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Smart sensor technology from Ulm can do more than just breath analysis

Detecting disease-specific molecules in human breath is technically feasible, but time-consuming and rather costly. "µbreath" could soon change this. The breath gas analysis device has all the necessary requirements for commercial success in the healthcare sector: it is compact, accurate, highly sensitive and fast. The chemist who developed µbreath, Prof. Boris Mizaikoff from Ulm University, and his partners are hoping to start producing the first prototypes for clinical and industrial application by the end of the year.

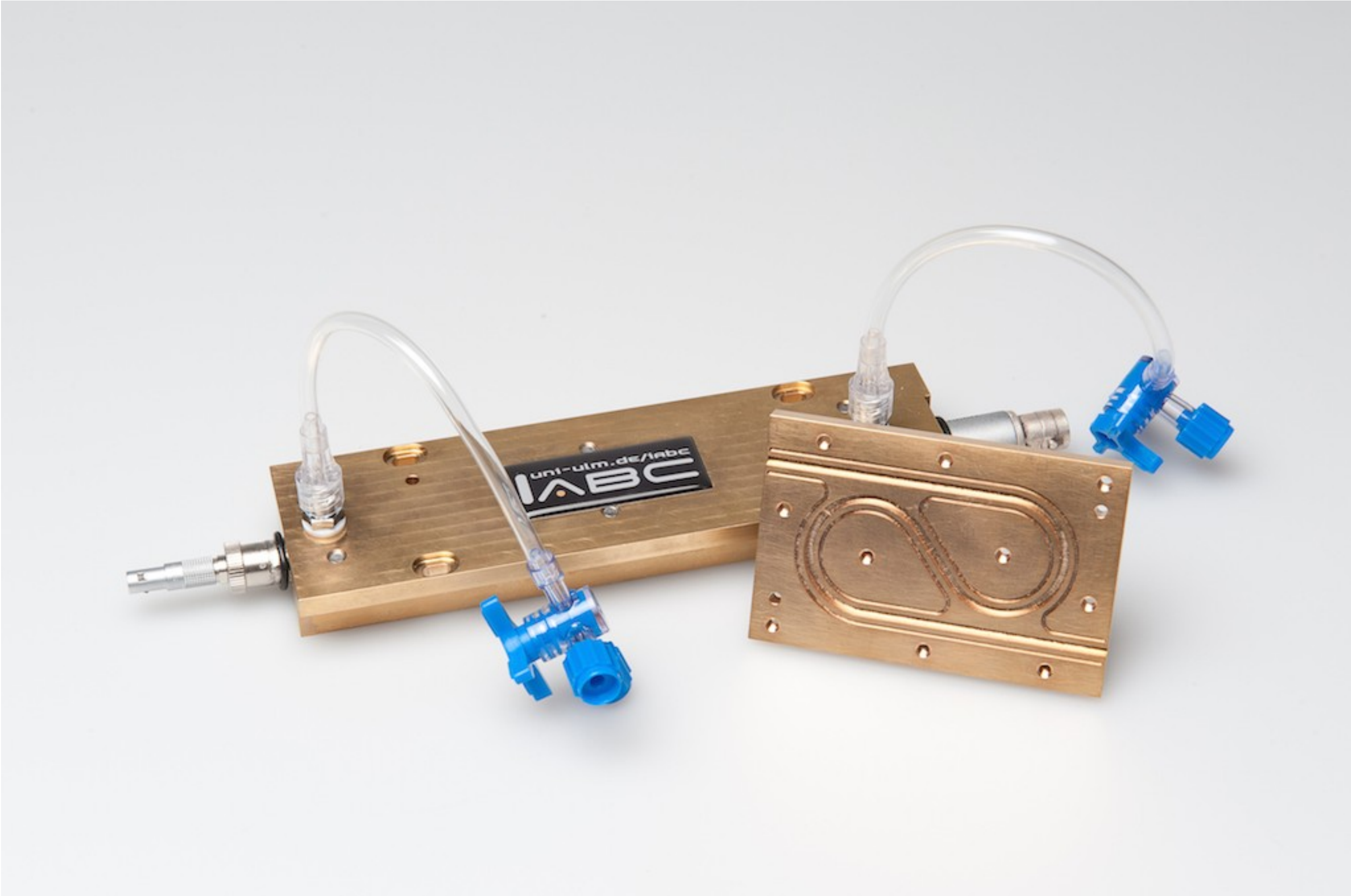
The system, which recently received a British Royal Society of Chemistry award for an excellent application-oriented device, consists of an infrared (IR) sensor involving a substrate-integrated hallow optical waveguide (1). The optical waveguide is extremely compact and easy to manufacture, and, according to Mizaikoff, the core of the device. The analysis of human breath is just one of the sensor's many areas of application. According to Mizaikoff, the hollow waveguide can be used “almost universally” with broadband spectrometers, narrowband laser light sources and all types of infrared sensor configurations.

µbreath determines biomarkers with an IR sensor

Infrared rays that enter the specially coated waveguide cavity are reflected on and transported along the waveguide wall. When gas (e.g. exhaled breath) is simultaneously pumped into the waveguide with the IR light, the IR light triggers the vibration of molecules in the breath gas. Each molecule has a specific optical profile. The sensor’s detection unit measures the amount of IR light that causes the molecules to vibrate. Since similar molecules produce similar vibration patterns, statistical data analysis methods are used to calculate how much each molecule has contributed to the overall signal.

Breath gas analysis has existed for quite some time. However, it is quite a complex task given the large number of different molecules human breath can contain. Gas chromatographic and mass spectrometric methods can be used for this purpose, but are costly and time-consuming and thus a limited option for everyday medical practice. The objective is to detect molecules specific to a particular disease, so that conclusions can be drawn on the stage of a disease or treatment progress.

µbreath can be used to determine volatile organic compounds (VOC). About 40 disease-specific



The sensor was developed at the Institute of Analytical and Bioanalytical Chemistry. © Eberhardt/kiz

VOCs, i.e. biomarkers, are currently known and can be used to detect respiratory tract diseases, cystic fibrosis, breast cancer (2, 3) and diabetes. Detection is based on disease-related molecules eventually reaching the lungs where gas exchange takes place, i.e. oxygen is taken up and carbon dioxide passes out of the blood into the air in the lungs. VOCs are part of this gas exchange.

In addition to pathological causes, non-pathological degradation products of physiological and metabolic progresses also affect the molecular composition of breath gas. At the moment, the sensor that has been developed needs to be combined with another analytical method to exclude measurement errors. Mizaikoff says that this is why it is still difficult to link changes in biomarker concentrations to a particular disease. As things currently stand, Mizaikoff's IR-based sensor is just an "add-on". However, the method is likely to become faster and cheaper in the future.

Important milestone achieved with mouse model

µbreath can detect a large number of disease-specific volatile biomarkers in breath gas. In collaboration with Prof. Peter Radermacher from the University of Ulm Institute of Anaesthesiological Pathophysiology and Process Development, µbreath has achieved an important development milestone. Using experimental mice that were administered ^{13}C-labelled glucose, the researchers were able to demonstrate that the new IR sensor can continuously monitor liver function from the $^{13}CO_2$ content of the gas exhaled by the mice when the µbreath analyser was connected to a lung ventilator (4, 5). As mice are very small, the new breath gas sensor must be able to determine the concentration of biomarkers in breath gas rapidly and accurately from small amounts of samples.

The animal experiments have not yet reached the preclinical phase, but have advanced far enough that the University of Ulm’s ethics commission gave the go-ahead for the sensor to be included in a cooperative research centre focused on trauma research involving mice. As the sensor technology is non-invasive, it can always run in the background in the “mouse intensive care units”. The continuous monitoring of breath gas enables Mizaikoff and his team to rectify faults and optimise the sensor.

Prof. Boris Mizaikoff is director of the Institute of Analytical and Bioanalytical Chemistry. © private

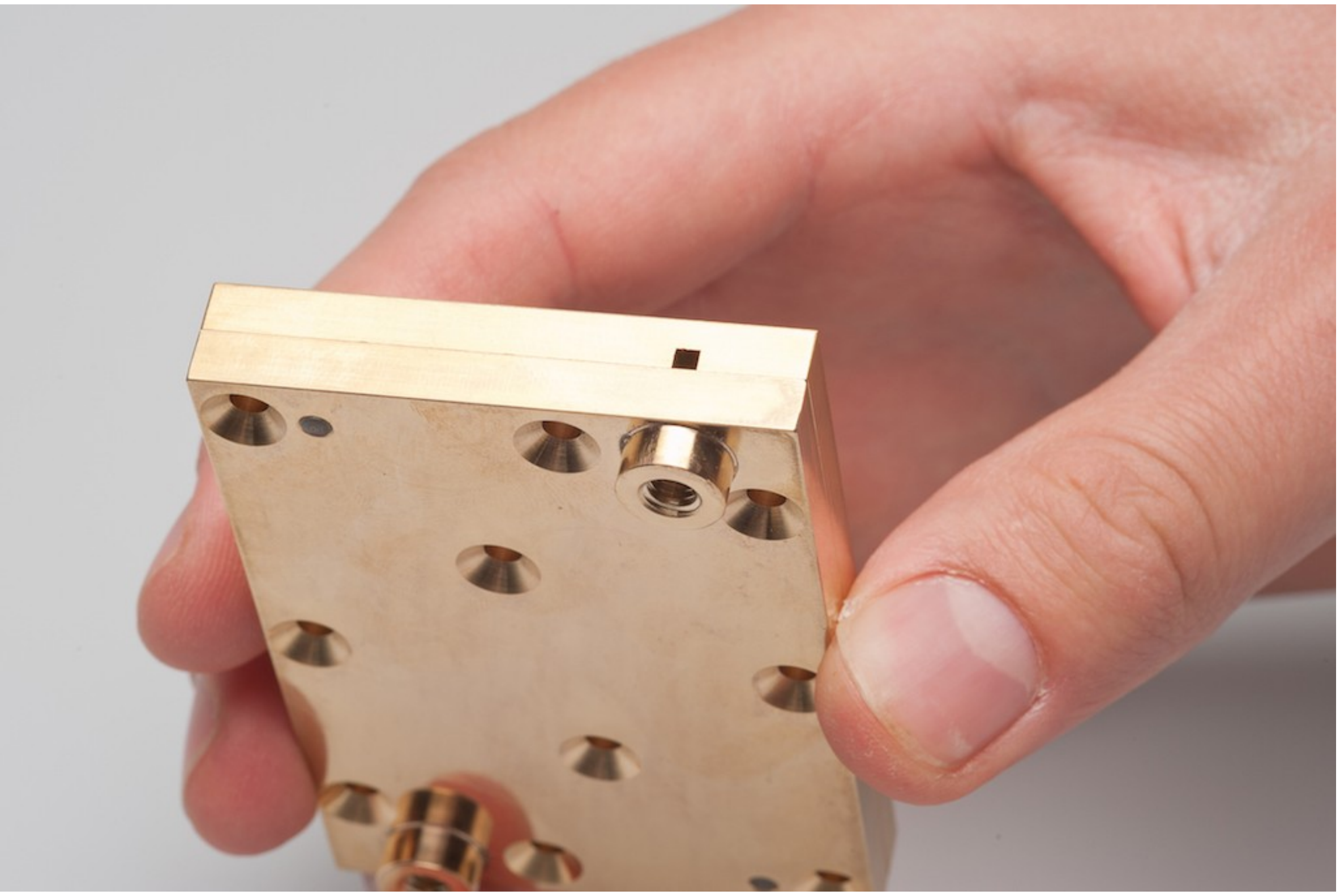
Prototypes will be ready sometime in 2017

The goal is to develop a device for non-invasive continuous analysis of breath gas. For this purpose, IR sensors will have to be integrated into ventilators, so that samples will not need to be either withdrawn from the patient or collected over a longer period of time. Other technologies (e.g. proton-transfer-reaction mass spectrometry (PTR-MS)) for monitoring volatile organic compounds are already on the market. PTR-MS is highly selective and highly sensitive, but also time-consuming and rather expensive. It will soon be seen whether existing sensor systems can be adapted to current needs or potentially replaced with the Ulm researchers’ IR-based breath gas sensor.

An EU project coordinated by Mizaikoff called Advanced Photonic Sensor Materials (APOSEMA), which runs until the end of 2017, is aimed at turning the device into a commercial commodity. APOSEMA brings universities and companies together to develop breath analysis prototypes using two complementary optical measuring methods (Mizaikoff's infrared sensor technology and fluorescence sensors). The chemist from Ulm hopes to have developed a prototype suitable for preclinical and preindustrial applications by the end of next year.

However, before the method can be placed on the market, the researchers will have to overcome a significant obstacle in the form of clinical trials that requires examining thousands of patients and entering the data obtained into a statistical database. The main problem is that breath gas differs from patient to patient, and in one and the same person, depending on when the samples are taken. The concentration of volatile organic compounds in breath gas depends on many factors, including diet, physical exercise, smoking and other habits. Disease-specific biomarker fingerprints can therefore only be determined from a large number of patients. Currently, the extent of variability, rather than the developmental stage of the technology, is therefore the major limitation of the new method.

Current prototypes are good for three application areas



Detailed presentation of the Ulm researchers' sensor. IR rays enter the substrate-integrated hollow waveguide (iHWG) by way of the rectangular opening (top right), which can be closed. The device can thus be used as waveguide and miniaturised gas cuvette. Gas to be analysed (in this case breath) is applied by way of the cylindrical connections (in the photo below the waveguide channel and on the bottom left-hand side) to the iHWG and can be continuously fed into the iHWG. © Eberhardt/kiz

At present, Mizaikoff sees three possible applications for µbreath: The first is using the technology in mouse intensive care units, which would benefit basic clinical and pharmaceutical research, as all physiological studies and new therapy tests require small animal tests. The method's positive aspects (small volume, high sample throughput, short measurement times) make it particularly suitable for this type of application.

Second, the method also has the potential to be used for human diagnostics, which requires scaling up. However, for the time being, the researchers are only planning to use it for identifying a small number of specific molecules that are easily detected. This makes the method an excellent alternative to existing time-consuming measurement technologies. And finally, Boris Mizaikoff is hoping that laser technologies that operate in the medium infrared range will become cheaper. This new technology is just starting to become part of analytical devices, and is therefore still quite expensive: "We hope that breath gas diagnostics will become one of the first device groups that contribute to reducing the price of medium-range IR laser technologies and enable precise measurements in a large number of patients."

The pharmaceutical industry is also interested in the researchers' innovative method for its use in so-called compliance tests. If the degradation products of drugs could be marked with a readily diagnosable label (e.g. ^{13}C or deuterium), a breath gas test involving an IR sensor would easily reveal whether clinical trial volunteers had taken a drug under investigation or not.

References:

1. A. Wilk, J. C. Carter, M. Chrisp, A. M. Manuel, P. Mirkarimi, J. B. Alameda, B. Mizaikoff, Substrate-Integrated Hollow Waveguides: A New Level of Integration in Mid-Infrared Gas Sensing, Analytical Chemistry 85, 11205–11210 (2013). DOI: 10.1039/C6AN01130F

2. S. G. Patterson, C. W. Bayer, R. J. Hendry, N. Sellers, K. S. Lee, B. Vidakovic, B. Mizaikoff, S. G. A. Gabram-Mendola, Breath Analysis by Mass Spectrometry: A new Tool for Breast Cancer (BC) Detection?, American Surgeon 77, 747-751 (2011).

3. K. S. Lee, M. F. Abouelnasr, C. W. Bayer, S. G. A. Gabram, B. Mizaikoff, A. Rogatko, B. Vidakovic, Mining Exhaled Volatile Organic Compounds for Breast Cancer Detection, Advances and Applications in Statistical Sciences 2, 1-16 (2009).

4. F. Seichter, A. Wilk, K. Wörle, S.-S. Kim, J. A. Vogt, U. Wachter, P. Radermacher, B. Mizaikoff, Multivariate Determination of $^{13}CO_2/^{12}CO_2$ Ratios in Exhaled Mouse Breath with Mid-ilfrared Hollow Waveguide Gas Sensors, Analytical and Bioanalytical Chemistry 405, 4945-4951 (2013). DOI: 10.1007/s00216-013-6824-2

5. K. Wörle, F. Seichter, A. Wilk, C. Armacost, T. Day, M. Godejohann, U. Wachter, J. Vogt, P. Radermacher, B. Mizaikoff, Breath Analysis with Broadly Tunable Quantum Cascade Lasers, Analytical Chemistry 85, 2697-2702 (2013). DOI: 10.1021/ac3030703

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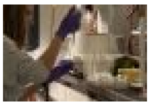

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