

Miniaturized GC-MOS Platform for Exhaled Breath Analysis

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Summary: The research aimed to overcome a key barrier to the clinical translation of breath analysis – the limited selectivity of portable sensor systems for analyzing complex volatile mixtures. To address this challenge, a miniaturized platform integrating analyte preconcentration, rapid chromatographic separation, and metal oxide sensing was developed. Initial modelling and validation demonstrate the feasibility of this approach for future medical diagnostics and monitoring.

Keywords: breath analysis, miniaturized gas chromatography, MOS-detector, in silico GC modelling.

Introduction

Volatile organic compounds (VOCs) in exhaled breath are of endogenous and exogenous origin and are generated by normal physiological and pathophysiological processes. During pulmonary gas exchange, a fraction of these volatile molecules enters the alveolar air, thereby becoming detectable in exhaled breath and providing indirect information about biochemical changes occurring throughout the body [1]. Over the past two decades, research has focused on the potential of exhaled VOCs as biomarkers for a wide range of diseases, from respiratory conditions to systemic disorders such as liver disease and cancer. Exhaled breath analysis is non-invasive and has potential for early screening, triage, and disease monitoring. However, significant challenges in standardization, reproducibility, and clinical translation remain [2].

GC-MS remains the gold standard for VOC identification and quantification, offering high sensitivity and specificity. Recent advances have enabled real-time analysis and multi-analyte detection with SIFT-MS, PTR-MS, and IMS, as well as enhanced separation and identification of complex VOC mixtures at low concentration levels using GCxGC-TOF MS. However, their complexity and cost limit widespread clinical use, driving innovation toward more accessible technologies. Sensor-based technologies meet this need by enabling the detection and quantification of trace-level biomarkers, with metal oxide semiconductor (MOS) sensors being widely explored due to their low cost and ease of integration into portable point-of-care devices.

GC-MOS systems can overcome limitations of standalone MOS sensors, which often suffer from poor selectivity, drift, and interference from environmental factors. Combining MOS sensors

with GC enables the pre-separation of complex VOC mixtures in breath before detection, improving sensitivity, reducing cross-sensitivity, mitigating sensor-to-sensor variability, and increasing the informativeness of the VOC profile by reducing the influence of background profiles of healthy controls and other sources of interference. In addition, the integration of ML algorithms further refines VOC classification and compensates for sensor drift, making these systems more robust for clinical diagnostics.

Description of the new GC-MOS platform and results

The GC-MOS platform (Fig. 1) comprises three main functional modules corresponding to: (i) sampling and preconcentration, (ii) chromatographic separation, and (iii) detection. The system operates at atmospheric pressure and uses purified air as the carrier gas, cleaned upstream by a hydrocarbon/moisture trap (Agilent).

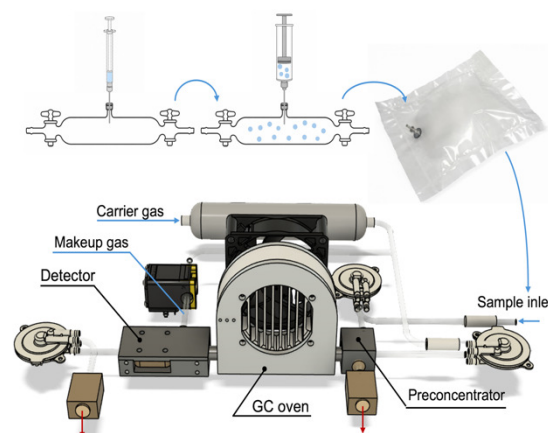


Fig. 1. Miniaturized GC-MOS Platform with synthetic breath mixture preparation for analytical validation

Gas handling is provided by a piezoelectric micropump system, while flow switching between sampling and analysis is controlled by solenoid valves integrated into the injector module. During sampling and preconcentration, the sample passes through a temperature-controlled injector containing an internal MOF preconcentrator coated with UiO-66-BDC [3], which also serves as a focusing trap. Analytes are trapped at 30°C and then desorbed at 220°C, generating a narrow injection plug that is transferred onto the separation column by the carrier-gas stream. In parallel, purified carrier gas continuously flows through the chromatographic line, while the injector-line flow is monitored by a flow sensor.

Chromatographic separation is carried out in a PID temperature-programmable circular oven, which can be operated either isothermally or under temperature ramps from 30 to 100°C with a thermal stability of $\pm 0.1^\circ\text{C}$. A stepwise flow program is applied to improve the separation of analytes with different volatilities. In addition, a make-up flow is introduced at the detector inlet to increase the total flow through the sensor chamber and minimize peak dispersion, while the outlet flow is monitored by another flow sensor.

After separation, the analytes enter a PID-controlled MOS detector chamber (ca. 100 μL dead volume, PEEK; see Fig. 2) equipped with two ENS160 (ScioSense) and two SGP43 sensors (Sensirion). Temperature modulation is applied independently to each sensor hotplate. In addition, a humidity sensor (SHT4x, Sensirion) continuously monitors the carrier-gas relative humidity (RH). The RH signal is used as an input for a compensation algorithm, improving the stability and comparability of the sensor responses.

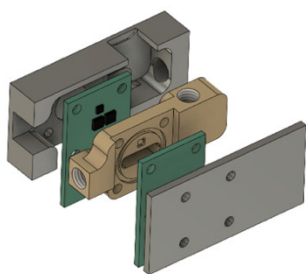


Fig. 2. MOS sensor chamber

As a starting point for developing an analytical method for the miniaturized GC-MOS platform, an *in silico* chromatographic modelling tool was developed for the prediction and optimization of rapid GC separations. Stationary phases covering a broad polarity range were compared, including Rtx-1 (non-polar dimethyl polysiloxane), Rxi-624Sil MS (mid-polar 6% cyanopropyl/phenyl, 94% polydimethylsiloxane), and Stabilwax (polar polyethylene glycol phase). The tool was used to predict the retention behavior of

target analytes on the selected capillary columns and to identify the best compromise between chromatographic resolution and analysis time under the selected operating conditions, including purified air as carrier gas, a constant column flow of 0.5 mL/min, an oven temperature window of 35 to 100°C, and a column length of 5 m (Fig. 3). Retention times were calculated by numerical integration of the analyte migration equation using a temperature-dependent van't Hoff model for the retention factor and a gas-flow model based on the Hagen-Poiseuille equation with James-Martin compressibility correction [4]. Thermodynamic parameters were taken from the Restek chromatogram modeler. Since not all target analytes were available in the database, the simulations were used primarily for comparative evaluation of stationary-phase selectivity and expected co-elution patterns.

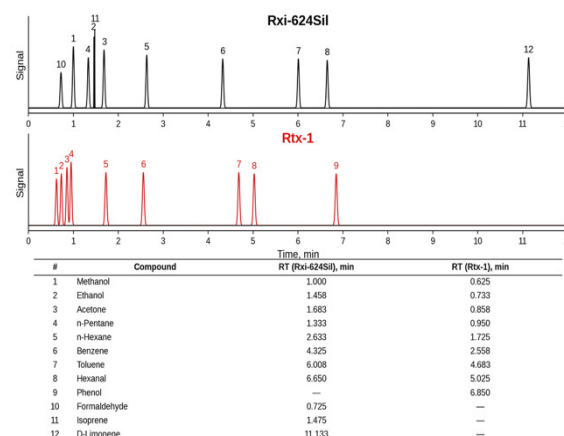


Fig. 3. Predicted chromatographic separation of target analytes

This enabled the selection of an initial shortened column configuration and an optimized temperature program for rapid breath VOC analysis. The analytical performance of the platform is currently being evaluated on synthetic exhaled breath mixtures using the Rxi-624Sil column. In parallel, based on the complementary selectivity of stationary phases with different polarities observed in the simulations, a dual-column approach with split flow to two detector channels is being investigated for improved compound discrimination.

References

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