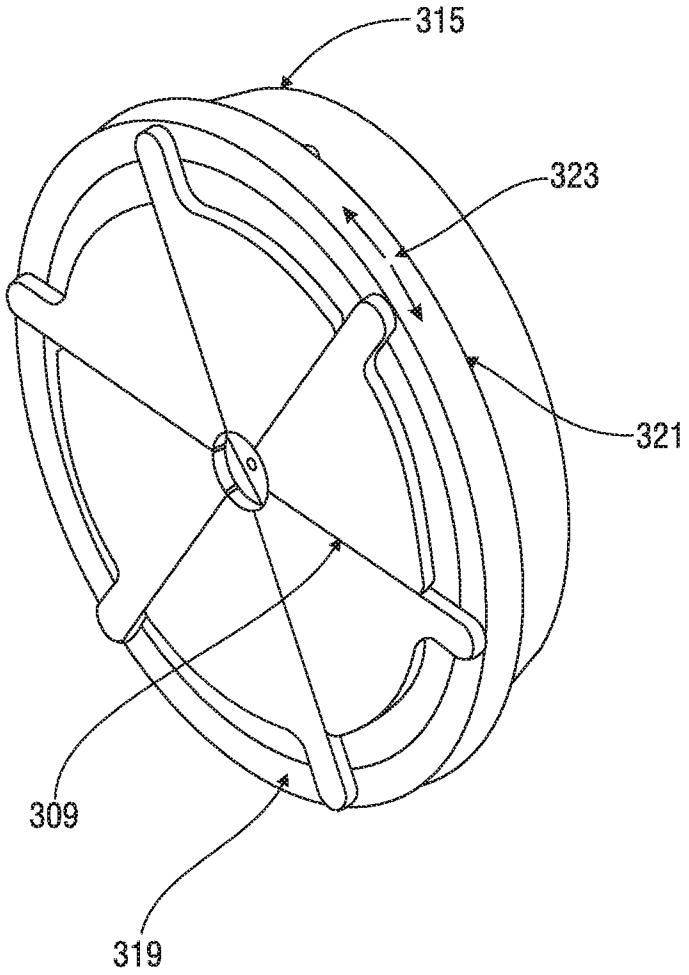


FIG. 17

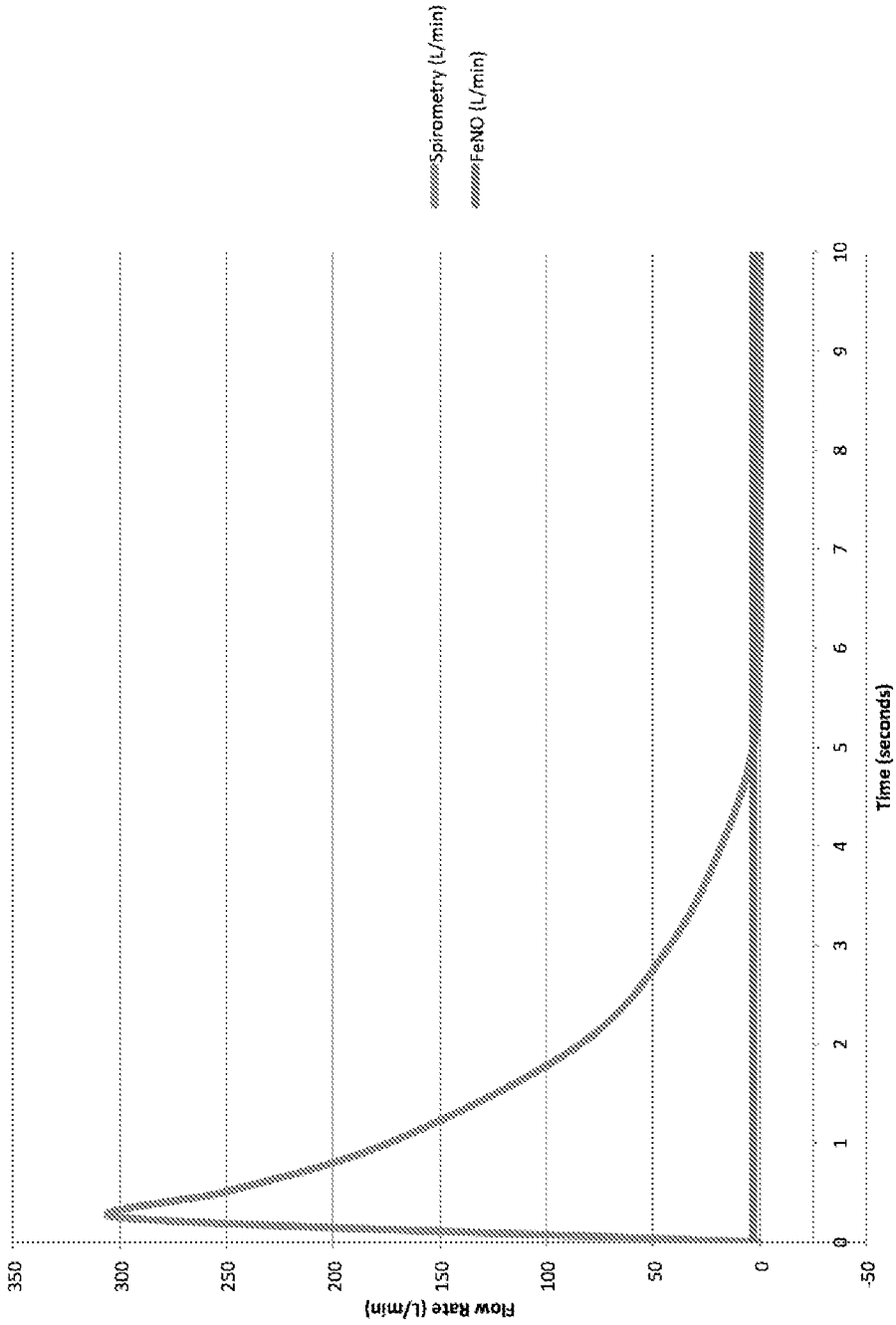

Spirometry (L/min)
FeNO (L/min)
Flow Rate (L/min)
350
300
250
200
150
100
50
0
-50
Time (seconds)
0
1
2
3
4
5
6
7
8
9
10

FIG. 18

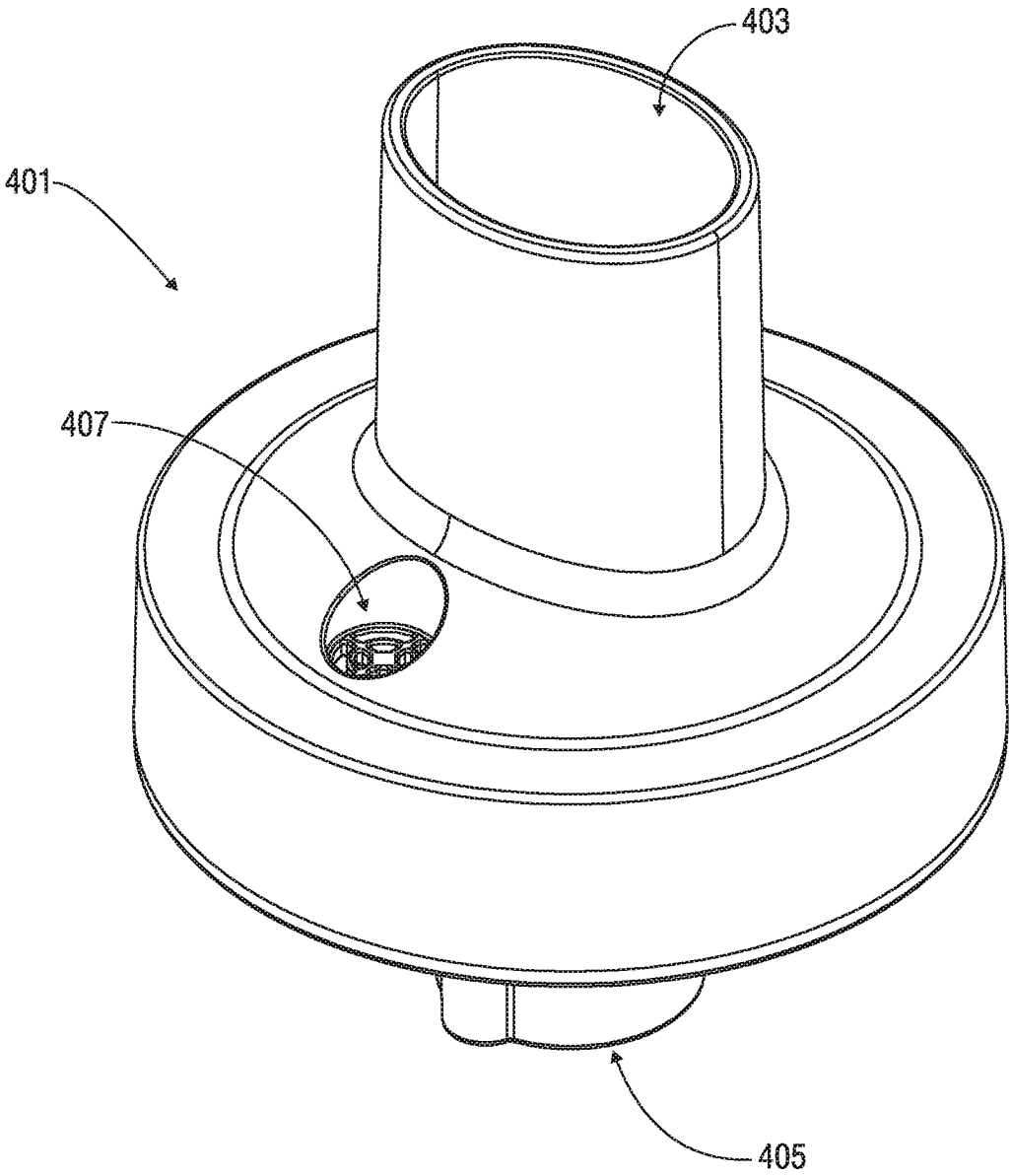


FIG. 19

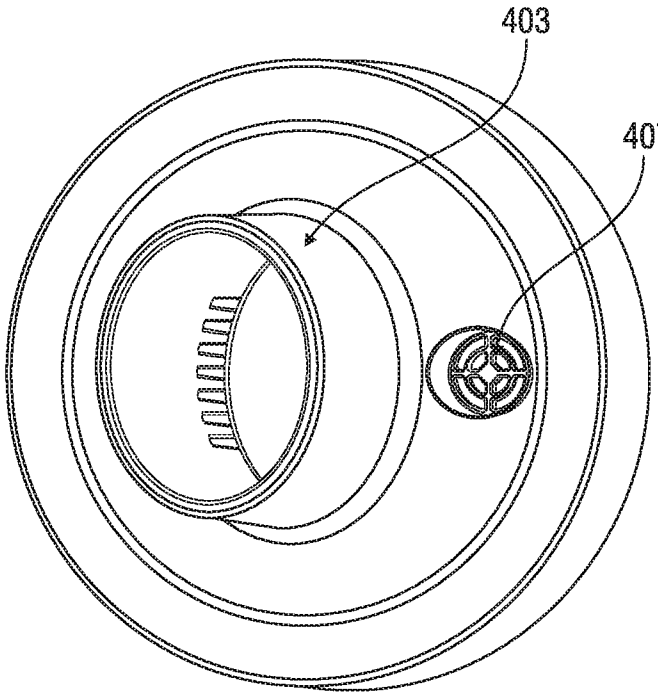


FIG. 20

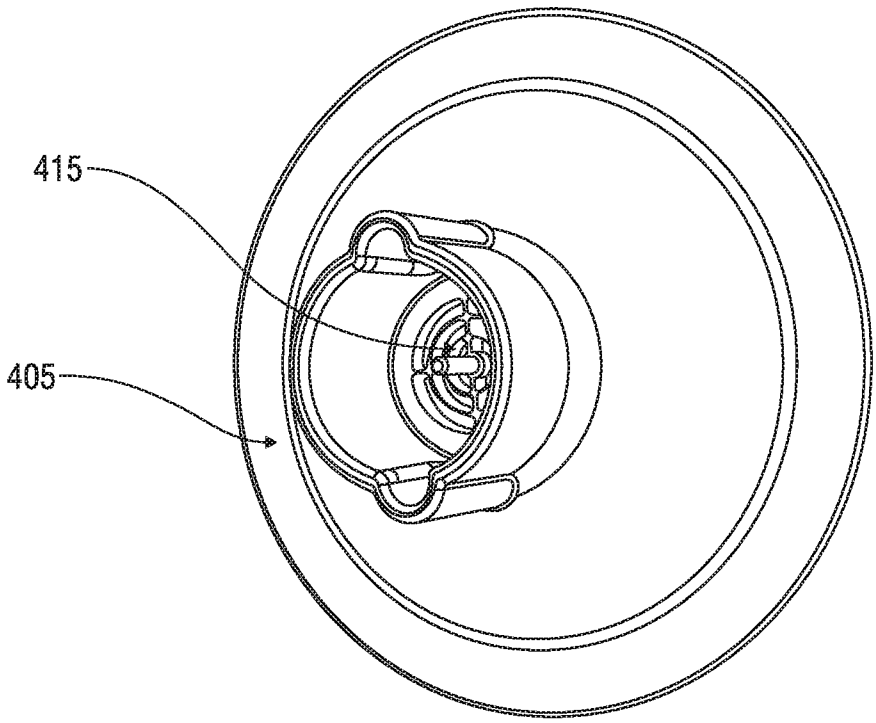


FIG. 21

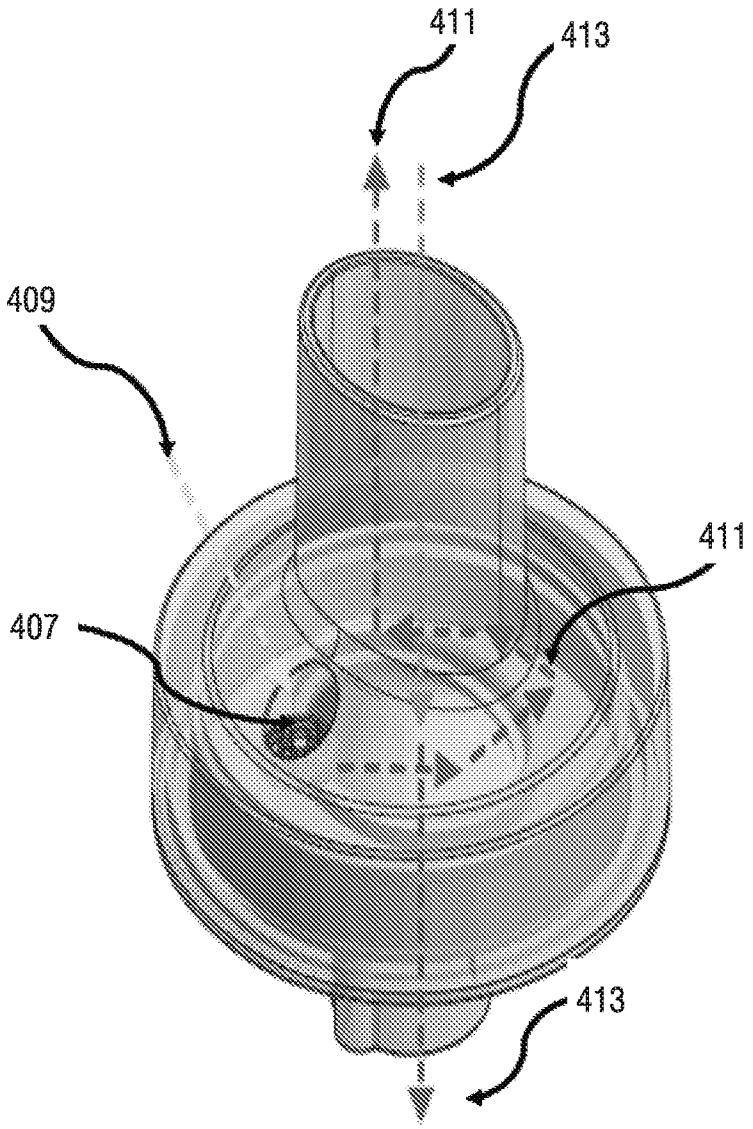


FIG. 22

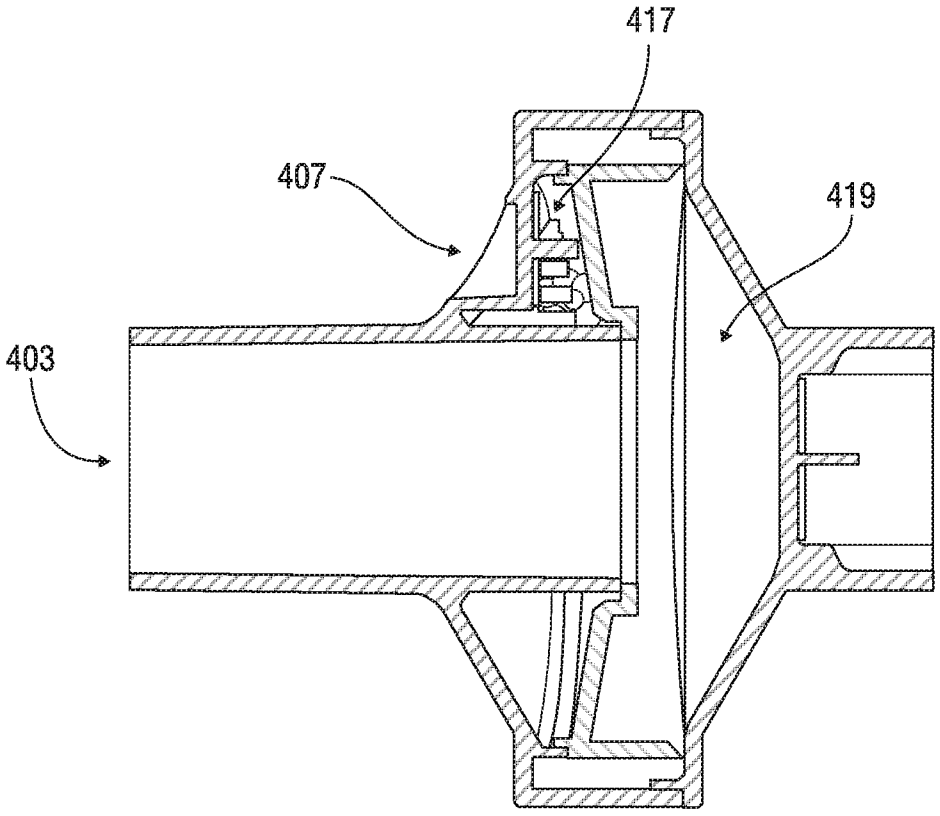


FIG. 23

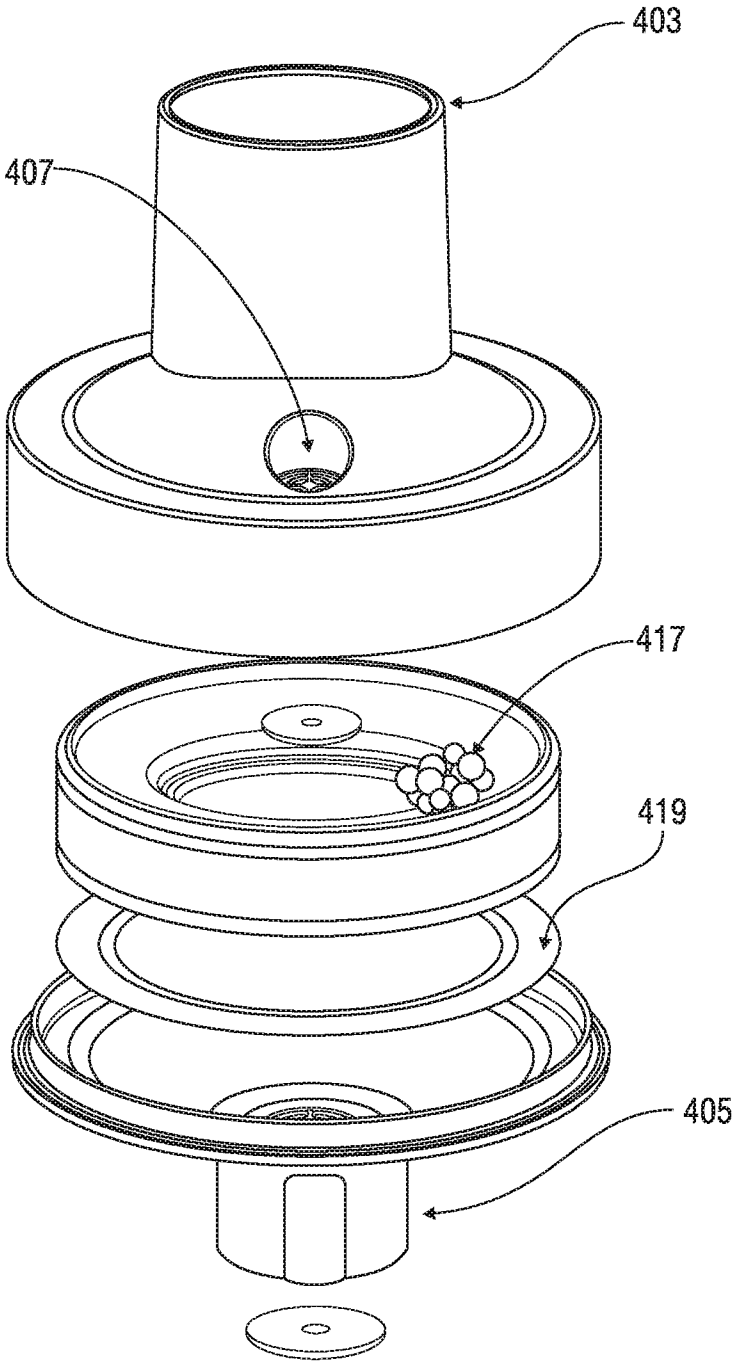


FIG. 24

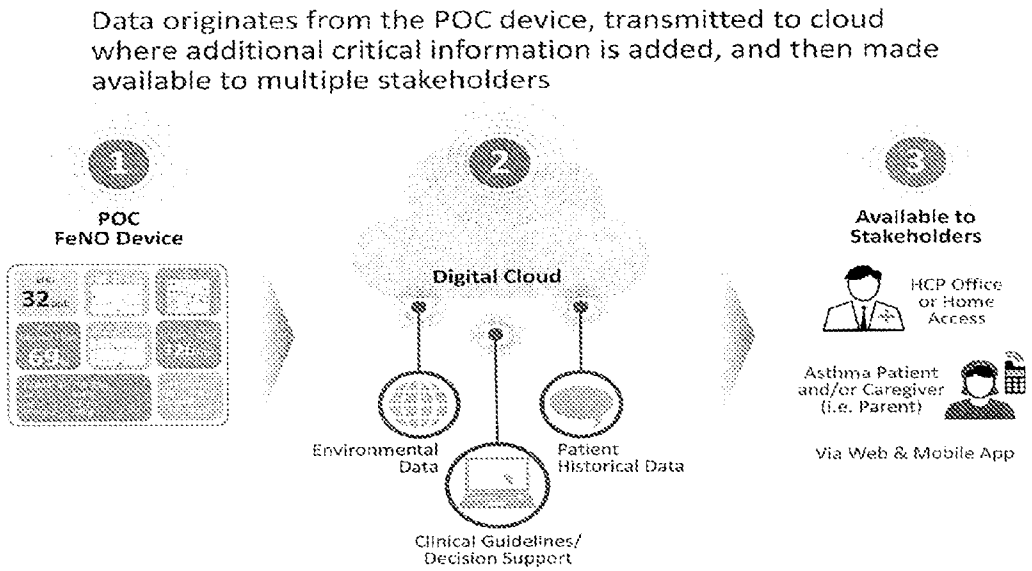

Data originates from the POC device, transmitted to cloud where additional critical information is added, and then made available to multiple stakeholders
1
POC
FeNO Device
2
Digital Cloud
Environmental Data
Patient Historical Data
Clinical Guidelines/ Decision Support
3
Available to Stakeholders
HCP Office or Home Access
Asthma Patient and/or Caregiver (i.e. Parent)
Via Web & Mobile App

FIG. 25

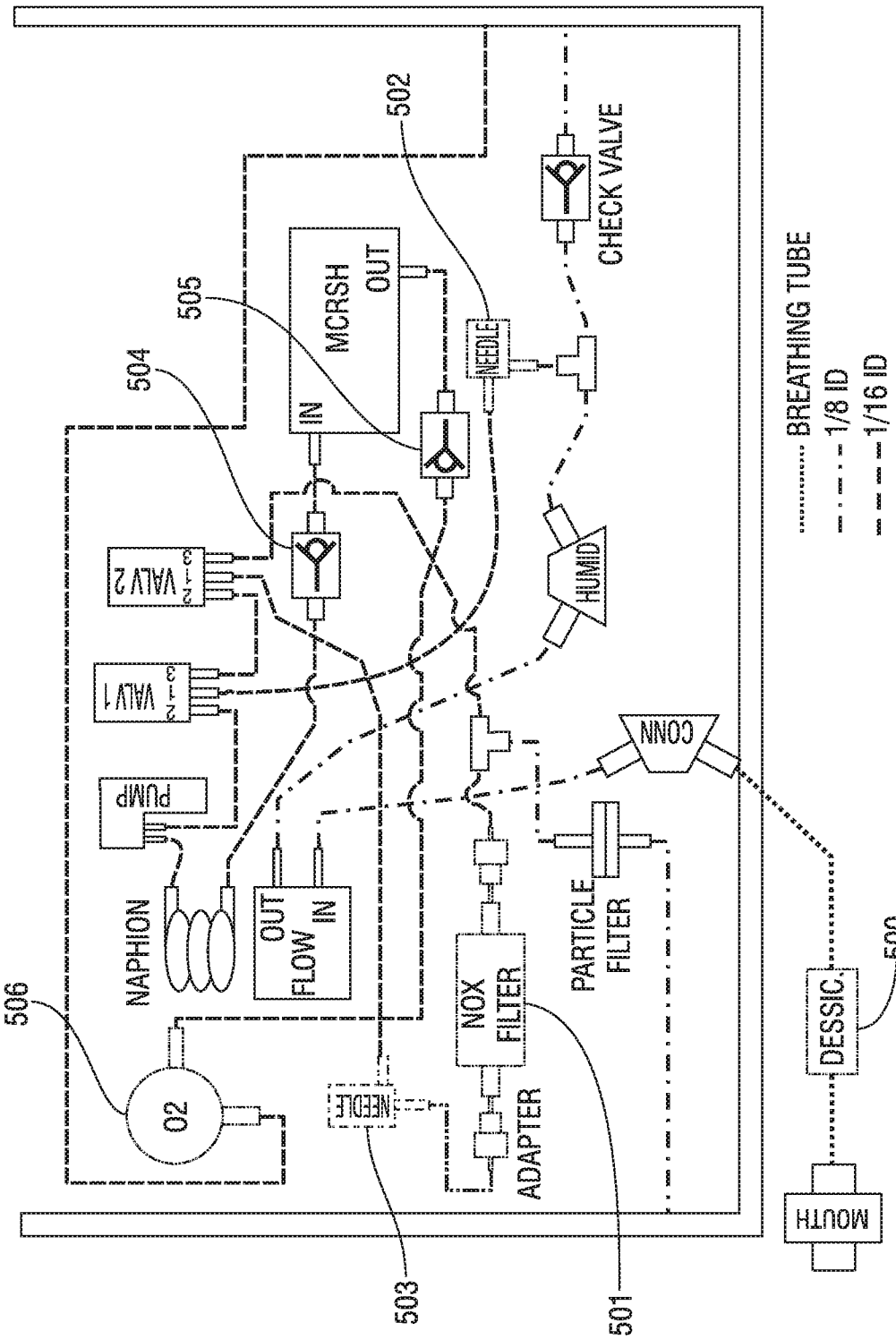

BREATHING TUBE
1/8 ID
1/16 ID
CHECK VALVE
502
505
504
MCRSH
OUT
IN
NEEDLE
HUMID
VALV 2
VALV 1
PUMP
NAPHION
OUT
FLOW
IN
CONN
PARTICLE
FILTER
NOX
FILTER
ADAPTER
O2
NEEDLE
DESSIC
500
506
503
501
MOUTH

FIG. 26

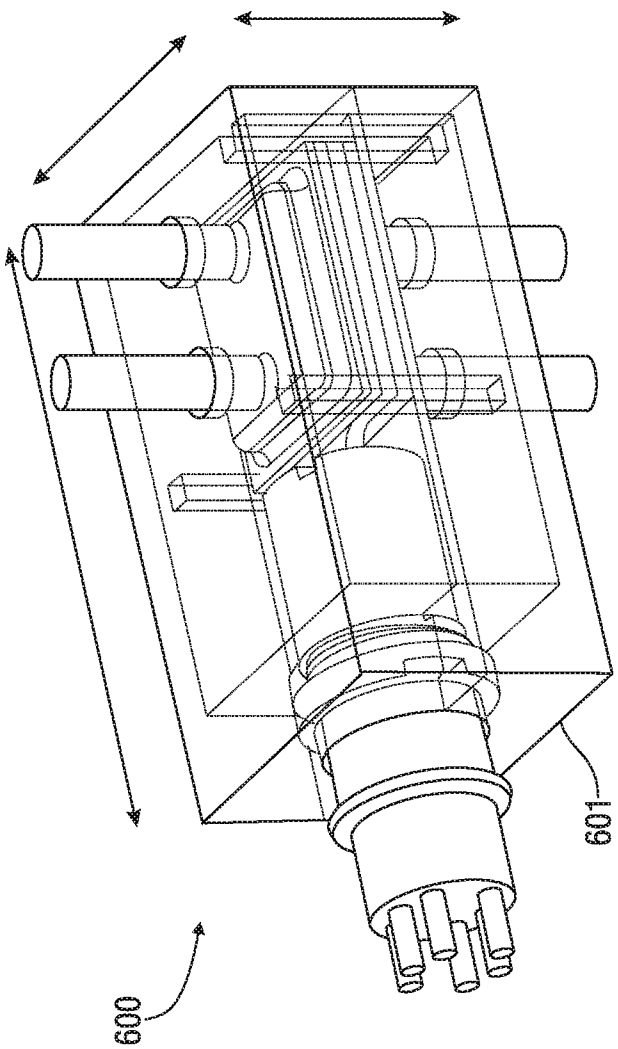


FIG. 27

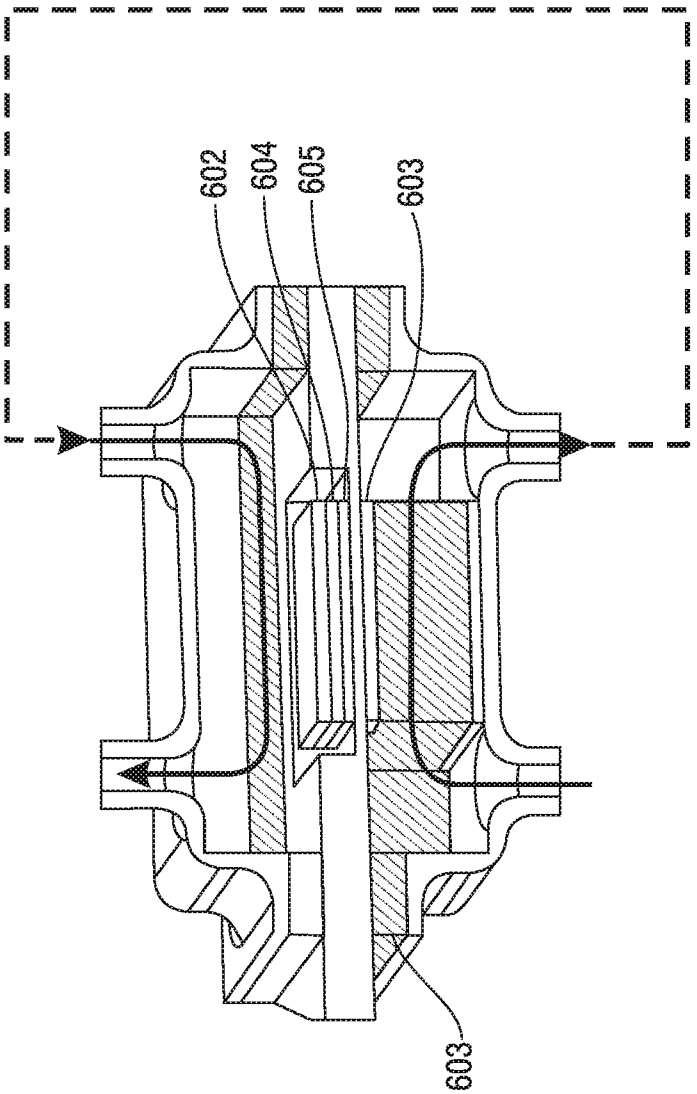


FIG. 28

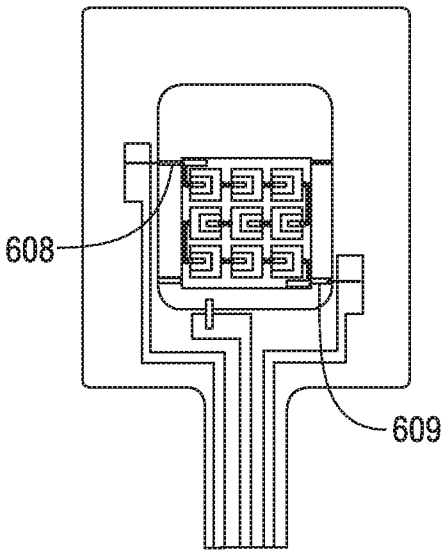


FIG. 29A

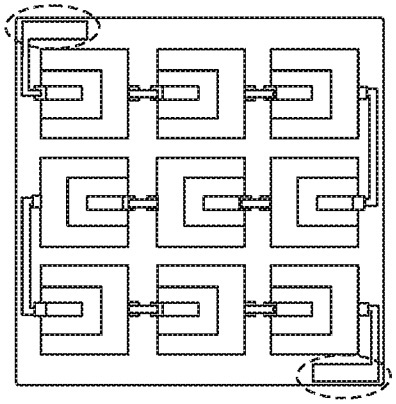


FIG. 29B

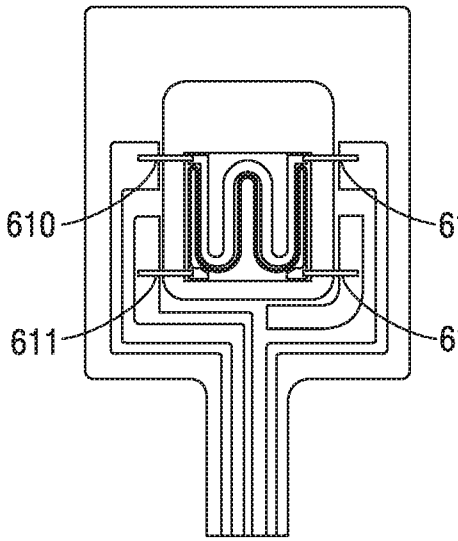


FIG. 29C

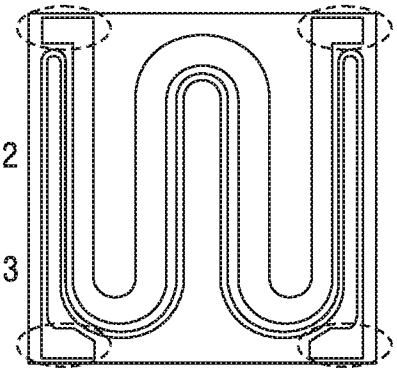


FIG. 29D

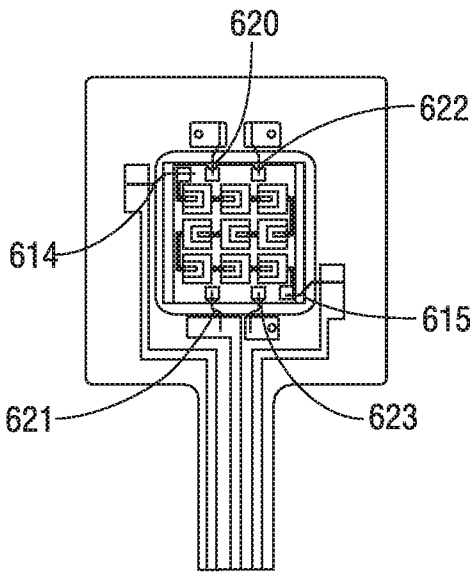


FIG. 30A

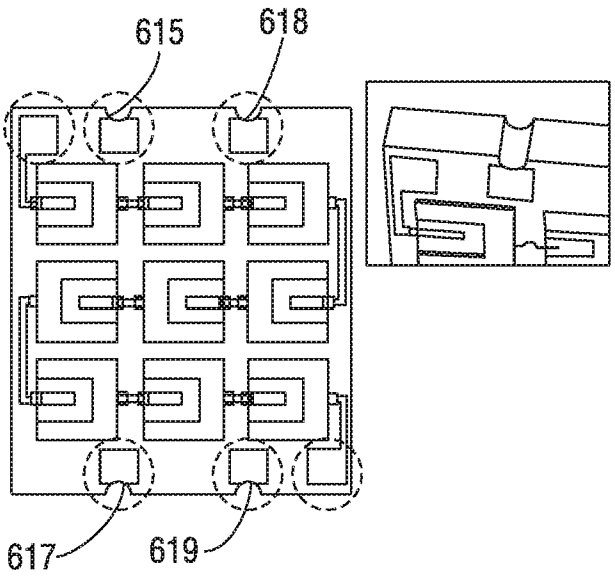


FIG. 30B

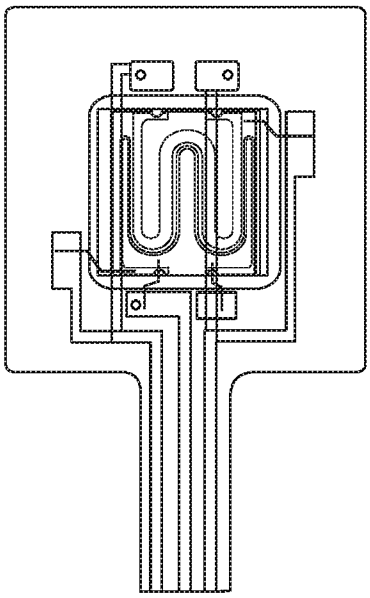


FIG. 30C

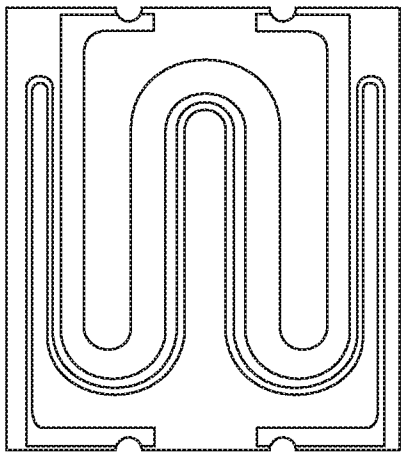


FIG. 30D

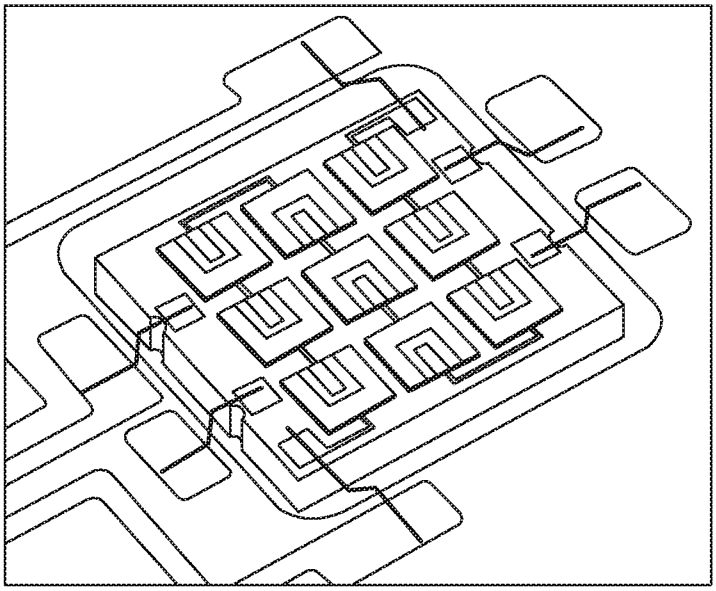


FIG. 31

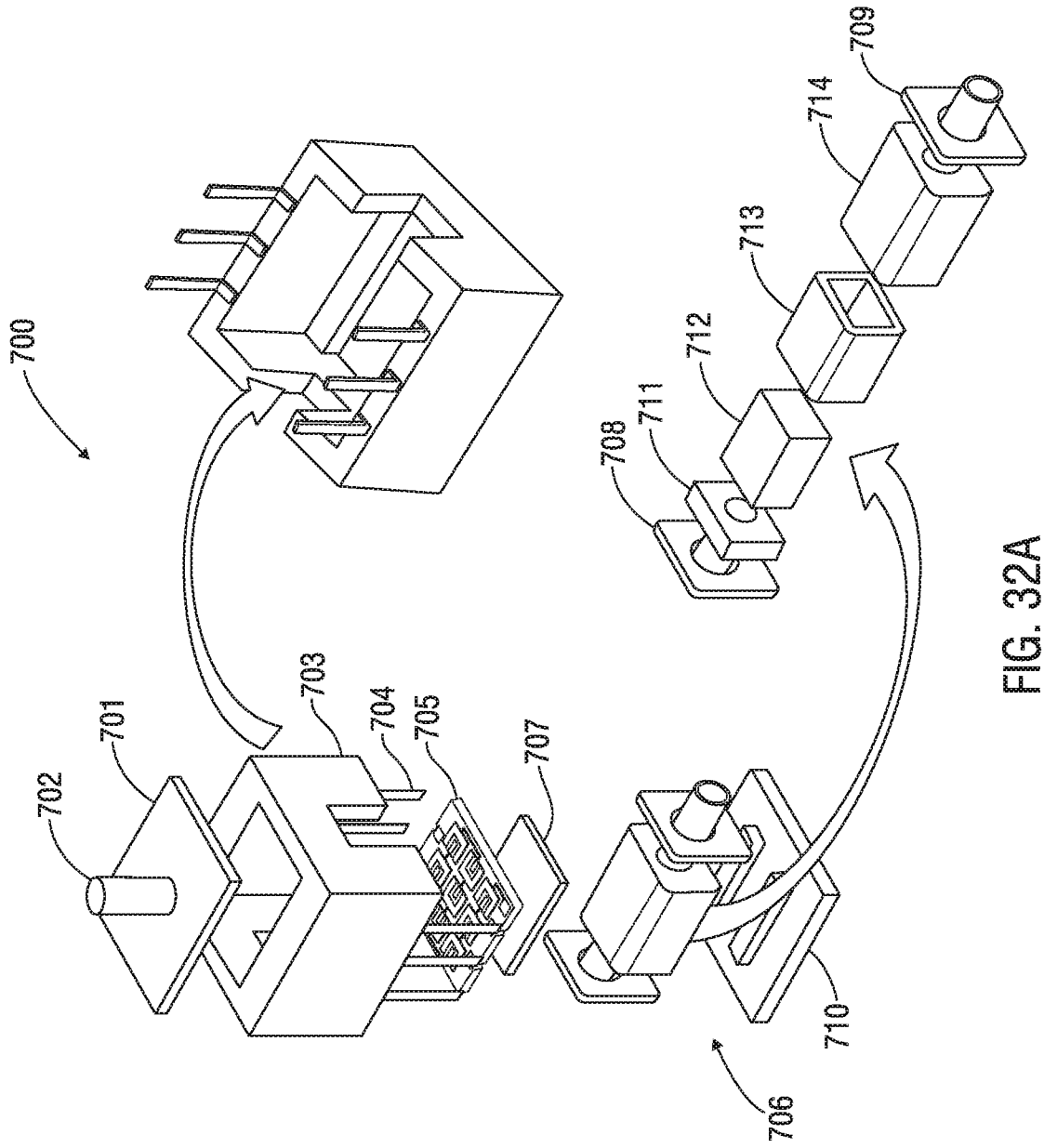


FIG. 32A

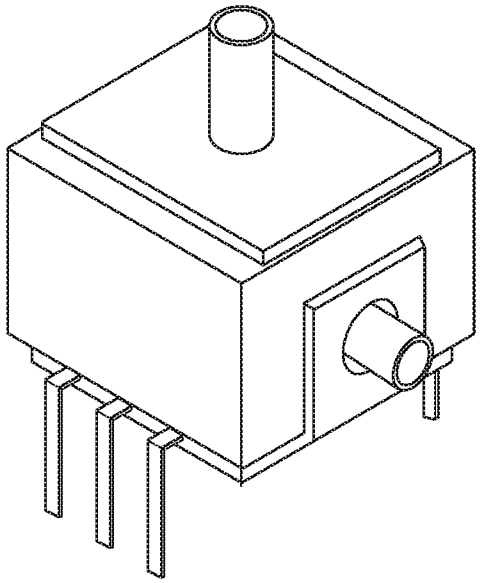


FIG. 32B

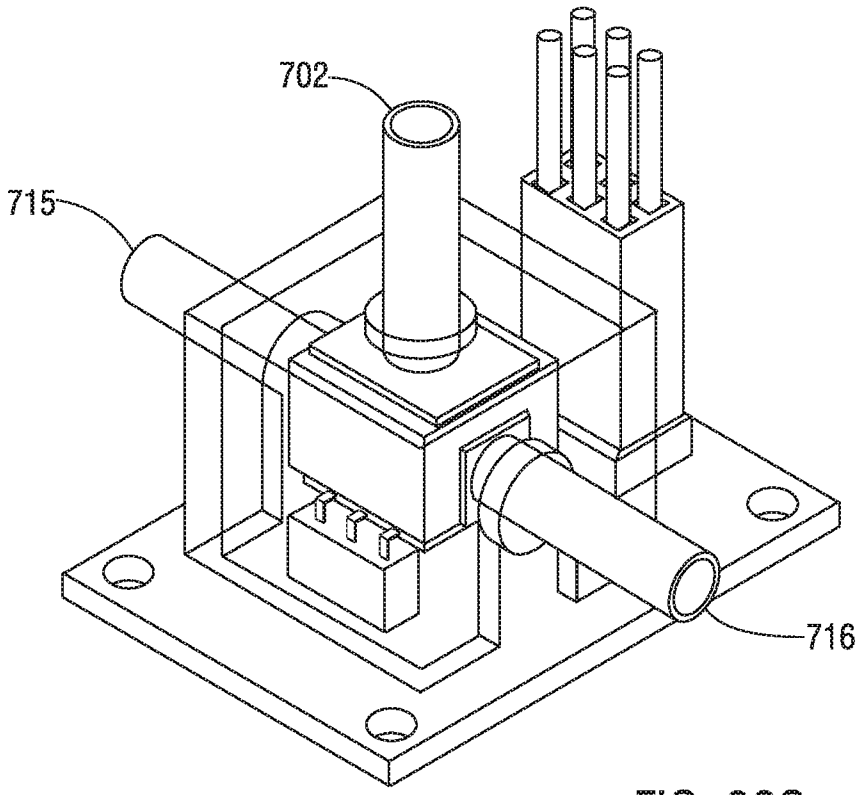


FIG. 32C

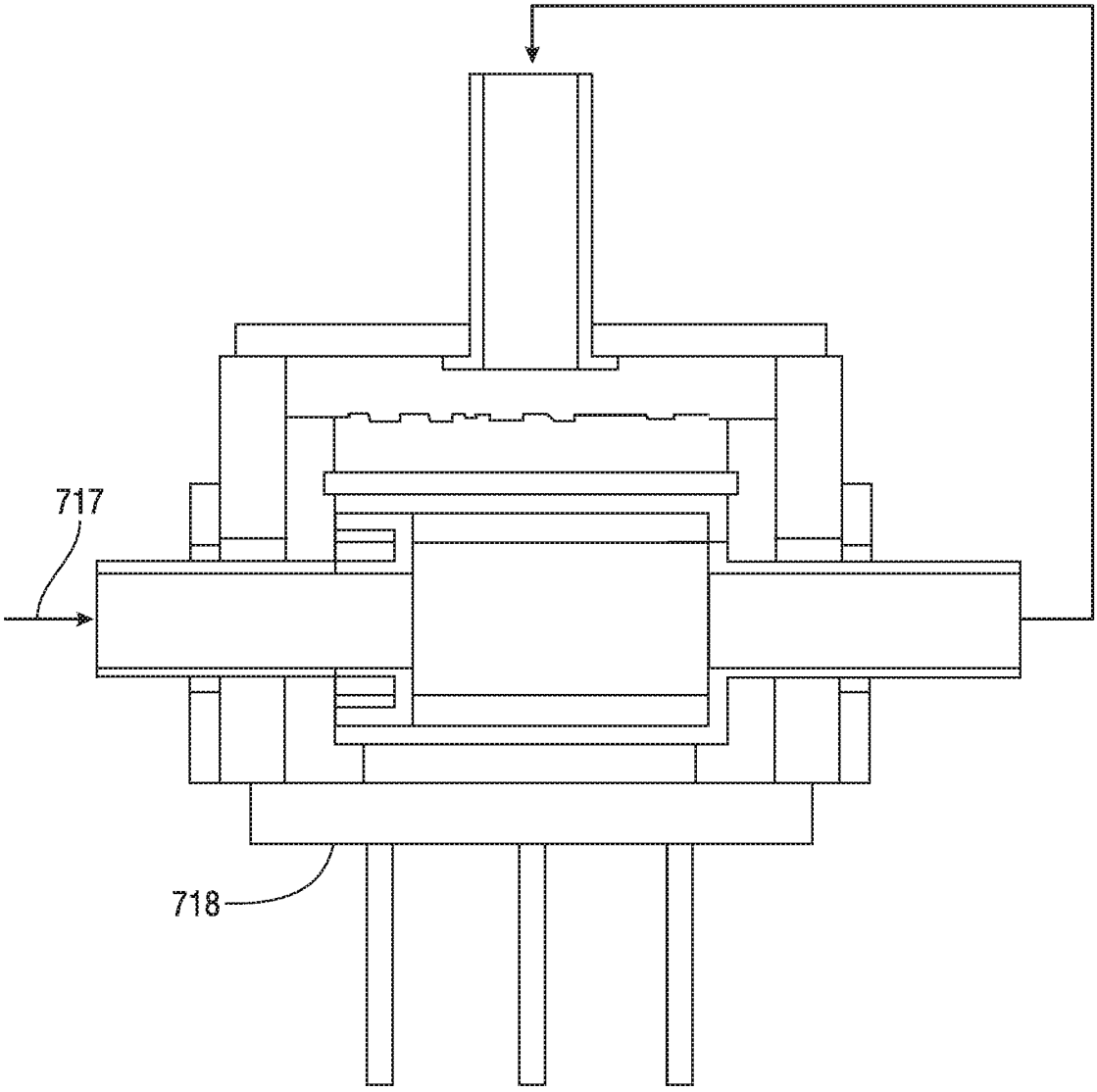


FIG. 33

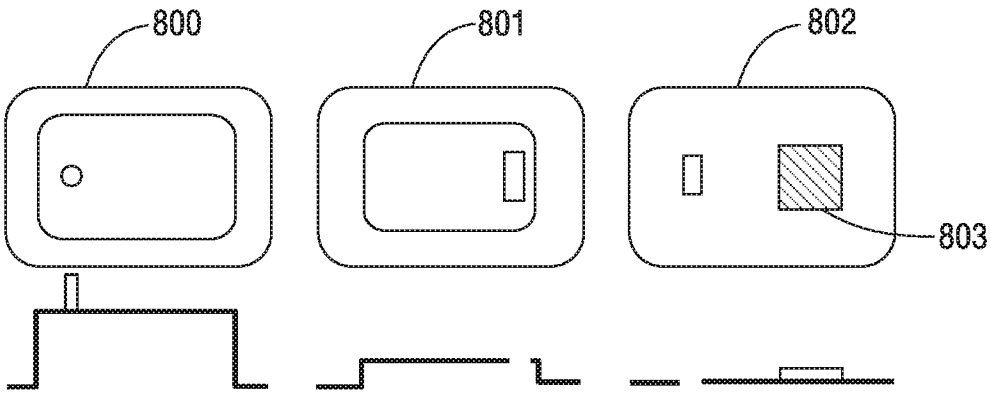


FIG. 34A

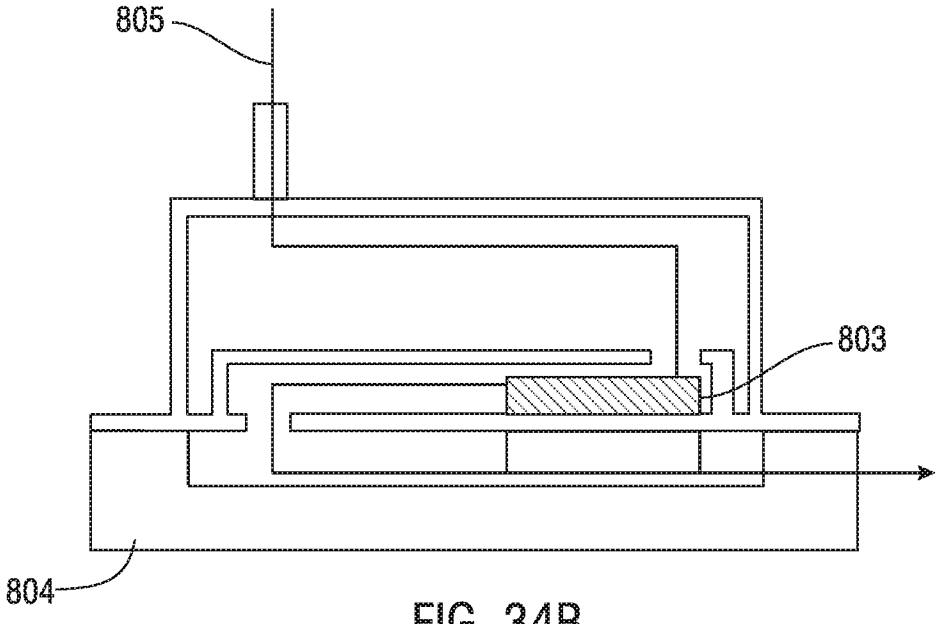


FIG. 34B

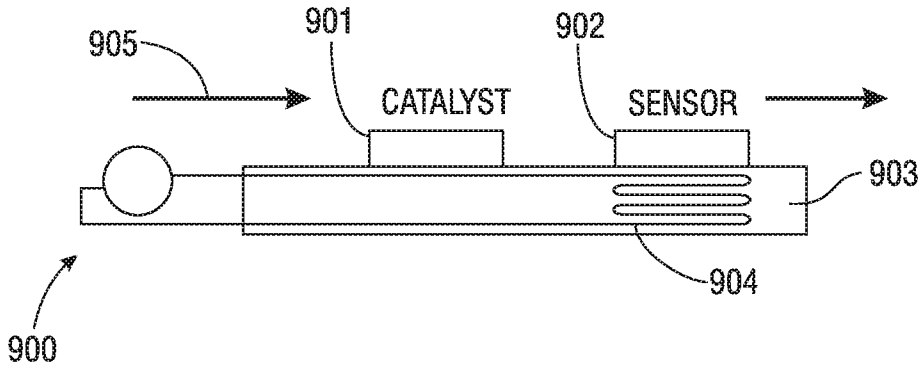


FIG. 35

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2017/042459

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61B5/083 A61B5/097 A61B5/08
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61B G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	US 2006/027465 A1 (NAIR BALAKRISHNAN G [US] ET AL) 9 February 2006 (2006-02-09) paragraphs [0002], [0032], [0037], [0038] -----	1-43 1-43
Y	US 6 764 591 B1 (DUTTA PRABIR K [US] ET AL) 20 July 2004 (2004-07-20) cited in the application column 4, line 18 - line 49 -----	1-43
A	WO 2011/055286 A1 (KONINKL PHILIPS ELECTRONICS NV [NL]; VAN KESTEREN HANS WILLEM [NL]) 12 May 2011 (2011-05-12) page 3, line 27 - line 33 page 4, lines 1-29 -----	1,7

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

[X] See patent family annex.

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
25 September 2017	02/10/2017

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Knüpling, Moritz

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Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2017/042459

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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A	US 6 475 158 B1 (ORR JOSEPH A [US] ET AL) 5 November 2002 (2002-11-05) column 1, line 35 - line 48	13
A	PANTALEI SIMONE ET AL: "Improving sensing features of a nanocomposite PEDOT:PSS sensor for NO breath monitoring", SENSORS AND ACTUATORS B: CHEMICAL: INTERNATIONAL JOURNAL DEVOTED TO RESEARCH AND DEVELOPMENT OF PHYSICAL AND CHEMICAL TRANSDUCERS, ELSEVIER BV, NL, vol. 179, 23 October 2012 (2012-10-23), pages 87-94, XP029001316, ISSN: 0925-4005, DOI: 10.1016/J.SNB.2012.10.015 abstract	19

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International application No
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US 6475158 B1	05-11-2002	NONE	