

Selective Low Concentration Ammonia Sensing in a Microfluidic Lab-on-a-Chip

Bjorn H. Timmer, Koen M. van Delft, W. W. Koelmans, Wouter Olthuis, and Albert van den Berg

Abstract—In the medical community, there is a considerable interest in a diagnostic breath analyzer for ammonia that is selectively enough to measure in exhaled air and small enough for the small volumes available in such an application. An indirect measurement system for low gaseous ammonia concentrations has been miniaturized and integrated on a chip in order to reach this goal. The detection limit of the system was calculated to be 1.1 parts per billion (ppb). The response time was determined to be 1.6 min with a gas flow of 50 ml/min. The required gas volume for one measurement is therefore sufficiently small, although sampling assistance is required for breath analysis. The selectivity of the system is sufficient to measure ammonia concentrations in the low-ppb range. The system is even sufficiently selective to be used in environments that contain elevated carbon dioxide levels, like exhaled air. The lower ammonia concentration expected in diagnostic breath analysis applications, 50 ppb, was demonstrated to be detectable.

Index Terms—Gaseous ammonia sensor, microfluidics.

I. INTRODUCTION

IN the medical community, there is a considerable interest in ammonia analyzers that can be applied to measure ammonia levels in exhaled air for the diagnosis of certain diseases [1]. Measuring breath ammonia levels can be a fast diagnostic method for patients with disturbed urea balance, e.g., due to kidney disorder [2] or *Helicobacter Pylori* bacterial stomach infection [3]–[5]. For such applications, often only a few hundred milliliters of exhaled air is available with ammonia concentrations down to 50 ppb in breath of healthy people and up to several hundred pounds per million (ppm) in a diseased state [5] and today no suitable ammonia breath analyzer exists [6]. The ammonia analyzer should be extremely selective because the levels of ammonia are very low compared with other gas concentrations like O₂ and CO₂ levels.

Many air ammonia detectors have been reported in literature based on different principles [7]–[13]. The most sensitive and selective systems, comprising laser setups, are not suited

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for miniaturization and integration on a chip and are therefore not applicable for measuring in the small available gas volumes. Methods for direct gas concentration measurement that are more suitable for miniaturization have been shown, like tin oxide film [8] or conducting polymer-film gas sensors [9]. These methods have been applied to measure ammonia concentrations [10]–[12] but most of them showed poor selectivity and inadequate detection limits and are thus not suited.

Other air analyzing systems for measuring ambient gasses make use of gas samplers like denuders or diffusion scrubber [14]–[16]. These systems have the advantage that they can concentrate the ammonia by sampling a volume of gas into a smaller volume of liquid where ammonium ions are formed [17], [18]. Many accurate ways to measure low ammonium concentrations have been shown [19].

An environmental monitoring system for ambient ammonia has been developed at the Energy Research Centre of the Netherlands (ECN) [20] that is accurate enough for breath analysis. However, the apparatus requires an analyte gas flow of 1 l per minute for more than 10 min. Miniaturization to reduce the analyte gas consumption is required. It can be expected that this will also make the device more rugged and less sensitive to disturbances [21], [22].

The apparatus comprises a gas sampler, a separator, and a detector [17], [20]. First, gas is sampled into an acid sample solution through a microporous water-repellent membrane. In the selector part, interfering acid gasses are removed and only ammonia will diffuse through a second membrane into a purified water stream. The resulting ammonium concentration is quantified by integrating an electrolyte conductivity (EC) sensor. The system is schematically shown in Fig. 1.

II. THEORETICAL

Normal ambient ammonia concentrations are in the low ppb range; an average of 2 ppb is assumed for the Netherlands [20]. The lower expected ammonia concentration for breath analysis is about 50 ppb [2]. Normal ambient CO₂ levels are about 300 ppm. Exhaled air can contain up to a hundredfold more, 30 000 ppm. The selectivity of the apparatus should be such that 50 ppb of ammonia is detectable [5].

Ammonia is the main alkaline gas, both in environmental applications and in breath analysis. The used detection principle is based on this fact. First, in the gas sampler, gas is sampled through a microporous hydrophobic membrane into an acid sample solution. In the acid solution, ammonia will react with water and form ammonium ions. This reaction is very fast, and at low pH values, the equilibrium will cause almost all ammonia to be converted to ammonium [17]. Weak acidifying gasses, like

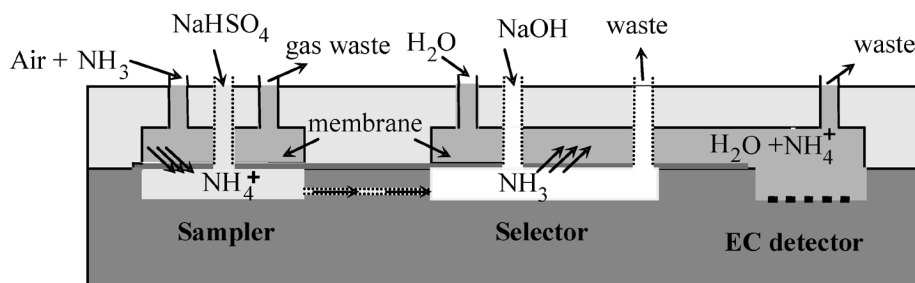
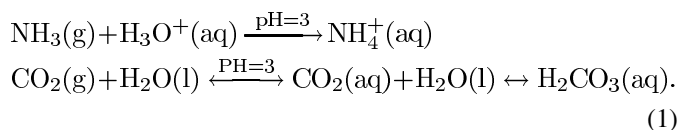
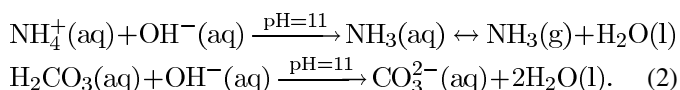


Fig. 1. Schematic of the air ammonia analyzer developed at ECN [19].

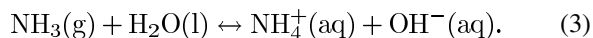
carbon dioxide, stay neutral in the acid solution. The overall reaction is given for ammonia and carbon dioxide in (1) (dissociation constants can be found in [17]), as follows:



Subsequently, the sample solution is pumped into the selector where the pH is increased by adding a strong alkaline solution. The high pH value shifts the equilibrium, neutralizing the ammonium ions back to ammonia and dissociating sampled acid gasses like CO_2 , as described by (2) [17]



The selector is formed by two opposite channels separated by a gas permeable, water-repellent polypropylene membrane, as illustrated in Fig. 1. The opposite channel is flushed with purified water. The dissolved ammonia turns gaseous at the phase separating membrane interface and can pass through the membrane into the purified water where it partly dissolves. The dissolved ammonia reacts with water due to the dissociation equilibrium, as follows:



All remaining ionized acid gasses are flushed out of the system as waste. The formed ammonium ions in the water stream are quantified using an electrolyte conductivity detector [24].

The obtainable selectivity is a function of the described chemical reactions. The Henry constant relates the concentrations in the gas sampler of the gaseous and the dissolved state. The concentration levels of the ions that are formed due to the dissociation reactions can be calculated using the dissociation constants of the equilibriums. Furthermore, the pH values of the solutions in the gas sampler, selector, and the detector stream should be known. These values, however, change when gasses like CO_2 and NH_3 are sampled and are therefore influenced by the amount of sampled gasses, the used internal volumes, and liquid flows as well as the speed at which the involved reactions occur. In a previous publication, a detailed analysis was

made that indicates that the desired selectivity can be reached, even for breath analysis conditions [17]. For breath analysis, the system described in this paper with an analyte gas to sample solution ratio of 3125 and an initial pH of 3.5 would sample more than 99.9% of the ammonia that is ionized for more than 99.9%, where only 0.001% of the CO_2 is sampled. After addition of the alkaline solution in the selector part of the system, 99.9% of the formed ammonium ions are transformed into gaseous ammonia again where only $3.5 \cdot 10^{-4}\%$ of the dissolved CO_2 is available in the gaseous state. Based on this estimation, a selectivity toward ammonia compared with CO_2 of several millions is expected.

III. EXPERIMENTAL

A. Miniaturized Detection System

The system shown schematically in Fig. 1 has been realized as an integrated miniaturized detection system. The key components, the gas sampler, the selector, and the electrolyte conductivity sensor have been realized in one chip. Both the gas sampler and the selector comprise two opposite channels separated by a gas-permeable water-repellent membrane. A membrane suitable for integration in a microfluidic gas detection system is microporous polypropylene (PP). These membranes are both gas permeable and water repellent, and they can be glued to glass and silicon using epoxy glue. The thickness of commercial microporous PP membranes, acquired from Schleider & Schuell (PP 0.22 μm hydrophobic membrane), is about 150 μm . Previous research taught us that the channels of the system are required to have a depth of at least 15 μm and a maximum width of about 1 mm to prevent clogging of the channel by buckling of the membrane into the channel.

The concentration enhancement ratio and thus the selectivity can be optimized by making the gas sampler as large as possible to be able to pump through a large gas flow and the selector as small as possible to reduce the flow through time of the selector solution. The depth of the sample solution and the selector solution channel was chosen as shallow as possible, 15 μm , to reduce diffusion distances. The gas channel of the sampler could be made deeper since gaseous diffusion is much faster. The optimized dimensions of the system have been obtained from mass transport simulations conducted in the finite-element program CFD-ACE from CFD Research Corporation.

Shallow channel structures, all channels except the gas channel have a depth of 15 μm and have been etched in glass using wet chemical etching. Borofloat glass wafers were first

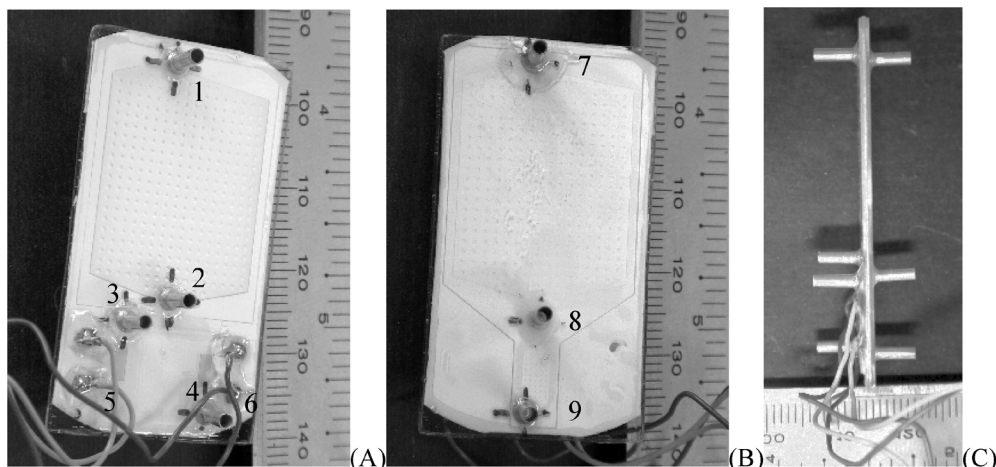


Fig. 2. Photographs of an assembled miniaturized ammonia analyzer showing (a) a top view, (b) a bottom view, and (c) a side view of the chip that comprises of a microporous membrane glued between two micromachined glass layers with 1—gas outlet, 2—gas inlet, 3—purified water inlet, 4—water outlet, 5—EC detector at the water inlet, 6—EC detector at the water outlet, 7—sample solution inlet, 8—alkaline selector solution inlet, and 9—solution outlet.

cleaned in fuming nitric acid. A chromium mask layer was deposited and structured using standard photolithography and wet chromium etching. Subsequently $15\ \mu\text{m}$ deep channels were etched in the glass in a 10% HF solution. The used photoresist was stripped from the wafer in acetone. Through-holes and deep channels like the gas channel with a depth of $100\ \mu\text{m}$ were made using powder blasting [25]. A photosensitive protective foil, Ordyl BF410, was laminated onto the wafer and structured using photolithography and developed in sodium carbonate. After powder blasting the through-holes with $9\ \mu\text{m}$ aluminum oxide powder, the foil was stripped in sodium carbonate and the wafer was ultrasonically cleaned in acetone to remove powder residue and diced.

A miniaturized EC detector optimized for measuring low ion concentrations in small volumes has been realized in previous research [24]. A comb-structured two electrodes conductivity detector with 95 electrode fingers with a width of $10\ \mu\text{m}$, a length of $1270\ \mu\text{m}$ and a spacing between the fingers of $30\ \mu\text{m}$ has been realized, resulting in a cell constant of $15\ \text{m}^{-1}$. After cleaning a Pyrex glass wafer, a negative image of the designed electrode structure was created on the wafer in photoresist using standard photolithography. After sputtering a chromium adhesion layer, a platinum electrode layer was sputtered over the entire wafer. The electrode structure was realized using a liftoff step by ultrasonically removing the photoresist layer. A glass cover to seal the electrodes was made by etching channels and powder blasting through holes. The cover was glued over the electrodes using epoxy glue. Two detectors were integrated in the system, one at the water inlet and one at the water outlet. The inlet detector is used as an indicator for changes that are not caused by a change in analyte gas, like temperature changes or pollutants in the purified water source.

The different parts were assembled by gluing the two glass parts together with the membrane in between. Fluid and gas connectors as well as wires were connected to the inlet and outlet holes and the bond pads of the electrodes, respectively. A photo of the integrated ammonia measurement system is shown in Fig. 2.

B. Measurement Setup

A 50 ml/min analyte gas flow was applied to the gas sampler. Pure nitrogen, pure CO_2 , and a mixture of nitrogen with 10 ppm ($\pm 10\%$) ammonia were acquired from Hoekloos. Gas flow was controlled using mass flow controllers from Bronkhorst High-tech, EL-flow F-110C. The mass flow controllers used for the ammonia and the CO_2 source have a maximum flow of 3 ml/min with a minimum controllable flow of 2%, which is $60\ \mu\text{l}/\text{min}$. The nitrogen flow was controlled with a 100 ml/min mass-flow controller. The mass-flow controllers should always be open, at least at 2%, to prevent back flow of the analyte gas, resulting in minimum attainable ammonia and CO_2 concentrations of 12 ppb and 1000 ppm ($0.1\%_{\text{v}}$) respectively, at a 50 ml/min gas flow.

The three liquid flows, the sample solution, selector solution, and purified water flow, were pressure driven using a CMA 102 microdialysis syringe pumps connected to a personal computer. Deionized water was purified by an ion exchange column filled with a Baker mixed-bed ion exchange resin.

The conductance between the electrodes in the detector was measured with homemade interface electronics that were connected to the same computer. The measurement frequency of the interface electronics was optimized to reduce capacitive influences to 1 kHz at a $66\ \text{mV}_{\text{RMS}}$ sinusoidal measurement signal [24]. A measurement and control Labview program was used to be able to adjust flow settings and perform measurements at the same time. A schematic of the used measurement setup is shown in Fig. 3.

C. Measurement Protocol

A $325\ \mu\text{M}$ NaHSO_4 sample solution, with a pH of 3.5, was pumped through the gas sampler at $16\ \mu\text{l}/\text{min}$. A 0.1 M KOH solution was added to the selector, with a pH of 13.0, at a flow rate of $4\ \mu\text{l}/\text{min}$. The purified water was pumped into the selector at a flow rate of $2\ \mu\text{l}/\text{min}$. Prior to the experiments, a calibration measurement was performed with the electrolyte conductivity

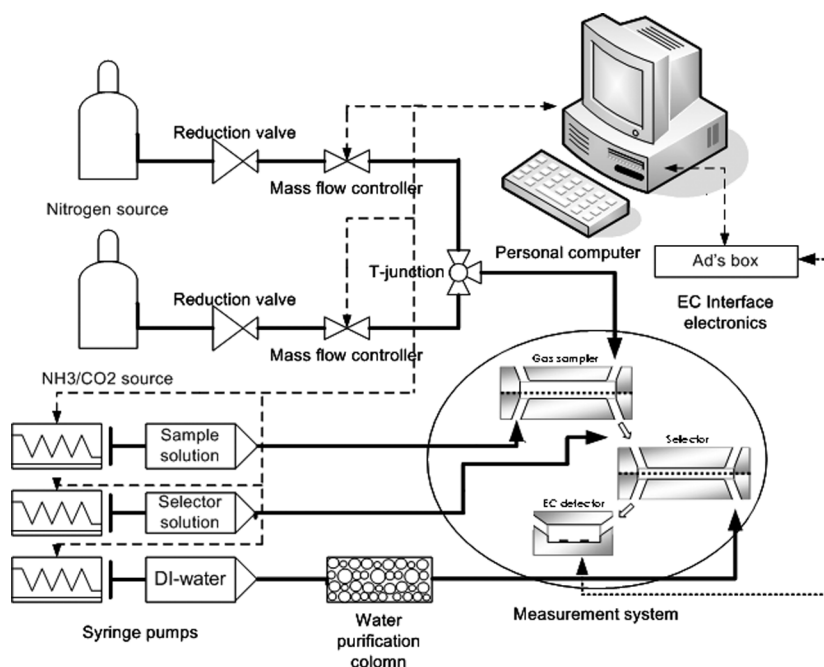


Fig. 3. Schematic representation of the used measurement setup.

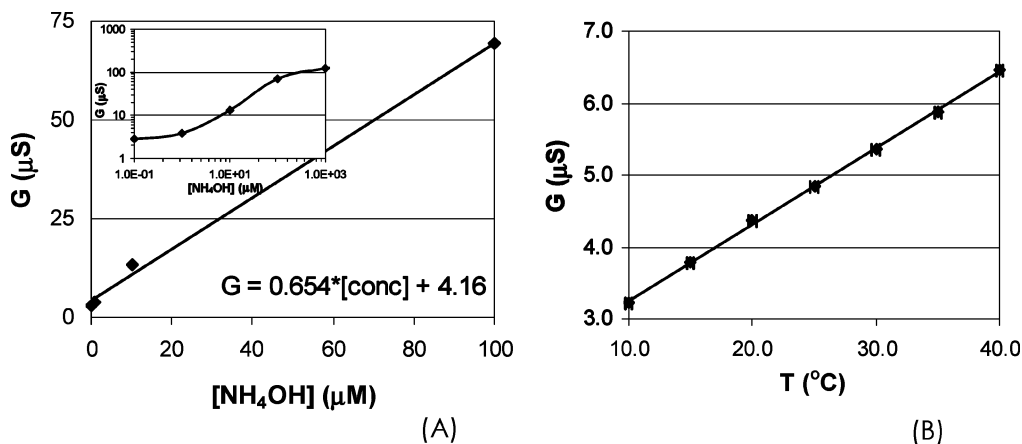


Fig. 4. EC detector calibration with NH_4OH solutions at (a) room temperature and (b) temperature dependence of the purified water conductance between 10°C and 40°C .

detectors. A solution with a known ammonium hydroxide concentration was flushed through the detector.

IV. RESULTS AND DISCUSSION

The calibration result of the detector is shown in Fig. 4(a). For the higher concentration range, the used measurement frequency was relatively low. This can be noticed from the flattening of the curve at concentrations above $100\ \mu\text{M}$, as shown in the inset. The lower conductance at these higher electrolyte concentrations causes an increased influence of the double layer capacitance at the electrode–electrolyte interface. The interface electronics do not measure at the optimal frequency anymore. For lower ion concentrations, up to $100\ \mu\text{M}$, the relation between the concentration and the measured conductance was linear within 2%. The equation of the linear fit was used in the rest of this paper as the relation to calculate the conductance as a function of the NH_4OH concentration.

It should be noted that this calibration is only valid at room temperature, 20°C , since electrolyte conductivity is also a function of the temperature. The temperature dependence of the conductance measured with purified water is plotted in Fig. 4(b), showing a temperature dependence of $2.4 \pm 0.3\%/^\circ\text{C}$ with respect to the conductance at 20°C .

The first experiment conducted with the measurement system was an ammonia sensitivity test. The system was first flushed with pure nitrogen for an hour. Once the output signal of the detectors became stable after cleaning of the selector channels and detector electrodes with purified water, ammonia was added to the nitrogen carrier gas. The measurement result obtained with an increasing ammonia concentration is shown in Fig. 5.

It is shown that the sensor responds to an increase in ammonia concentration. The response time of the device seems to be a function of the ammonia concentration. This is an artefact caused by the analyte gas preparation setup shown in Fig. 4.

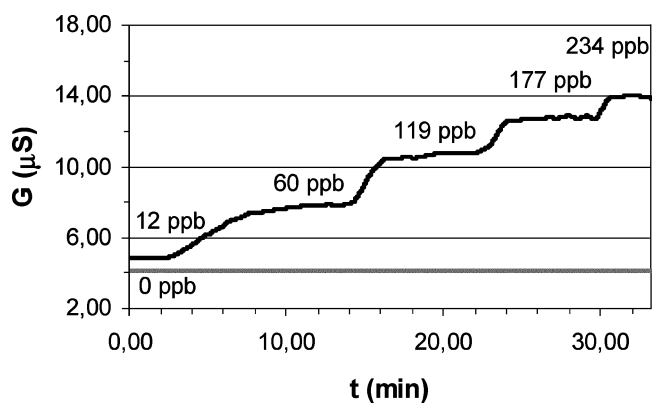


Fig. 5. Ammonia sensitivity experiment showing the measured conductance of the two detectors at the water inlet and the water outlet as a function of the ammonia concentration in the analyte gas.

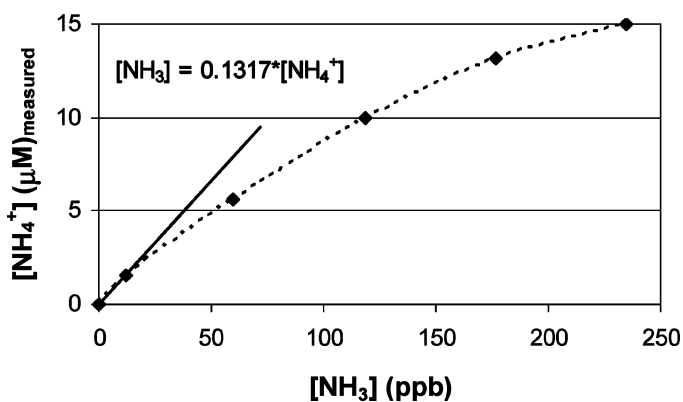


Fig. 6. Conductance as a function of the applied ammonia concentration with a linear fit through the lowest concentrations to determine the slope of the relation.

Teflon tubing was used as interconnect to transport the gasses from the mass-flow controllers to a T-junction that was connected with the gas inlet of the measurement system. When making very low ammonia concentrations, the flow from the source is so slow that it takes more than a minute before the desired gas composition actually reaches the sensor. Diffusion inside the tubing causes dispersion of the step in concentration. The response time, the time it takes for the signal to reach 90% of the end value, was thus several minutes. When the flow from the ammonia source was higher, the response time of the measurement system itself becomes the dominant factor, resulting in a response time of 1.6 min. Although this is a significant reduction compared with the large-scale apparatus that this device was based on, an additional breath sampling device will still be required.

In order to determine the detection limit of the system, the ammonium concentration corresponding to the measured conductance values is plotted in Fig. 6 as a function of the applied ammonia concentration. The ammonium concentration was calculated using the concentration–conductance relation determined from the calibration measurement of which the result was shown in Fig. 4(a). The error bars indicate three times the standard deviation of the conductance during the last minute before the concentration was increased, taken from Fig. 4.

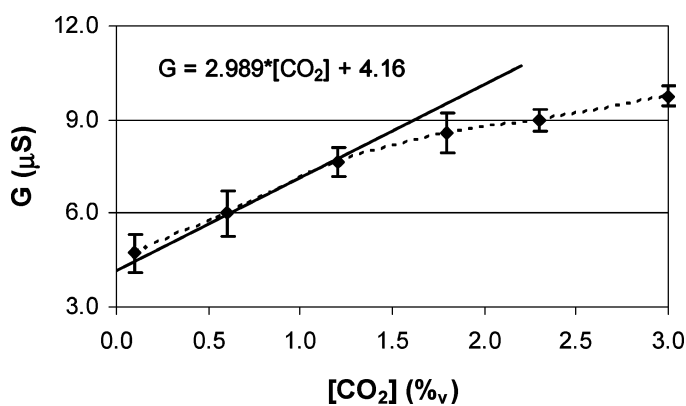


Fig. 7. Conductance measurement result with CO₂.

Manually, a fit to the curve was made through the lowest applied concentration of 12 ppb and the response to ammonia-free nitrogen. Three times the standard deviation value of the response to 12 ppb, the noise level of the first “flat” area in the measurement shown in Fig. 6, was calculated to be 0.14 µM. With this value and the relation, the theoretical detection limit was calculated to be 1.1 ppb—a significant improvement compared with previous results obtained with a modular sensor, described in [17], where a detection limit of several hundred ppb was obtained. This lower detection limit could be further lowered by reducing the deviation in output signal, which seems to be caused mainly by flow variations inside the system. Gas flow variations in particular largely influence the conductance signal.

The above results showed that the system was fast and accurate enough for a diagnostic breath analysis tool. For such a system, however, a high selectivity toward ammonia is required. In exhaled-breath carbon dioxide levels are much higher than in normal air, as discussed in the introduction. To investigate the selectivity of the measurement system, the conductance response to a 50-ml/min analyte gas of nitrogen containing known partial pressures of CO₂ concentrations was determined. The result is shown in Fig. 7.

In Fig. 7, it is shown that the measurement system did respond to increasing partial CO₂ pressures in the analyte gas. The maximum tested CO₂ concentration, 3 vol., corresponds to the higher level that can be found in exhaled breath. The resulting conductance value can be compared with the ammonia measurement result shown in Fig. 5 and corresponds to an ammonia concentration of about 90 ppb. This means the selectivity of the system toward 3 vol.% of CO₂ and ammonia is about 330 000. It was our goal to reach a selectivity of 600 000 so that the conductance response to the CO₂ level in exhaled breath would be comparable with the desired ammonia detection limit of 50 ppb. Although this selectivity was not reached completely, exhaled CO₂ levels are relatively stable [23]. Therefore, it still seems possible to detect 50 ppb of ammonia. Further tests are required with both CO₂ and NH₃, or even better exhaled air, which could unfortunately not be conducted with the used measurement setup.

With the linear fit to the lower carbon dioxide concentration responses forced through the conductance level at pure nitrogen, as shown in Fig. 7, an estimation of the system response to

normal atmospheric CO₂ concentrations can be made. A concentration of 300 ppm or 0.03 vol.% corresponds to a conductance of 4.24 μ S. This equals the response of the system to an ammonia concentration of 1.0 ppb, according to the results shown in Figs. 4 and 6. This means that the system can be used for environmental monitoring in areas where the ammonia concentration is in the low-ppb range.

V. CONCLUSION

A miniaturized measurement system for low gaseous ammonia concentrations has been realized on a chip. The system comprises three main parts: a gas sampler that converts gaseous ammonia to dissolved ammonium ions, a selector that removes interfering gasses like CO₂, and a detector that quantifies the electrolyte concentration that is directly proportional to the ammonia concentration in the analyte gas. A phase separation membrane was integrated by gluing polypropylene membranes between two glass chips comprising micromachined channels.

The detection limit of the system was calculated to be 1.1 ppb. The response time of the measurement system was determined to be 1.6 min. In environments with normal acidifying gas concentrations, the selectivity of the system is sufficient to measure ammonia concentrations in the low-ppb range. The system is even sufficiently selective to ammonia to be used in environments that contain elevated carbon dioxide levels, like exhaled air. The lower ammonia concentration expected in diagnostic breath analysis applications, 50 ppb, is easily detectable. It should be noted, however, that a breath sampling device is required because 1.6-min sampling time is too long for directly measure exhaled breath.

The system comprises two electrolyte conductivity detectors: one to determine the conductance of the water that is pumped into the system and one to quantify the ammonium concentration as a result of the ammonia uptake. This first detector can be used as an indicator for sudden changes in input boundary conditions like pollution in the water flow or changes in temperature. It is shown that the temperature dependency of the water conductance is nearly linear at temperatures in the range from 10 °C to 40 °C.

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