Mobile Sensor that Quickly and Selectively Measures Ammonia Gas Components in Breath

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Amid the increasing trend of aging societies across the world, there are now expectations for healthcare tailored to individuals that helps to more quickly detect diseases and improve lifestyles to ensure health and longevity for the current generation. Therefore, it is thought that it will be effective to use device technology and information and communications technology (ICT) to monitor an index related to the state of the body, easily and continuously in the home, clinic, and such like. We have focused research on diagnostic methods using breath analysis to examine the gaseous components of a person's breath as an indicator of the condition of his or her body, and developed a mobile breath sensor. This paper describes a breath sensor system that can selectively measure the concentration of ammonia that is present in everyone's exhaled breath. By applying the ammonia-adsorbing characteristic of copper(I) bromide films, we successfully developed a sensor that measures tiny amounts of ammonia in a person's breath at a sensitivity differential that is more than treble that of a gas having other living body origins. By using the sensor device, we have developed a breath sensor system. As a result, it has become possible to continuously and easily examine changes in components of the breath in relation to lifestyle without any accompanying pain such as the pain of collecting blood, similar to using a clinical thermometer.

1. Introduction

Amid the increasing trend of aging societies across the world, both the increase in overall medical costs and the decrease in work force have become serious problems at the state level. In Japan, costs of medical treatment were in excess of 40 trillion yen, corresponding to 8% of GDP, in 2013.

Lifestyle diseases such as high blood pressure and metabolic syndrome occupy a large percentage of such costs because they often lead to other serious diseases, and they can cause a large loss to society in both aspects of medical cost and work force. Early detection and treatment of lifestyle illnesses are being touted as the key to health and longevity for the current generation. New healthcare services are requested by using information and communications technology (ICT) including state-of-the-art devices to solve this issue.

A person's breath includes many chemical substances that were in the blood but that evaporated in the lungs and were exhaled. By using breath analysis to measure the concentrations of these gases, the objective is to detect specified substances and effectively use that information for the early detection of lifestyle diseases, leading to improved lifestyle habits.[1] Breath analysis is non-invasive. This means, this technology makes it possible to avoid the unpleasantness of drawing blood while at the same time making it easier to study the effects of changes in breath components resulting from lifestyle habits, on an ongoing basis.

Ammonia in a person's body is generated by intestinal bacterial decomposing nitrogen compounds such as proteins and amino acids. But ammonia is converted into urea in the liver and then expelled in urine. Therefore, the concentration of ammonia in the breath is kept low if a person is healthy. Ammonia in a person's breath is said to be correlated both with liver metabolism and *Helicobacter pylori* infection, which is a risk factor for stomach cancer.[2] It is reported that ammonia has a high possibility of being useful as a biomarker because it is increases when a person is tired and with aging.

In this paper, we describe a mobile breath sensor that can measure changes in ammonia level caused by lifestyle.

2. CuBr: a novel ammonia sensing material

A promising research result has reported on lung cancer detection using breath analysis and a pattern recognition approach, in which surface-modified gold nanoparticles were used as sensing material.[2) However, this kind of approach can only recognize known patterns, and thus unexpected abnormalities may be missed. The authors therefore focused on developing a sensing device to detect molecules and detect only ammonia, which is included in the breath in the order of 100 ppb (**Figure 1**).

There are many semiconductor materials that indicate a response to ammonia. For example, widely used metal-oxide semiconductor gas-sensor devices can also detect ammonia. In these cases, the semiconductor devices are used at a high temperature of around 300°C to raise the carrier density amount of the current flowing in a semiconductor and surface activity. Such condition enables the devices to be sensitive to ammonia, similar to other kind of gases.

For the molecular recognition approach, however, it is ideal if the sensor device detects only ammonia, and shows no response to other gases. From the perspective of selectivity to ammonia, the authors chose copper(I) bromide (CuBr) as a sensing material. CuBr is known as a selective ammonia-sensing material; its response to ammonia is orders of magnitude higher than that for other gases. The difference in response magnitude among the gases can be explained by the fact that ammonia tends to link up with Cu^+ ions and produce a complex. Since CuBr is a p-type semiconductor and a solid electrolyte, Cu^+ ions in a crystal migrate to the surface with exposure to ammonia, and coordinately bond to ammonia molecules. As a result, the carrier density in CuBr crystals decreases because of an excess negative charge inside the crystals.[3) Accordingly, the sensitivity of a CuBr gas-sensor device is expected to improve with a decrease in the sensing film's thickness.

However, the reported sensitivities of CuBr gas-sensor devices made by known fabrication procedures, brominating a Cu film in an aqueous solution of copper(II) bromide ($CuBr_2$),[4) or sputtering,[5) are orders of ppm. This is because it is difficult to fabricate a thin and stable CuBr film with ppb orders of sensitivity.

The authors therefore developed a novel procedure to fabricate a CuBr thin film, in which a thin Cu film is brominated with a $CuBr_2$ methanol solution. This procedure can fabricate a stable CuBr crystal structure because there is no variation in the chemical composition, unlike that which results from the sputtering method. Also, methanol has less affinity to CuBr than water. Therefore, stable CuBr films that are hard to be exfoliated can be created in the methanol solution procedure because smaller crystalline grains can be obtained than in the aqueous solution procedure.

The procedure of fabricating a thin CuBr thin-film gas-senor device is as follows.

1) On a pair of gold electrodes, a 5 mm square copper film with a thickness of 60 nm is deposited by using the vacuum deposition technique.
2) The aforementioned structure is immersed into a $CuBr_2$ methanol solution with a concentration of 0.2 mol/L for 60 s, then washed with pure methanol and dried. The thickness of the obtained CuBr film is approximately 300 nm.

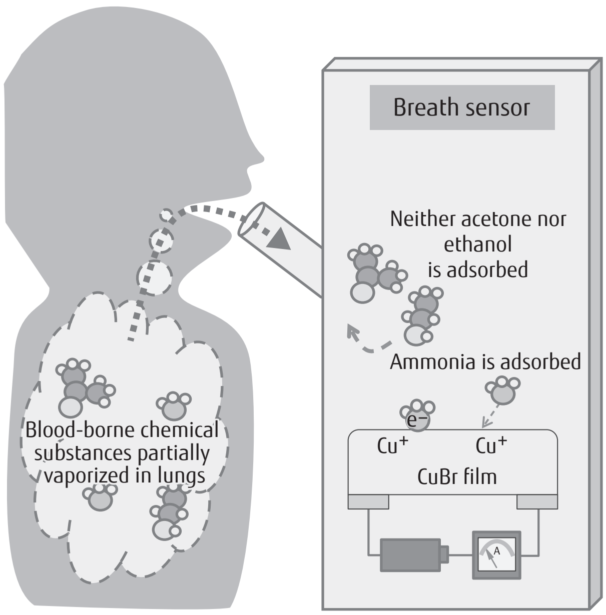
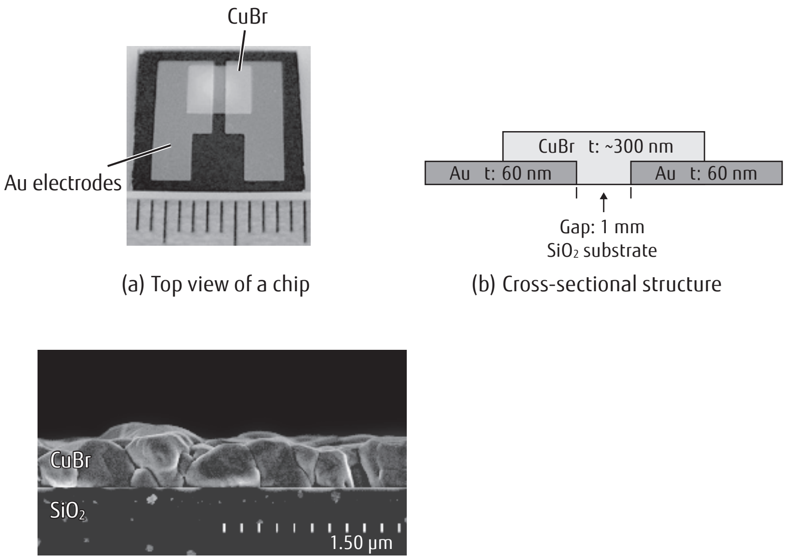


Figure 1
Conceptual image of composition and usage of developed technology.

3. A highly sensitive and highly selective ammonia sensor device

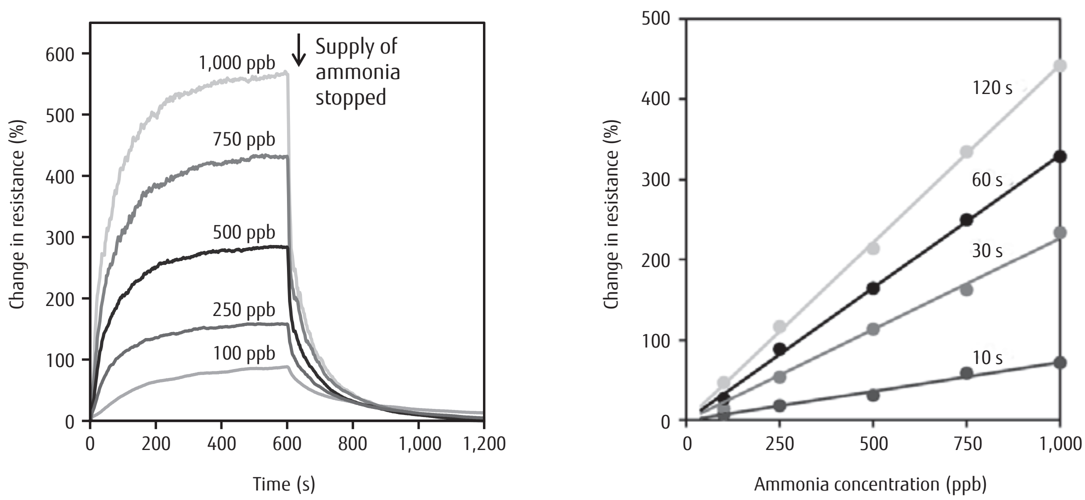
Figure 2 shows the appearance and cross-sectional structure and a cross-sectional scanning electron microscope (SEM) image of the CuBr thin-film gas-sensor device described in section2. Typical responses of the CuBr device to ammonia with various concentrations in the atmosphere are indicated in **Figure 3**. The range of ammonia concentration shown in Figure 3 is 100–1,000 ppb (0.1–1 ppm).

As shown in Figure 3, the relationship between ammonia concentrations and the device response indicates good linearity up to 10 ppb, and this is an adequate sensitivity for measuring ammonia concentrations in human breath. Figure 3 also shows that the saturation values of the device resistance have a



(a) Top view of a chip
(b) Cross-sectional structure
(c) Cross-sectional SEM image of CuBr film

Figure 2
Gas sensor device made from CuBr film.



(a) Time response
(b) Calibration curve

Figure 3
Typical responses of sensor device to ammonia gas.

good linearity against ammonia concentrations, suggesting that this adsorption system fits to the Langmuir model,[6] implying that fast measurement using initial response is applicable to CuBr thin-film sensor devices.

The measured responses of a CuBr sensor device for acetaldehyde, ethanol, acetone and hydrogen sulfide are 0.01%, 0.06%, 0.045 and 1.8% in relative values to that for ammonia, respectively. Generally, metal-oxide semiconductor gas-sensor devises show responses for these gases around 10% of relative values to that for ammonia. In contrast, ammonia causes far stronger responses on the CuBr sensor device than hydrogen sulfide and those organic gases, by two digits and four digits, respectively. The aforementioned selectivity of the CuBr sensor device thus means that the device can measure only the ammonia concentration in human breath substantially, among many gas-phase components in the breath. Especially, this is the first case to reveal the possibility of directly measuring ammonia concentration in human breath, without being affected by chemically active hydrogen sulfide.

4. Quick and easy-to-use sensor system for breath

The breath sensor system developed in this work is intended to be used easily at home or in the office in daily life, not only in medical facilities. Therefore, in order to minimize the user's burden, we established a fast measurement method by using the initial response of the gas sensor device mentioned in the previous section. The sensor unit is small and designed to be operated by a battery. Furthermore, it is equipped with a Bluetooth low energy (BLE) module to transmit the measured data to a smartphone. In the near future, smartphones will connect this breath sensor system to a medical cloud, and measurement history management and detection of abnormal values are expected to be done in the medical cloud.

In order to simplify the operation, we did not use complicated operating buttons or a display device in the sensor unit. There is only a power switch on it. In the sensor chamber of the sensor unit, there is a CuBr sensor device and three metal oxide semiconductor (MOS) gas sensor devices, and sensors for temperature, humidity, and pressure. When the power switch is turned on, a microcomputer starts to transmit the resistance data of each gas sensor, and the temperature, humidity and pressure values to a smartphone every second in real time.

The application software installed on the smartphone indicates instructions for the user, and receives the measured data from the sensor unit. It also does calculations and displays and stores the gas concentration data.

When tapping the start button in the application software, a message appears asking the user to blow into the sensor unit. While a countdown timer of ten seconds is indicated, the user blows into the sensor unit. During this process, the microcomputer monitors each sensor value. Since variations between individuals in exhaled ammonia concentration are relatively large, we used changes in the resistance of the MOS gas sensor to check whether the user is blowing properly.

The MOS gas sensor is suitable for this purpose because it has a wide sensitivity to many kinds of organic compounds contained in the breath. After checking that the user is blowing properly, the software calculates the ammonia concentration by using the difference in resistance between the CuBr gas sensor before and after blowing. The relationship between the resistance change and gas concentration was examined in the previous section.

Figure 4 shows the prototype of the sensor unit and the smartphone when operated. In the application window, the gas concentration is indicated in parts-per-billion (ppb). The standard score based on the sampling measurement (to be mentioned in the

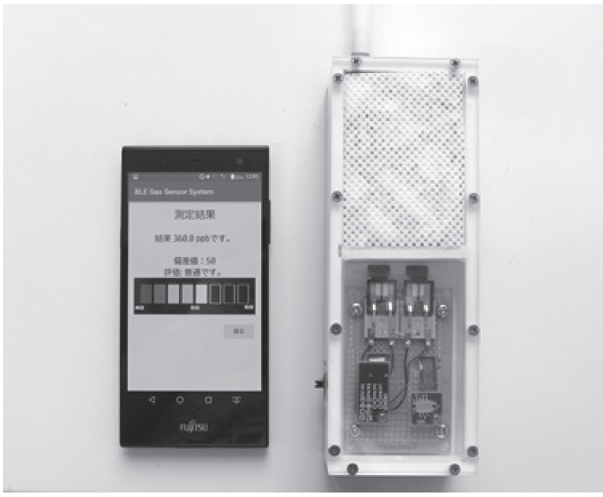


Figure 4
Prototype of breath sensor system.

next section) is also indicated by color bars; therefore, the user can know his or her position among a group. All measurement data are stored in the smartphone, and the latest ten pieces of data can be recalled. In the near future, the data will be sent to a medical cloud via the Internet.

5. Sampling measurement of ammonia concentration in breath

We conducted a sampling measurement of ammonia concentration in the breath of 128 employees from our laboratory (the average age of employees was 43). We obtained their consent to the measurement in advance, and their age and past illnesses were not examined because this measurement was done anonymously.

Figure 5 shows the result of the measurement. The measured data have a logarithmic normal distribution with a median value of 440 ppb, and geometrical standard deviation (GSD) is proved as 2.30. Spanel et al. reported that the median value is 833 ppb, and GSD is 1.62 based on their measurement on examinees aged between 20 and 60.[7] They also reported that the concentration distribution shifts depending on the age distribution of the sampling group. Considering the difference in age distribution between Spanel's group and ours, our measurement result is coherent with Spanel's. Based on the results above, we confirmed that our sensing system works properly.

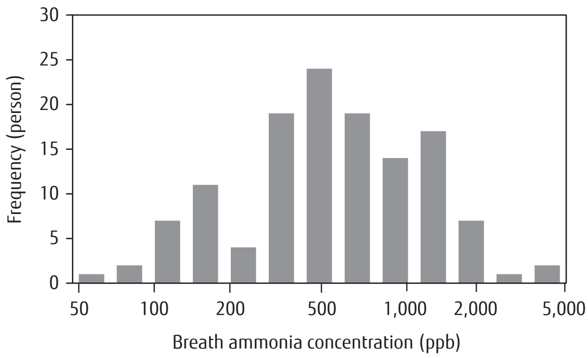


Figure 5
Distribution of measured breath ammonia concentrations.

6. Conclusion

In this report, we introduced a mobile breath sensor that can measure the ammonia concentration in the breath accurately. The biggest advantage of breath analysis is its ease of use, non-invasiveness and lack of accompanying pain like that related to collecting blood, though it is worth in principle comparing it with a blood examination.

It becomes possible to continuously examine changes in ammonia related to lifestyle in real time because it is possible to measure ammonia quickly with a portable device.

The breath sensor will be installed in a smart device and a wearable device in the future. In contrast, it is difficult to install a conventional large-scale analyzer in them. Moreover, we are aiming to develop an easy way to measure the breath also at home and roll out new healthcare services on the medical cloud.

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