Health care application of gas sensors

— Medical devices of breath analysis —

Woosuck Shin*, **Toshio Itoh and Noriya Izu**

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For the research goal of exhaled breath detection system in human health care or medical application, gas-selective and sensitive gas sensors have been developed. High performance sensors satisfying the boundary conditions, such as fast response and highly sensitive and selective detection, were developed with three essential components of a novel working principle, nanoparticle technology, and a ceramic integration process of sensing materials.

Keywords : Halitosis sensor, hydrogen sensor, VOC sensor, breath analysis, nanoparticle

1 Introduction

As aging of the population progresses in Japan, preparing sufficient supply of health care devices and services as well as curbing the expense of social welfare are raised as social issues. Against this background, medical examination using the breath has the advantages of being non-invasive, allows easy collection of samples, and provides quick results, and is gaining attention as new diagnostic technology.

The main gas composition of human breath consists of nitrogen that is the most common in atmosphere, carbon dioxide produced by respiration, oxygen that was not consumed, and water vapor generated from bodily fluids. It is composed of more than 100 types of gas components, and the components and concentration offer information that may be useful to monitor health conditions such as the presence of disease or stress. For such analysis or health checkup, technologies are necessary to selectively detect various gas species in the breath, and to measure the concentration of important gas species that are correlated with halitosis, metabolism, and disease.

Private companies already have high levels of gas sensor technology and solid manufacturing technology. Therefore, to differentiate from such technologies, we developed a sensor with a detection mechanism different from the conventional gas sensors. We developed a sensor that rapidly and sensitively measures the halitosis components in the mouth using oxide nanoparticles, and succeeded in commercializing a halitosis detector. Also, we are developing a detector for monitoring hydrogen and carbon monoxide in the breath using a new thermoelectric sensor. Moreover, we are developing a sensing technology utilizing the separation technology of gas chromatography (GC) and semiconductor gas sensors, to detect volatile organic compound (VOC) gas that is thought to be a marker for lung cancer. Currently, we are actively collaborating with medical fields from the perspective of public acceptance, in realizing the practical use of the sensors and systems that we developed.[1]

In the future, the gas analyzer developed in this research will make daily breath monitoring possible and enable self-management of health conditions by individuals, and this will greatly contribute to lowering medical costs. The demand for health care and medical care around the world is projected to increase from 32 trillion yen in 2011 to 40 trillion yen in 2020.[2] Many devices used in health care are imported, and health care business development is difficult. The problems of medical devices are the following: the market is small; collaboration of medicine and engineering, such as, chemical tests for practical use including obtaining official approval is not actively done compared to Europe and the USA; and the Japanese manufacturers have very little experience in development. Therefore, marketing of new technology that can be used clinically in Japan and overseas is difficult through conventional product development. In this paper, we discuss how the R&D achievement of our sensor technology development can lead to the creation of a new medical application, focusing mainly on the health care field.

2 Social demand for the sensors (performance)

Recently, the capacity to monitor health conditions and to predict disease non-invasively and easily without violating the Medical Practitioner's Act is coming into the spotlight.

Inorganic Functional Materials Research Institute, AIST 2266-98 Anagahora, Shimo-Shidami, Moriyama-ku, Nagoya 463-8560, Japan * E-mail: w.shin@aist.go.jp

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One of the simple ways is to make predictions based on biogas, just as in the old days when the physicians made decisions by smelling the odor from patients. Figure 1 is a summary of the sensing methods and the relationships between the physical conditions or diseases and various biogases. A representative example is alcohol detection in the breath, and alcohol breath checkers are commercially available. However, drunkenness is caused by an external factor, and it is not an index of a human state. While, there are devices of urea breath test to find *Helicobacter pylori*, and devices used by asthma patients to measure nitric oxide.

Recently, hydrogen is in focus. Health care supplement business is spreading based on the claim that drinking hydrogen water will make a person vigorous. This keen interest in hydrogen was initiated by a paper published by the Nippon Medical School reporting that cytotoxic oxygen radical, which is considered harmful in high concentration, is reduced by hydrogen.[3] Humans do not produce hydrogen, but hydrogen is produced by bacteria in the intestinal environment. When food is not absorbed in the small intestine, it goes directly into the large intestine where the bacteria grow in large amounts and produce abundant gas.[4]

This means that hydrogen may be produced or not produced in abundance depending on whether the food is agreeable with one's stomach (digestive system). There is a demand for measuring hydrogen, and a hydrogen detector is being developed for this purpose. We are working on monitoring mainly the intestinal environment, or hydrogen, methane, and carbon monoxide. The majority of the Japanese exhale hydrogen only, while it is said that other Asians and Europeans exhale hydrogen and methane.

In digestion and metabolism, acetone and isoprene are gaining attention as metabolic gases. In the past, it was believed that breath acetone reflected the real time glucose level in blood, and much R&D was conducted, but it was found that there was no correlation between acetone and the glucose level. Currently, acetone has been applied to diet control. For example, people worried about body shape have the desire to burn the fat off efficiently but wish to eat as much cake as the fat that was burnt off, and the "harapeko (hungry)" sensor has been developed to measure breath or acetone of the skin responding to this desire.[5] Acetone is an index for burning fat and isoprene is said to be the index for using energy produced by metabolizing the muscles, and the detection of such metabolic gas is in extremely high demand. Research is being conducted actively to clarify the relationships between various diseases and breath components, such as monitoring the liver function using ammonia, evaluation of cholesterol metabolism by isoprene, and monitoring the blood caroboxy hemoglobin by carbon monoxide.

The periodontal disease detector using the composite analysis of breath odor components is already on the market. The measurement of halitosis (bad breath) and the measurement device are used by dentists. The main cause of halitosis is methyl mercaptan that is produced by periodontitis.[6] Sulfur biogas such as methyl mercaptan is also reported to be a marker for colon cancer or liver disease, and the demand for the measurement for this purpose can be expected in the future. Since the dentists can directly see inside the patient's

Category	Chemical formula	Name of gas	Relation to physical condition (literature)	Sensing method
Reducing	H_2	Hydrogen	Abnormality of intestinal anaerobes	Semiconductor (ppm)
	CH_4	Methane	Abnormality of intestinal anaerobes	
	CO	Carbon monoxide	Smoking, oxidation stress	El-Chem(ppm)
	C_2H_5OH	Ethanol	Drinking	Semiconductor (ppm)
	CH_3COCH_3	Acetone	Diabetes, obesity, dieting	Semiconductor (ppm)
	H_2O_2	Hydrogen peroxide	Smoking	
	C_5H_8	Isoprene	Cholesterol synthesis intermediates	
Sulfur	H_2S	Hydrogen sulfide	Periodontitis	GC/MS(ppb)
	CH_3SH	Methyl mercaptan	Periodontitis, liver disease, colon cancer	GC/MS(ppb)
Amine	NH_3	Ammonia	Hepatitis, *H. Pylori* test	Semiconductor (ppm)
VOC	$C_9H_{18}O$	Nonanal	Lung cancer	GC/MS(ppb)
		Benzene	Lung cancer	

High precision and high response
Hydrogen detection without effect of humidity
Same response to all gases

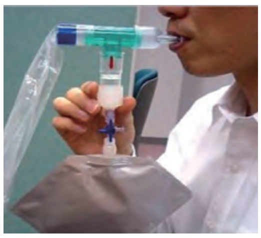

Fig. 1 Relationship between biogas types and physical conditions or diseases. The sensing methods are included.

mouth, the presence of periodontitis can be determined immediately. However, since many people are conscious of halitosis, there is a demand for halitosis detectors as patients are more satisfied if they can see the decrease of halitosis in gas concentration, before and after the treatment of periodontitis.

Lung cancer is the primary concern in our society, as it is the top cause of death by disease in Japan. The background of high mortality of lung cancer is because it is often too late when lung cancer is diagnosed at the hospital and the patient is notified. If the sign of lung cancer can be detected early, it can be treated by surgery, but there is no good measurement method for early diagnosis. It is hard to find by chest x-rays, and diagnosis is given after sputum analysis and extensive examination with CT. While the technology of breath analysis is a long way from being realized, whenever we see that lung cancer may be detected by smell in the news, we feel that there is high expectation for such technology. In fact, aldehyde VOC is considered to be a marker for lung cancer and particularly there are many studies on nonanal gas.[7] Nonanal is suspected to be related not only to lung cancer but also to other types of cancer, and measurements are made using high-precision analyzers. Nonanal is also said to be the source of body odor of the elderly, but its detection is quite difficult with an ordinary semiconductor sensor due to its high molecular mass.

3 Synthesiological elements in the gas sensor development

3.1 Elemental technologies necessary for breath analysis

At present, it is rare that a patient's biogas is collected, analyzed in the pathology lab, and used for diagnosis in the clinics. However, the number of cases where breath and other gases are analyzed for research are increasing. This new trend is due to the fact that the performance of gas analyzers, as exemplified by the gas chromatography mass spectrometer (GC-MS) that is used most frequently in medical institutions, has greatly improved in terms of speed and accuracy.

As shown in Fig. 2, the general flow of breath analysis is to separate the gas species with GC and to measure the gas concentration with the MS. In some cases, flame ionization detector (FID) that is an easier device to handle may be used. However, for these devices, helium must be used as flow gas, facility may be large, or operators may be necessary and a physician cannot conduct the analysis by him/herself, and we still do not have an environment where the measurement can be done easily. As the demands for the analyses of biogas and environmental gas increase, many gas detector products are being developed using semiconductor sensors and GC to meet these demands. We have developed a similar semiconductor sensor for lung cancer analysis, and the differences and characteristics of ours will be discussed later.

For the wide use of gas analysis, it is necessary that such an analyzer be used easily and readily. In this research, a goal was to realize a breath gas detection system with high performance and accuracy at a level where medical diagnosis is possible, by providing sufficient sensitivity and gas selectivity to a gas sensor element, without the complex pretreatment system. In the simplest structure, as shown in the red dashed line in Fig. 2, the measurement is made directly from the breath without passing through the gas separation mechanism, and a sensor technology that allows both gas selection and highly sensitive detection is necessary

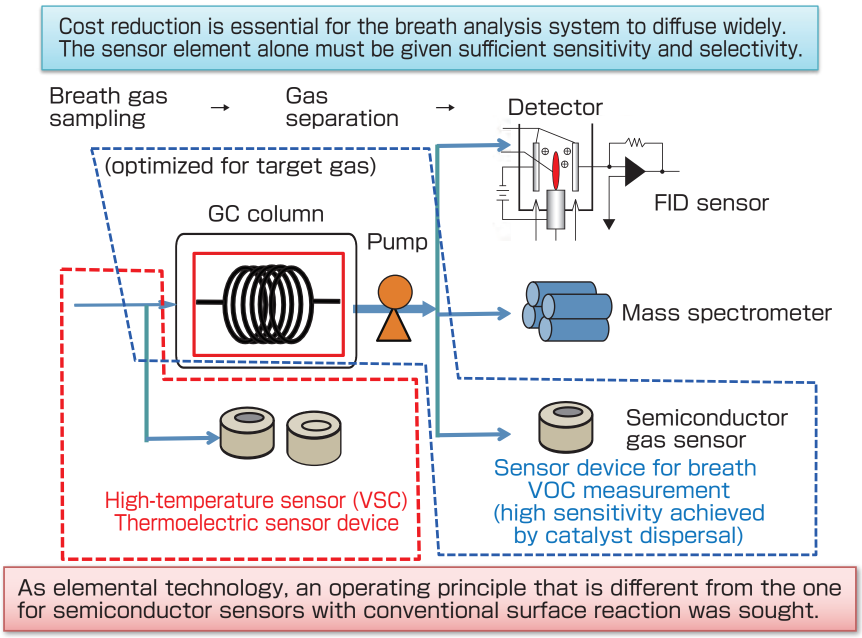

Fig. 2 General flow of the measurement method for breath analysis

for its realization. It was a challenge to create new technology that did not exist before, and it was an opportunity for us to review the weakness of the conventional technology.

3.2 Two main elemental technologies

Two simple breath measurement systems have been developed with the integration of high-temperature ceria sensor and the thermoelectric hydrogen sensor. These two sensor devices can measure the breath gas directly and the systems immediately display the amount of ppb or ppm in about a few tens of seconds.

Methyl mercaptan of sulfur biogas is the main component of halitosis caused by periodontitis. Recently, it has been reported that it may be also related to colon cancer or liver diseases. We succeeded in developing a new sensor that quickly measures volatile sulfur compound (VSC) gas in a highly humid environment. Figure 3 shows the comparison between the mechanism of the high-temperature ceria sensors to detect selectively methyl mercaptan and the principle of conventional surface reaction sensors. The semiconductor sensor that uses the conventional surface reaction is highly sensitive, but is easily affected by humidity and is slow in response. We sought a bulk response type device with different operating principles, and realized a method using the concentration of conductive carrier of the entire material as the gas detection function.

The high-temperature operating ceria sensor that we developed is a bulk response type,[8] and it detects gas by the variation in carrier electron concentration generated from the oxygen vacancy of the electron-conductive oxide. Since the diffusion rate of the oxygen vacancy produced by surface reaction $2Ce_{Ce}{}^{x} + O_{o}{}^{x} \rightarrow 2Ce_{Ce}' + V_{O}^{\cdot\cdot} + 1/2O_2$ is extremely quick, the change in carrier electron concentration involves the entire bulk, not just the surface. Therefore, it is necessary to raise the sensor temperature, and it is operated at a temperature of 500 ºC or higher. This operating temperature is an important point in the application as a VSC sensor. Since gas species other than VSC undergo oxidation near ceria of the gas sensor thick film due to high temperature, the contribution of ceria to carrier density variation is reduced. Therefore, it was possible for the high-temperature operating ceria sensor to achieve both the selective detection and high sensitivity at ppb level against the VSC gas. The response is fast due to high temperature operation, and this was employed instead of the old sensor. The “II” was added to the product name for differentiation.[9]

For the breath hydrogen which is the index of the intestinal environment, the catalyst of the thermoelectric is maintained at as low as 100 ºC. In the thermoelectric hydrogen sensor, the temperature of the catalyst is kept low so that the combustion catalyst burns hydrogen only. For this hydrogen sensor, its operating principle of converting combustion heat into electric signals was new, and we could conduct the development of new applications such as breath hydrogen measurement with hydrogen concentration of 0~200 ppm at high humidity. This technology does not operate on the principle of resistive semiconductor sensors, but is an efficient method using the small heat of hydrogen combustion and the thermoelectric conversion principle, which can eliminate the effect of humidity or other flammable gases, and therefore, highly sensitive gas detection became possible.[10] The measurement is quick, in one minute per sample since retention time for the separation of gases is unnecessary. We developed a prototype detector that allows simple and easy operation by medical personnel on site by adding functions such as automatic calibration, automatic aspiration, and measurement.

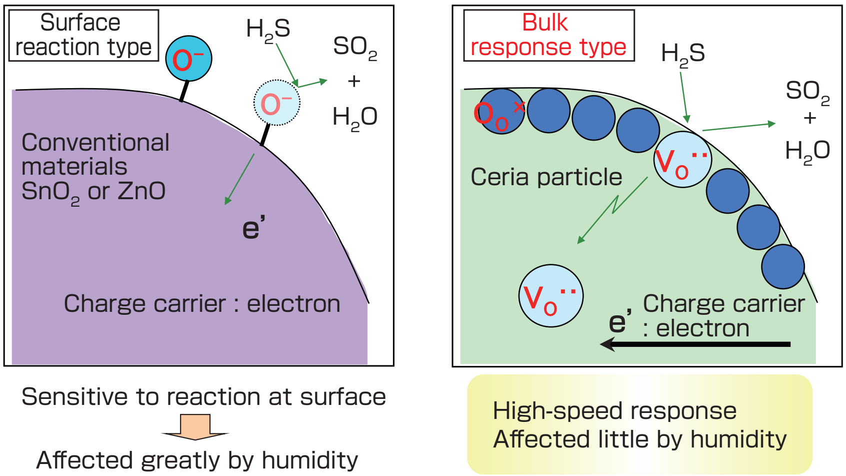

Fig. 3 Even for the same resistive type sensors using oxide semiconductors, the surface reaction and bulk response types have fundamentally different mechanisms, and their reliabilities differ in practice. ($O_o{}^x$ and $V_o^{\cdot\cdot}$ indicate the oxygen in crystals and the oxygen vacancies from which oxygen have escaped.)

3.3 The third technology was system integration of elements

The third gas sensor technology was the sensor for odor (VOC) related to diseases. Commonly, a very expensive and difficult-to-operate analyzer was used to investigate the relationships between the aldehyde VOC and lung cancer or other cancers. However, if the focus is on some specific VOCs, it is not necessary to measure all gas species, and only a few VOCs should be measured. In this case, the issue is which performance should the sensor have. First, the concentration of the odor substance VOC is at the ppb level, and it is necessary for the sensor to have high sensitivity that can measure very low gas concentration. The breath contains a high concentration level of hydrogen, and the sensor must have selectivity against humidity and other various gases. It is extremely difficult to achieve both high sensitivity and high selectivity simultaneously.

Therefore, a system that combines a sensor with GC to separate the gases, as shown in a blue dashed line in Fig. 2, was considered. In the case of a system consisting of simple GC and a sensor, the gas separation mechanism is added by combining with GC, so the sensor must be able to measure all gas species evenly, rather than measure any specific gas selectively. To increase the breath VOC sensor sensitivity, we tried to demonstrate an extremely sensitive gas detector using thick film coating that uses dispersion technology of nanoparticles carrying much catalysts.

To enhance response, we attempted to achieve high sensor sensitivity by developing a dispersion paste of the sensor material and by investigating the relationship between film thickness and sensor response. To fabricate a homogenous paste of sensor material of SnO_2 fine particles carrying Pt, Pd and Au, a dispersion process using a vehicle 'organic dispersion agent' containing ethyl cellulose was developed. By applying and sintering this paste on a substrate, we formed a film with homogenous thickness and pores that allowed diffusion of gas. By optimizing the film thickness for sensor response, the detection of 55 ppb nonanal, a candidate for a lung cancer marker, was achieved.[11] Utilizing this semiconductor sensor and GC separation technology, the ppb level VOC detection in breath was attained.

4 Research result

4.1 Element and boundary condition

Using the halitosis sensor described above, a new detector has been released on the market by greatly improving the response performance of the old model. The hydrogen sensor allows simple breath hydrogen measurement, and has been used in the breath measurements for mass examinations at medical institutions. The breath VOC sensor is being developed as a prototype system for early detection of lung cancer. However, the main point of detector development in this paper is a strategy how to achieve a practical level rather than technical details of each sensor. Figure 4 shows the value or benefit of the product for the user, which are the boundary conditions of the technological component, and the integration of components that were developed for these conditions is organized.

For the halitosis sensor, the old detector using the sensor element with slow response speed requires 45 seconds for sampling and measuring the target gas. It feel like a long time if one actually experiences it. For gas sampling, one

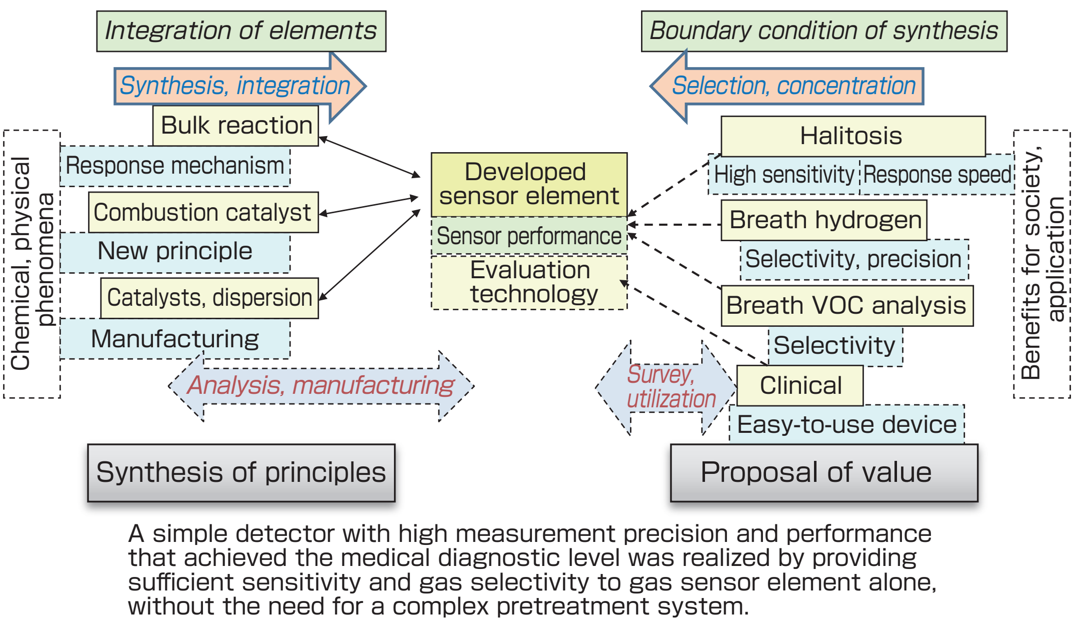

Fig. 4 Correlation diagram of the synthesiological elements in sensor development and the boundary conditions for synthesizing the elements

must hold the tube (mouthpiece) in the mouth and shut the mouth tightly and breathe through the nose, but it is hard to maintain this position for 45 seconds. Without concentration, the mouth eases open or one may start breathing through the mouth. People who experience this test strongly feel the need to shorten the sensor response time. It must be noted that the response speed of the detector and of the sensor are not the same. It is necessary to shorten the response time of the sensor element by enough margin compared to the product on the market.

For the hydrogen sensor, breath hydrogen detectors with the hydrogen sensors were used for quick, easy, and highly precise hydrogen gas concentration measurements at the Aichi Kenko Plaza. Detailed interviews were done of the subjects to clarify the relationship between hydrogen gas concentration and lifestyle and diet, or disease.[12] Measurements of hydrogen concentration was taken from breath gas of about 200 subjects, and the following results were obtained: 1) correlations were found between breath hydrogen gas concentration and age, exercise, intake of milk, hyperlipidemia, and anemia; and 2) hydrogen gas concentration in the breath was apparently high in the group positive for exercise, milk intake, hyperlipidemia, and anemia. Since sufficient number of breath hydrogen concentration measurements has not been collected, further measurements are ongoing. If measurements of over 600 subjects could be obtained, it will be considered as the average value of breath hydrogen concentration for the Japanese (the average breath hydrogen value has not been reported anywhere in the world).

For the lung cancer sensor or the breath VOC detector, the breath before and after surgery of about 200 lung cancer patients at Aichi Cancer Center was analyzed by GC-MS. The breath gas markers were investigated and applied as patents with the system for detecting them. The invention involved the combination of several gas components rather than using just one gas species such as nonanal.

The system combined the GC and the sensor. The sensor should respond equally to various gas species separated by GC and it must be easy to calibrate. The developed system should be user-, physician-friendly, that is, simple enough to be used in the clinical field, and thus contribute to our society.

4.2 Scenario for product realization

In order to release something new through R&D, the synthesiological technological element and the social demand that serves as the boundary condition for their synthesis must be matched. Up to now, the flow was explained in the following four steps.[13] However, for the health care and medical devices, further considerations are necessary.

(1) Idea: discover through new ideation or uncover demands
(2) Fusion of knowledge: specify ideas and demands by quantative experiments
(3) Synthesis: set necessary properties for application goals and run the development
(4) Finalization: summarize the research results and prepare for next research

Substantial resources and large effort are necessary for the R&D of medical devices, and more time and money are needed to confirm the clinical efficacy. However, the actual market is not big enough to pay back such investment. There is extremely high risk for R&D and product realization, and sharp business decisions are necessary. To reduce these risks from the engineer's perspective, it is necessary to develop platform technology.

Taking a bakery as an example, the same technology and machine are used to bake various types of bread. For medical devices of gas sensors, it is necessary to have a solid foundation of micro-heaters, integration technology to add catalysts, ceramic technology that allows catalysts to be applied firmly and well dispersed on the devices, and a gas measurement and evaluation system where the gas can be passed through to evaluate the response. The number of university labs working on the R&D of gas sensor has reduced, and we are the only lab in AIST engaging in this research. It is important for us to keep a strong foothold of this technology.

The final issue in the realization of the device is the collaboration of medicine and engineering. Figure 5 shows the three sensors in three detectors discussed in this paper. The halitosis sensor on the left has been already commercialized. The hydrogen sensor in the middle is scheduled for commercialization in 2016. With the VOC detector on the right, steps toward practical use are on-going, such as verification tests in clinical settings. For the breath hydrogen sensor, the breath of about 600 volunteers have been measured at the Aichi Kenko Plaza since 2014, and the clinical research to study the correlation between the hydrogen concentration and health conditions was conducted. Without this study, the planning of commercialization would have been difficult. Without validation of use in medical institutions, the measurement device will be nothing more than a research facility or a toy.

As a future issue, a method for sampling breath gas must be considered. As shown in Fig. 5, gas sampling methods differ according to the biogas species or disease. In the case of hydrogen, the subjects are instructed to inhale, hold the breath for 2 or 3 seconds, exhale for 1 or 2 seconds, and then the end-tidal breath is collected. For halitosis, on the contrary, the subject is asked to breathe through the nose and the gas in the mouth is suctioned with a pump. In the case of nitric oxide measurement used by asthma patients, the subject blows on the device at a certain flow rate. Gas samplings from the skin or fecal matter are complicated and there is no clearly established method. From the viewpoint of the research group trying to develop the sensors, it seems that there is no specific research issue, but we believe we will gain new ideas and discoveries in the process of completing this project.

5 Discussion: What follows the scenario

5.1 We must actively propose how the device should be used

As it was mentioned in the scenario for practical application, even if a simple detector is made, the quantification of the relationship between gas concentration and health index or disease is essential for the device to be used in medical practice. Although collaboration with health care and medical fields is important for device application, there is a barrier between the different fields. When excellent technology is obtained through R&D at AIST, we wish to reach the final goal of commercialization. However, in the case of health care and medical businesses, it is difficult to move on to practical use regardless of whether the company which does the development is a small, medium, or major enterprise. Particularly in Japan, we have very little experience in commercialization and do not understand the value chain.

To change this situation, we have founded an AIST consortium of the sensing technology for health care application. It is composed of industrial members of various manufacturing companies such as of materials, measuring device development, medical standard gas, gas sensor, and medical devices, as well as academic members from universities, public institutions, and medical institutes. Along with the industrial members, we are seeking the direction of how we should associate with the medical people in clinics, what kind of demands there are, and what will be necessary in the future. A series of seminars held by the consortium are used as a place to seek the possibilities of collaboration with life science researchers of AIST as well as medicine-engineering collaboration between the different organizations. I hope interesting projects will be born from this.

In the development of new technology, a challenging proposal is important. I have asked the physicians in medical schools, who are members of the joint research, about the case studies of hydrogen gas measurement and the relationship with disease. However, after several disussions, I ended up researching medical papers and creating a summary. It is a very different culture compared to the USA. The medical partners are waiting for the proposal from engineers.

It is expected that a smart phone equipped with electronic nose that smells the air contamination or odor will be marketed in about two or three years. In the future, the medical device will become available as a general home electric appliance or a mobile device. We must accelerate the development for downsizing and achieving higher precision so such devices can be used for health monitoring to find early signs of disease and health management.

6 Conclusion

In the human gas, breath, monitoring technology from which human bioinformation can be obtained non-invasively, decreasing the cost of the system is essential for the spread of the breath analyzing system. In this research, we developed a sensor device and a detector that aimed at a high-performance breath gas detector at the level medical

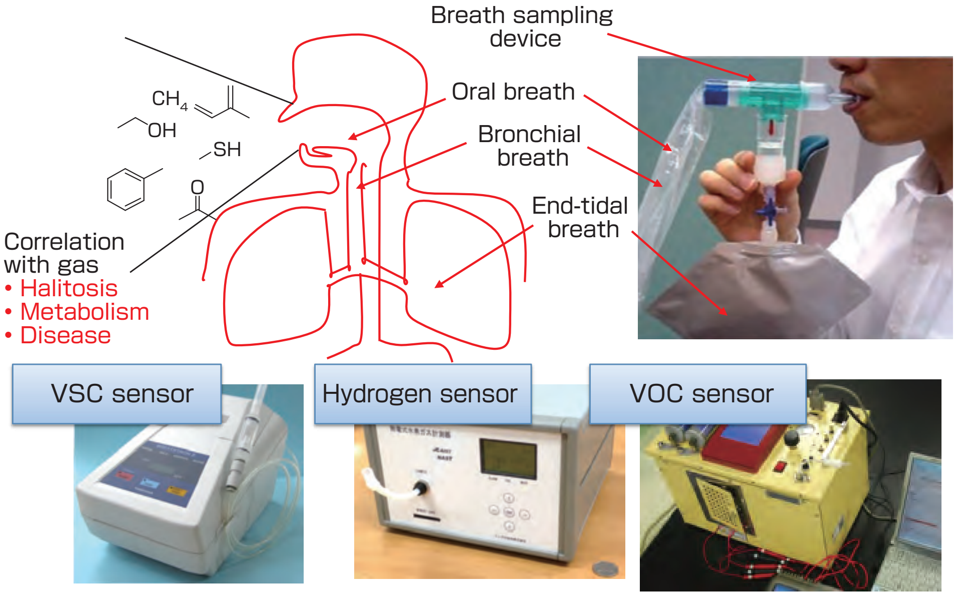

Fig. 5 Summary of the correlation of human biogas and sensor technology used in breath measurement

diagnosis can be made, by providing sufficient sensitivity and gas selectivity to the gas sensor element that does not require a complex pretreatment system. To realize this device, the combination of nanoparticulation technology, paste technology, and small high-temperature heater technology that have been developed in the basic research was important. However, commercialization is difficult with the technologies only, and we must be active in making proposals on what to do to make the device usable for the physicians who will be actually using the detector in clinical application, or what we can know from the breath gas.

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Authors

Woosuck SHIN

Completed the doctor’s program at the Department of Applied Chemistry, Graduate School of Engineering, Nagoya University in 1988. Joined the National Industrial Research Institute of Nagoya, Agency for Industrial Science and Technology in 1998. AIST in 2001; Associate Professor (concurrent), Department of Frontier Materials, Graduate School of Engineering, Nagoya Institute of Technology since 2008; and currently, Group Leader, Electroceramic Group, Inorganic Functional Materials Research Institute, AIST. Entrepreneur of sensor technology by starting up NAST Co., Ltd., a venture company with technological transfer from AIST. Specialties are developments of hydrogen sensor, thermoelectric conversion material, thermoelectric property measurement, and microdevice processing. In this paper, worked on the thermoelectric hydrogen sensor device as well as the overview of overall concept.

Toshio ITOH

Completed the doctor’s program at the Graduate School of Engineering, Nagoya University in 2005. Joined AIST in 2005. Currently, Senior Researcher, Electroceramic Group, Inorganic Functional Materials Research Institute, AIST. Engages in the development of VOC sensor and semiconductor hybrid materials. Works on international standardization projects such as ISO. In this paper, was in charge of the development of VOC sensor and the analysis of response mechanism of VSC sensor by ceria nanoparticles.

Noriya IZU

Completed the master’s course at the Department of Materials Science and Processing, Graduate School of Engineering, Osaka University in 1997. Joined AIST in 2001. Senior Researcher, Tailored Liquid Integration Group, Inorganic Functional Materials Research Institute, AIST. Specialties are gas sensor, crystal chemistry, and nanoparticles. Engages in the development of core shell nanoparticles and

its application technology, and the development of high-temperature operating gas sensor. In this paper, was in charge of the development of halitosis sensor (VSC sensor), and specifically developed the ceria nanoparticle that is the material of the sensor.

Discussions with Reviewers

1 Overall

Comment (Tetsuhiko Kobayashi, AIST)

This paper describes the technology to provide inexpensive health monitoring and medical diagnosis by analyzing the gas components of breath and other gases using the gas sensor. It is not only about the development of the gas analysis system, but it also verifies the usefulness of the developed technology through collaboration with health care and medical institutions. The development is done with strong awareness of social demand, and I believe it is suitable for publication in *Synthesiology*.

Comment (Katsuhiko Kadoguchi , AIST)

Development of medical and measuring devices to determine the health condition and presence of disease easily without affecting the human body is a topic that precisely grasps the demand in the globally-expanding market of the health care and medical treatment. The process of improving the authors' original breath sensor and analytical measures and integrating the elemental techonologies systematically into a product, with the cooperation of medical institutions and volunteers, is worth being depicted synthesiologically.

2 Development method and approach in the medical field (foreign field)

Question (Katsuhiko Kadoguchi)

The present research was carried out with the help of a large number of samples obtained through the cooperation of a medical institution and subjects (patients). On the other hand, in order to ensure the widespread and easily available use of the device developed in this research in the future, it would be most ideal for the researcher to be on site when the physician treats the patients, to observe the work, to understand the instructions and guidance given to the patients, to ethnographically pick up the diagnostic needs that even the physicians themselves may not be aware of, and then to conduct the research with the obtained information taken into consideration. However, this is almost impossible from the viewpoint of the patient's privacy protection, and I assume the difficulty of technological development lies there. I would suppose that understanding the demands through the activity of the consortium tends to be indirect, but how is it actually?

Answer (Woosuck Shin)

In device development, it is important for the researcher to be in company with the physician sampling the patient's breath. In fact, we have communicated to the physicians the proper instructions to give to the patients during breath sampling. The breath sampling of lung cancer patients is done in the examination room, and it is difficult to be there actually. In the case of breath measurement at regular medical checkups for groups, we directly instruct the breath sampling method at the venue. As you indicate, I think it is important to ethnographically collect the needs that the medical practitioners may not be aware of. If we engage in any development by medicine-engineering collaboration in the future, I hope to include this in the research plan. Also, it is impossible for an engineering research group to be in charge. Therefore, collaboration with people within AIST or external organizations is mandatory, and how to create a comprehensive, organic organization will be the point in raising the quality of the R&D.

3 Prospect and future development

Comment (Katsuhiko Kadoguchi)

From the viewpoint of health care, daily self-diagnosis at hospitals or at home can be assumed. In such cases, the device users are not physicians nor nurses but ordinary people. Therefore, I think it is also possible to take an approach of asking cooperative subjects for making a tentative use of the prototype for the development. I think the current technological development targets the use at the site of medical practice. Please give some comments on how the authors intend to correspond to these widespread practical needs in the future, eg. rearrangement of devices for specialist use to those for ordinary use, changing the purpose of the application from treatment of disease to management of pre-disease, etc.

Answer (Woosuck Shin)

I addressed the point that you indicated in the last part of discussion along with the demands accompanying the evolution in recent mobile devices.

4 Detection of abnormality

Question (Katsuhiko Kadoguchi)

How do you treat the individual differences in applying this technology (such as man/woman, adult/child, or height/weight variations, and others)? Also, for an individual, won't the breath component be affected by physical conditions, an empty or full stomach, being fully rested or exhausted, for example?

Answer (Woosuck Shin)

For the medical questions like the ones you asked, pertaining to breath hydrogen gas, an experiment was done with 426 volunteers in FY 2014.

The average value of breath hydrogen was 20.2 ± 21.1 ppm, and there was no sexual difference. The standard range of breath hydrogen (95 % confidence interval of breath hydrogen measurement value) was thought to be 0~79.4 ppm. For breath hydrogen, weak positive correlation was seen in age, and high values were measured in elderly females. For the relationship between breath hydrogen and lifestyle, correlations were seen for items of milk intake, defecation, and exercise. This article has been submitted to *Antei Doitai to Seitai Gas* (Japan Society for Medical Application of Stable Isotope and Biogas) (November 2015).

5 Sensor technology

Comment (Tetsuhiko Kobayashi)

I think the understanding will deepen for the reader who may be a sensor engineer, if you add a little more detailed technological explanation of the sensor. For example, I think you should add the following: 1) the reason why there is selectivity in the VSC sensor, 2) the reason why you can achieve high sensitivity even in the bulk response type VSC sensor, and 3) the merits of using thermoelectric conversion rather than conventional catalyst combustion in the thermoelectric hydrogen sensor.

Answer (Woosuck Shin)

I added the technological explanations of the gas sensors in this paper.

6 Collaboration of different research fields within AIST

Question (Tetsuhiko Kobayashi)

You describe the medicine-engineering collaboration with the external organization, but what do you think about the collaboration between the life science researchers and material/device researchers within AIST?

Answer (Woosuck Shin)

Although we have not reached concrete collaboration, we are seeking collaboration by inviting the life science researchers of AIST to the consortium lectures. I hope some interesting "chemical reaction" will occur soon.