Editorial
The Future of Sensors and Instrumentation for Human Breath Analysis

THE previous three decades have provided a wealth of information on the identity of chemical compounds that are exhaled in human breath. Also during this time pioneering advances in the analytical assessment of chemical constituents and metabolites exhaled in human breath have helped to push forward the research field. While the physiological relevance and presence of many components in breath is not yet fully elucidated, it is evident that the composition of exhaled breath (EB) and breath condensate (EBC) provide a complex mirror image of the biochemical processes within the body, which may be correlated to the physiological status, disease progression, or therapeutic progress of a patient.

Much progress has been made on determining the identities of many volatile and nonvolatile breath biomarkers using mainly bench-top traditional analytical equipment. Although work still continues and is still urgently needed in the biomarker area, more recent engineering research efforts on this topic area have concentrated on advancing compact analytical techniques, in particular, novel sensor concepts enabling monitoring of known biomarker constituents in EB at appropriate concentration levels.

It is anticipated that in the coming decade a wealth of technologies will emerge as commercial products, making clinical breath analysis tests and personalized breath monitors a reality. However, success in these areas will largely depend on how well the adapted sensing concepts will meet a range of engineering, design, and analytical challenges that are specific to breath analyte detection. This Special Topics Issue provides an overview of currently explored sensing techniques and methods that are being researched and developed in academic and industrial settings, often at various technology maturity levels. The purpose of this Special Issue is to represent a sampling of research approaches from within this dynamic development area, and to also educate readers as to the demanding challenges of this emerging research area.

I. History of Breath Analysis

There is historical anecdotal evidence that both ancient Greek and Chinese medical texts mention the idea that unique breath smells can frequently be associated with physiological disorders or disease. It was not, however, until the modern era that researchers have approached the concept of breath analysis with scientific rigor to understand the problem. In the late 1790s, Lavoisier and Laplace renewed interest in studying respiration and breath constituents, and their work resulted in an increasing range of instrumentation for studying the function of the lungs and breath mechanics. This "renaissance" of medical diagnostics allowed for more functional physical lung diagnostics utilizing percussion and auscultation (e.g., listening with a stethoscope) later that decade. With the development of the first spirometer by John Hutchinson in the mid-1800s, instrumental techniques for studying breath and lung function established a continuous presence in clinical diagnostics. This has subsequently been followed by a wide variety of technological improvements enabling quantitative analysis of respiratory activity, as well as operation outside a traditional hospital environment.

Before the introduction of X-ray techniques, prevalent community-acquired respiratory diseases such as tuberculosis were increasingly diagnosed utilizing breath function tests largely based on spirometric techniques. During the 1900s, this simple test was then augmented with methods for the analysis of blood gas (work by Severinghaus), and lung and thoracic pressure (work by DuBois).

While physical measurement techniques have contributed early on to the diagnosis of diseases affecting or relating to the respiratory system, it was not until the early 1970s when Linus Pauling pioneered the analytical assessment of breath components by gas chromatographic (GC) analysis of exhaled air. He identified a wide range of blood-borne volatile organic compounds (VOCs) that were exhaled via the blood/air interface in the lungs [1]. Historically, the analysis of breath is probably among the oldest diagnostic techniques in medical practice utilizing disease-specific odors for assigning a physiological status to a patient. However, the molecular complexity of breath has rendered the quantitative analysis of breath constituents and metabolites present at nanomolar to picomolar (10^{-9} up to 10^{-12} mol/L) concentration levels an analytical challenge requiring modern instrumental techniques with adequate sensitivity and discriminatory power at a molecular level.

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II. The Complexity of Breath

Breath is composed of a highly complex molecular matrix, which contains both abundant chemical mixtures as well as trace constituents. The abundant compounds, such as nitrogen, oxygen, water, and carbon dioxide are prevalent at very high concentration levels, while the nearly 3500 volatile organic compounds exist at extremely low concentrations [2]. Related studies utilizing measures in the late 1980s and 1990s have estimated that approximately 50% of the identified VOCs are of endogenous origin with approximately 200 VOCs detected in average breath samples, although further instrumentation development in the last decade has lengthened the list of compounds that are reported in the literature.

From the biological side of the problem, a further complication of representative breath analysis for diagnostic purposes results from the within-patient variations and patient-to-patient variations. Across diverse studies, the most prevalent endogenous VOCs appear to be isoprene, which is a by-product of cholesterol synthesis during the conversion of mevalonate to mevanolate-5-pyrophosphate and isopentenyl pyrophosphate, and acetone, which is a metabolic component occurring in blood, urine, and human breath resulting from endogenous fatty acid oxidation. In addition, small molecules including, e.g., ammonia, methane, or carbon monoxide add to the complexity of the molecular breath signature, which also spans a wide range of molecular weights and dimensions next to the molecular functionality.

Clearly, constituent signatures characteristic for certain disease pathologies, therapeutic progress, or diagnosis have to be quantitatively discriminated against a molecularly complex and widely varying background composed of endogenous and exogenous compounds. Given these considerations, it appears unlikely that a single constituent may emerge as a sufficiently indicative diagnostic marker for a disease. Hence, it is fair to hypothesize that similar to gene regulation entire regulatory patterns of biomarkers in EB may have the potential serving as reliable diagnostic panels for diagnosing and tracing diseases and their progression.

As a consequence, the breath matrix and its variability present a significant analytical challenge that requires quantitatively tracing patterns of molecular signatures within entire biomarker panels with sufficient reliability providing a solid basis for clinical diagnosis. Therefore, the successful implementation of diagnostic devices analyzing EB requires that the characteristic changes of such biomarker patterns are unambiguously assigned to certain pathological or physiological conditions, and/or an associated therapeutic progress.

III. Challenges in Breath Analysis

Next to appropriate sampling techniques, the analysis of breath requires either separation, selective preconcentration, or direct analysis with analytical techniques providing appropriate molecular selectivity. Frequently, diagnostically relevant biomarker concentration levels of indicative markers are estimated to range from the (parts-per-billion) ppb down to parts-per-trillion (ppt) concentration levels, which are difficult to address with most conventional instrumental techniques. Hence, breath sample collection and/or preconcentration are frequently mandatory prior to analysis. However, EB is not inherently a homogeneous sample, and each breath consists of approximately 150 mL of air from the upper airways in an area with only gas exchange with blood (also known as the "dead volume") and approximately 350 mL of air from the blood-vessel rich tissue of the lungs (also known as the "alveaolar volume"). This second fraction of EB has extensive gas exchange with the blood, and by directly sampling this fraction into an analyzer or onto a preconcentrator, one can achieve superior analytical results.

With few exceptions such as alcohol tests, nitric oxide (NO) tests, and isotopic CO_2 analysis, the absence of clinical breath tests—and even less so personalized breath monitors—may be attributed to the absence of reliable, compact, and rapidly responding analytical devices and sensing techniques capable of addressing diagnostic biomarker panels within this complex matrix with sufficient molecular selectivity and sensitivity in real time. Currently, analysis of EB is predominantly performed by GC in combination with mass spectrometric (GC/MS) detection for separation and identification of trace constituents, which may be considered the gold standard in breath research [3]. Consequently, an increased adoption of breath analysis in routine clinical environments, and the future introduction of personalized breath monitors requires the accelerated development of advanced portable sensing system for EB analysis.

IV. Are Novel Sensors the Solution?

The evident progress in chemical sensor and biosensor technology during the recent decades has clearly established sensors as a supporting pillar of modern analytical chemistry and instrumental analysis next to the separation sciences, mass spectrometry, optical spectroscopies, and electrochemical analysis. Coincidentally, medical analysis and clinical diagnostics are increasingly adopting novel concepts developed in these areas for advancing analytical platforms used in the health sciences toward enhanced reliability and throughput. The most evident convergence between medical needs and technical solutions is currently observed in the area of personalized medicine, which demands for advanced miniaturized analyzers providing reliable diagnostic data outside a hospital environment.

An important prerequisite for personalized diagnostics is the noninvasive access to an excreted matrix of the human body that reflects a disease state or progression in molecular detail. In contrast to saliva and urine, EB appears to be the matrix with the highest diagnostic value, which is most conveniently

accessed, sampled, and analyzed within any environment. Hence, the combination of adequate sensor technology with EB as the diagnostic matrix appears a highly promising approach toward personalized noninvasive diagnostics for ubiquitously monitoring the physiological status.

One of the most challenging obstacles that the sensor community still needs to overcome, is the ability to measure multiple constituents with sensitivity at trace levels. This feature along with molecular selectivity while dealing with a frequently changing background signal makes breath sensor research a challenging task.

It is expected that first-generation commercial breath sensors may not be able to directly diagnose some prevalent diseases (e.g., pulmonary diseases such as ARDS, or various cancers), but they may assist in the identification whether a patient responds—or not—to treatment with certain drug regimes. For many disease pathologies, it is essential to discriminate responders from potential nonresponders for deciding on the correct treatment or medication strategy, and so this function alone will provide an advance to the medical community. Still, within reasonable timeframes in the upcoming decade, it seems possible that commercial breath tests for very specific diagnoses will become widely used. For all of these reasons, we hope that this Special Topics Issue will help to organize new and important work in the field and motivate others to enter this exciting research area.

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