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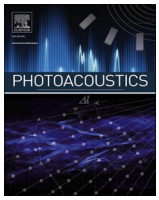

Simultaneous detection of methane and carbon dioxide in human exhalation based on photoacoustic spectroscopy

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ABSTRACT

To address the demand for simultaneous multi-gas detection in medical diagnostics, this work develops an online breath sensing system based on photoacoustic spectroscopy (PAS), achieving real-time simultaneous monitoring of multiple exhaled gases using PAS. The system exploits the inherent difference in response amplitude between the fundamental and overtone resonances of the photoacoustic cell, where the highly sensitive fundamental signal is used to detect trace methane (CH_4), while the weak overtone response enables the measurement of high-concentration carbon dioxide (CO_2). This approach allows a single photoacoustic cell to simultaneously detect multi-component gases spanning several orders of magnitude in concentration. The minimum detection limits for CH_4 and CO_2 reach 320 ppb and 450 ppm, respectively. Real-time breath measurements from multiple volunteers demonstrate excellent stability, sensitivity, and repeatability of the system, confirming its feasibility and application potential for early disease screening.

1. Introduction

The detection of exhaled gases has gained significant attention in recent years as an emerging diagnostic tool for various diseases. Compared to traditional blood tests or imaging methods, exhaled gas analysis is non-invasive, convenient, and provides valuable information regarding an individual's health status. The simultaneous monitoring of CH_4 and CO_2 in exhaled gases has shown tremendous potential in disease diagnosis. The gases exhaled by the human body contain various compounds produced by physiological or pathological processes, reflecting the individual's health condition. The emission of CH_4 and CO_2 is closely linked to the activity of the gut microbiota. In a healthy state, the gut microbiota ferments carbohydrates, producing certain amounts of CH_4 and CO_2. However, in pathological states, especially when the gut microbiota is imbalanced, the concentrations of these gases change significantly, making them important indicators for disease diagnosis. With further research, dynamic changes in these exhaled gases have been recognized as critical markers for assessing human health [1–5].

PAS has emerged as an advanced detection technique, known for its excellent selectivity, high sensitivity, long lifespan, and low maintenance costs [6–9]. PAS utilizes laser excitation of gas molecules, generating photoacoustic effects in the photoacoustic chamber. When gas molecules absorb photons, they undergo a transition from the

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ground state to the excited state, and subsequently relax back to the ground state through non-radiative decay, releasing energy. This energy causes the gas to expand and contract cyclically, producing sound waves. By using microphones or quartz tuning forks as acoustic-electric transducers to demodulate these sound waves, the gas concentration can be precisely measured, yielding a signal strength directly related to the laser power [10–17].

In recent years, there have been multiple reports on the application of PAS for non-invasive exhaled gas diagnostics [18]. In 2016, the team led by J.W. Gardner at the University of Warwick used PAS technology to detect CO_2 in exhaled gases for accurate metabolic rate analysis of patients [19]. In 2021, the team led by Jan C. Petersen at Danish Fundamental Metrology employed PAS for the isotopic analysis of CH_4, contributing to diabetes metabolism research [20]. In 2022, the team led by Santhosh Chidangil at Manipal Academy of Higher Education utilized PAS to analyze acetone in breath for asthma detection [21]. In 2023, the team led by Mao X proposed a photoacoustic spectroscopy system for breath analysis with a single resonant photoacoustic cell, which realized the quasi-simultaneous detection of H_2, CH_4 and CO_2 by utilizing time-division multiplexing with three sequentially triggered DFB lasers all modulated at the same resonant frequency of the cell [22]. In 2024, the team led by Pangerl J proposed an inexpensive UV-LED based photoacoustic sensor system with a compact photoacoustic cell, which realized the real-time detection of exhaled trace acetone by utilizing a UV-LED emitting at ~278 nm (matching acetone's absorption band) and a CO_2-triggered breath sampling system [23]. In 2024, the team led by Popa C proposed a photoacoustic spectroscopy system for ammonia measurement, which realized the measurement of ammonia in human breath of subjects with Helicobacter pylori by utilizing the photoacoustic spectroscopy technology targeting ammonia's characteristic absorption [24]. In 2024, the team led by Liu Kun proposed a multi-resonator photoacoustic spectroscopy system with a self-designed three-channel photoacoustic cell, which realized the synchronous detection of CH_4, CO_2 and N_2O by utilizing three fundamental frequencies with similar values of the cell's three channels [25]. In 2025, Zhang et al. developed a multi-resonator T-type photoacoustic cell integrated with three channels of distinct lengths to achieve a more compact volume design, and realized the synchronous CH_4, CO_2 and C_2H_2 by utilizing the fundamental frequencies of the three channels with different lengths in this photoacoustic cell [26]. However, their design targets industrial gas detection scenarios, where the concentration difference between the detected gases is narrow (within one order of magnitude), and the system adopts a multi-resonator structure that is bulky and not suitable for non-invasive exhaled gas monitoring in medical settings. In contrast, the concentration difference between CH_4 and CO_2 in human exhalation reaches nearly four orders of magnitude, and medical applications require miniaturization, real-time performance, and non-invasiveness—demands that existing simultaneous detection technologies have not yet fully met. While current reports primarily focus on the detection of individual exhaled gases or multi-gas detection with similar concentration ranges, few studies have addressed the specific need for simultaneous monitoring of CH_4 and CO_2 in exhaled breath with a wide concentration span using a compact PAS system. In the field of disease diagnosis, relying on a single gas marker can lead to misdiagnosis or missed diagnosis, making simultaneous multi-gas monitoring critical. Existing studies indicate that simultaneous monitoring of CH_4 and CO_2 can be used for the early diagnosis of gastrointestinal diseases such as Small Intestinal Bacterial Overgrowth (SIBO) [27,28], improving diagnostic accuracy. For instance, SIBO patients often show elevated levels of CH_4 in their breath, typically exceeding 10 ppm, while healthy individuals usually have CH_4 concentrations in the range of 1–3 ppm. The concentration of CO_2 reflects the metabolic state of the gastrointestinal system, with healthy individuals typically exhaling CO_2 at levels of 2–5.5%. In pathological states, particularly associated with gastrointestinal diseases (such as Helicobacter pylori infection or liver dysfunction) [29–32], CO_2 levels may increase. Therefore, the simultaneous monitoring of CH_4 and CO_2 provides a precise and non-invasive method for early disease screening, improving diagnostic accuracy and reducing false-negative results [33–37]. Compared with two common exhaled breath multi-gas detection technologies, the proposed PAS-based method has obvious advantages. Compared with TDLAS, which requires complex multi-optical path systems and thus has bulky equipment and poor anti-interference, our method adopts a single photoacoustic cell, featuring higher compactness, integration and anti-interference. Compared with Gas Sensor Array (Electronic Nose) which only achieves qualitative or semi-quantitative detection with low sensitivity, our method has higher detection sensitivity and can realize accurate quantitative detection of target gases.

The implementation of simultaneous online multi-gas monitoring based on PAS faces two main challenges. First, PAS relies on a piezoelectric transducer to detect photoacoustic signals and measure the target gas concentration. However, traditional piezoelectric transducers cannot distinguish the source of the sound waves, making simultaneous monitoring of multiple gases difficult. Second, there is a significant concentration disparity between different target gases. For example, the concentration difference between CH_4 and CO_2 in exhaled gases can reach nearly four orders of magnitude, which places high demands on the data processing program and measurement precision.

To address the application requirements for online exhaled gas monitoring, this work develops a compact differential photoacoustic cell combined with frequency division multiplexing technology, enabling simultaneous detection of two gases with concentration differences spanning four orders of magnitude. The system leverages the inherent vibrational characteristics of the photoacoustic cell: the high-response fundamental mode detects low-concentration CH_4, while the low-response overtone mode measures high-concentration CO_2. This approach achieves the cooperative detection of multi-component exhaled gases within a single device. Through experimental optimization of parameters such as modulation depth and gas pressure, the system achieves high-precision online measurements of CH_4 and CO_2, with detection limits well below the typical exhaled concentrations. Real-time measurements from multiple volunteers further validate the effectiveness and feasibility of this photoacoustic sensor for practical applications.

2. Construction of the PAS system

In traditional PAS sensors, the target gas is introduced into an acoustic resonator, inside which a highly sensitive microphone is placed. The microphone is typically small in size and does not affect the resonator's mode of resonance. Since the resonant cavity also functions as a gas chamber, it is referred to as a photoacoustic unit [38–42]. However, even high-sensitivity microphones struggle to directly detect the weak sound signals generated by gas molecules absorbing laser energy. Therefore, the acoustic resonator is often used to amplify these sound signals. Researchers have designed various photoacoustic cell structures with different shapes and volumes based on theoretical simulations and experimental validation to meet diverse application needs. This study designed a differential resonant photoacoustic cell, with each chamber measuring 90 mm in length, 8 mm in diameter, and a volume of only 18 milliliters. A highly sensitive capacitive microphone is placed at the center of each chamber to detect the accumulated acoustic energy. The photoacoustic unit is equipped with two quartz windows (diameter: 25.4 mm, thickness: 5 mm), which are made of calcium fluoride (CaF_2) with a transmittance of over 90% in the near-infrared band, ensuring the sealing of the resonant cavity while allowing efficient transmission of near-infrared photoacoustic excitation light into the chamber to interact with the target gas.

The fundamental and first harmonic frequencies were simulated using COMSOL. Fig. 1a and b show the simulation results of the fundamental and first harmonic frequencies of the photoacoustic unit in COMSOL. The fundamental frequency and the first harmonic frequency

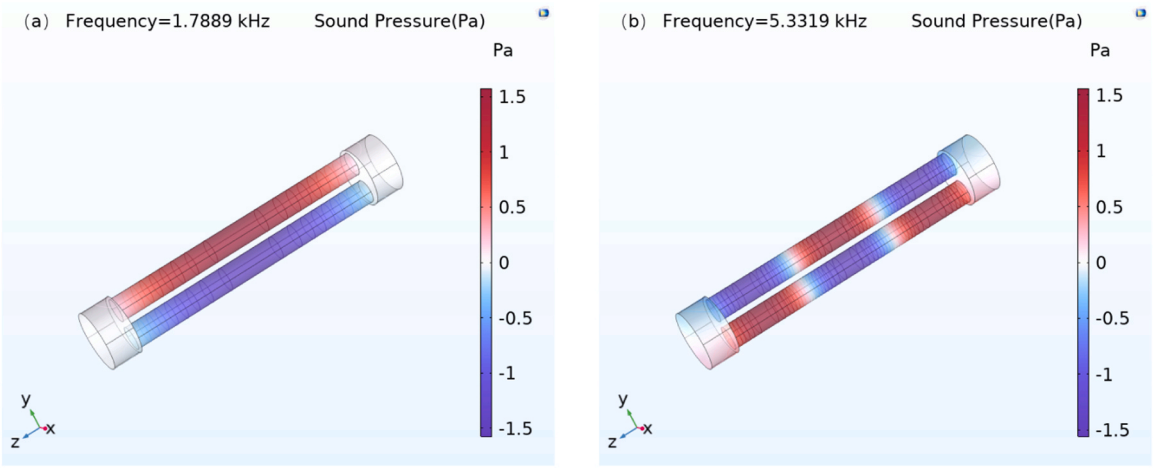

Fig. 1. Sound pressure simulation of the differential photoacoustic cell. (a) Simulation of fundamental frequency; (b)Simulation of first overtone frequency.

were found to be 1788.9 Hz and 5331.9 Hz, respectively. Fig. 2 presents the resonance curves of the realized cell prototype, where the fundamental frequency and the first harmonic frequency were measured to be 1800 Hz and 5267 Hz, respectively. These results are in high agreement with our simulation values, confirming the accuracy of our photoacoustic cell model. The quality factor (Q factor) of the photoacoustic cell was calculated as the ratio of the peak frequency of the resonance curve to the full width at half maximum (FWHM). The Q factors of the fundamental resonance frequency and the first harmonic resonance frequency were 44 and 27, respectively.

The photoacoustic signal depends on the gas absorption line intensity, gas concentration, and laser power. Therefore, selecting strongly absorbing spectral lines of target gases that do not interfere with each other is crucial. In addition to CH_4 and CO_2, potential interfering gases in exhaled gas include H_2O, NH_3, etc. Fig. 3 shows the absorption spectra of these gases between 6035 cm^{-1} and 6378 cm^{-1}. As shown, the CH_4 absorption line at 6046.97 cm^{-1} (1653 nm) and the CO_2 absorption line at 6361.24 cm^{-1} (1572 nm) do not overlap with the absorption lines of other gases and have relatively high spectral line intensities. We selected the CH_4 absorption line at 6046.97 cm^{-1} and the CO_2 absorption line at 6361.24 cm^{-1}.

The system incorporates two lasers: the laser used for CH_4 detection is designated as laser 1, while the laser used for CO_2 detection is

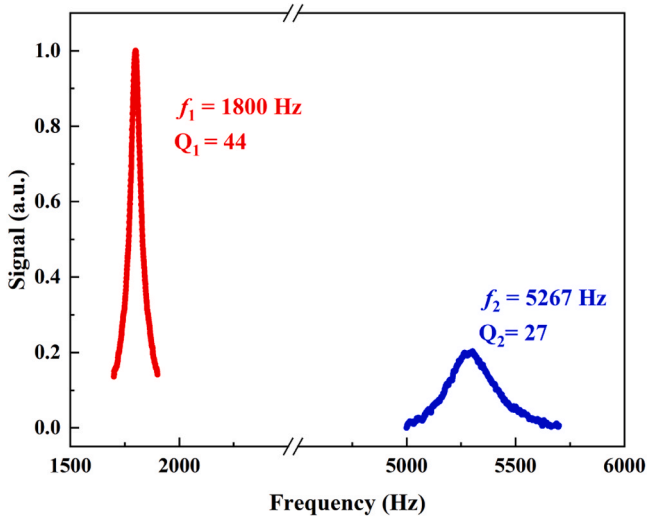

Fig. 2. Photoacoustic cell fundamental (red line) and first overtone (blue line) frequency curve.

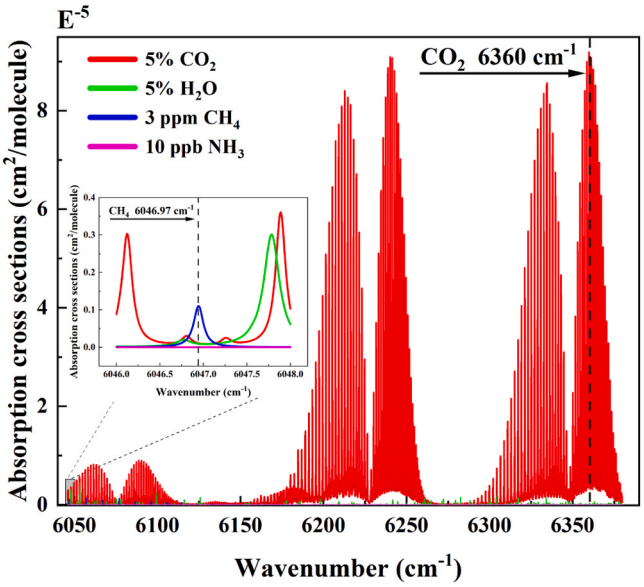

Fig. 3. The absorption cross-sections of CH_4 (blue line) and CO_2 (red line) in the spectral range from 6035 to 6378 cm^{-1} under room temperature and standard pressure conditions were obtained using the HITRAN database. The absorption cross-sections of water and ammonia were also reported within the same spectral range.

designated as laser 2. Both lasers are mounted on separate driver units. Laser output is controlled via current terminals on the driver board, superimposing a sine wave onto a sawtooth wave. The sawtooth wave scans wavelengths, while the sine wave modulates the signal. By regulating temperature and current, the output center wavenumbers of both lasers are set at 6046.97 cm^{-1} and 6361.24 cm^{-1}, respectively. The measured output powers at these points are 7.5 mW and 15 mW.

The device schematic is shown in Fig. 4. To improve the detection sensitivity of the device, this study employs a second harmonic modulation and demodulation technique. The drive current for each laser consists of two components: the scanning current and the modulation current. Taking laser 1 as an example, function generator (Tektronix AFG 3022) 1 outputs a sawtooth wave signal and a sine wave signal, which are transmitted to laser driver 1 through an adder. The sawtooth wave signal slowly changes the laser current from 78 mA to 102 mA over 50 s, causing the laser to output wavelengths ranging from 6046.6 cm^{-1} to 6047.3 cm^{-1} . The frequency of the sine wave signal is set to half of the fundamental frequency (f_1) of the photoacoustic cell's

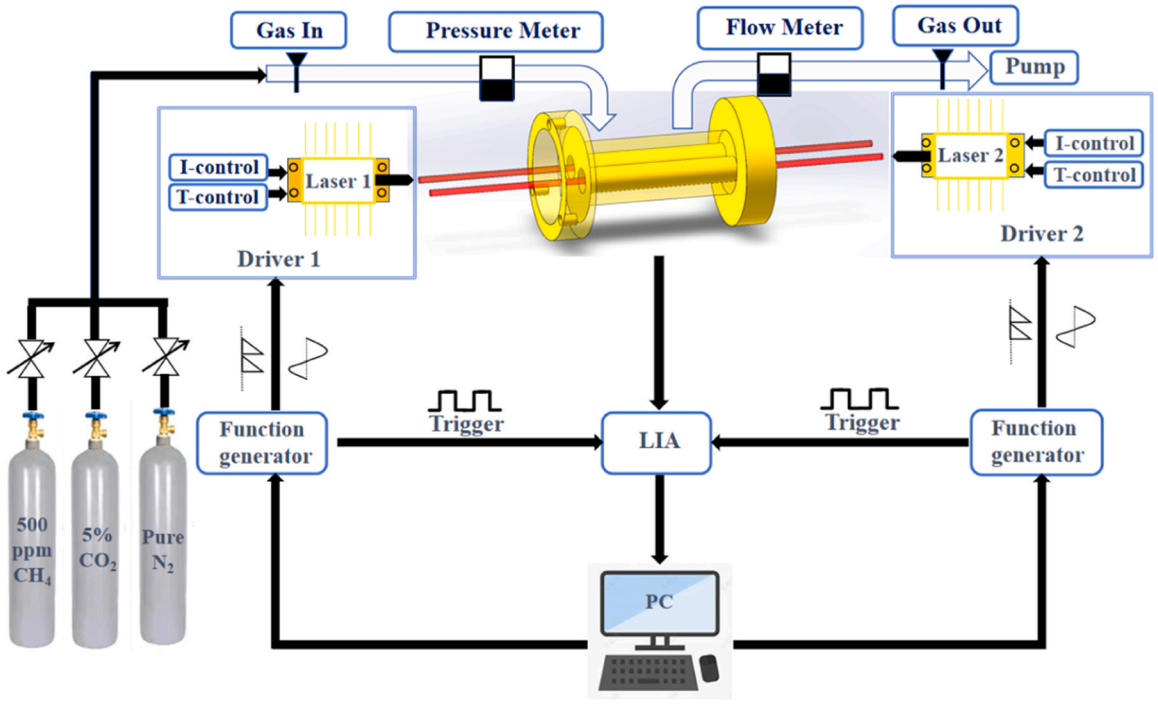

Fig. 4. Schematic diagram of a multi-gas simultaneous monitoring system based on a differential photoacoustic cell.

resonance, ensuring that when the photoacoustic signal detected by the microphone is demodulated at f_1, the second harmonic signal can be obtained. Similarly, the scanning and modulation signals from function generator 2 ensure that the output wavelength of laser 2 covers the range from 6360.9 cm^{-1} to 6361.5 cm^{-1} , with the photoacoustic signal frequency generated by this laser corresponding to half of the photoacoustic cell's first harmonic resonance frequency (f_2). The sound signal generated by the photoacoustic effect is detected by a microphone and converted into an electrical signal. This signal is then transmitted through a differential circuit and a preamplifier to a lock-in amplifier (LIA) (Zurich Instruments, HF2LILIA). The LIA demodulates the signal using the synchronized signals from function generator 1 and function generator 2, allowing for the synchronous extraction of the second harmonic signals of CH_4 and CO_2. The integration time of the LIA is set to 1 s, and the scan slope is set to 12 dB. The demodulated signal is then transmitted to a computer for processing by a LabVIEW program to determine the gas concentration. The gas handling system includes a needle valve, a pressure gauge (MKS Instruments, model 649B), a mass flow meter (Alicat Scientific, Inc, model M-500SCCM-D), and a vacuum pump (KNF Technologies Ltd., model N816.3KT.18), which are used to measure and adjust the gas pressure and flow in the photoacoustic cell. A commercial gas dilution system (MCQ Instruments, model GB100 series), not shown in Fig. 4, is placed at the inlet of the absorption cell to generate CH_4 and nitrogen (CH_4:N_2) and CO_2 and nitrogen (CO_2:N_2) mixtures at fixed concentrations.

3. Results

The photoacoustic signal is dependent on the current modulation depth, with the maximum signal occurring when the wavelength modulation depth matches the absorption feature linewidth. This linewidth is pressure-dependent within the photoacoustic cell. Therefore, the modulation depth that maximizes the PAS signal is also pressure-dependent.

To optimize the conditions, 500 ppm of CH_4 and 5% of CO_2 in nitrogen were injected into the photoacoustic cell. Fig. 5a and b illustrate

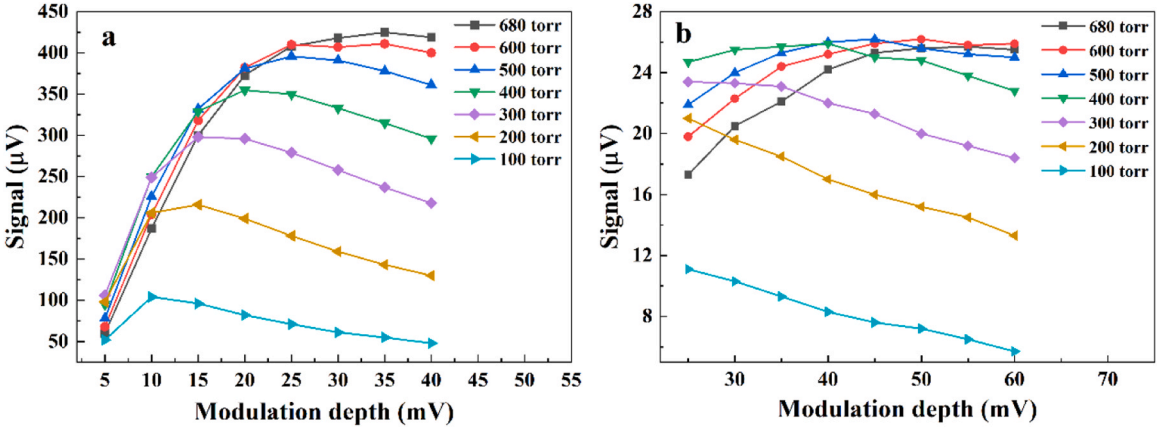

Fig. 5. Photoacoustic signal-modulation depth relationship at different pressures. (a) 500 ppm CH_4, room temperature, 1 s integration time, 50 sccm flow rate; (b) 5% CO_2, room temperature, 1 s integration time, 50 sccm flow rate.

the relationship between the PAS signal and modulation depth for CH_4 and CO_2, respectively, with the pressure inside the photoacoustic cell adjusted from 100 Torr to 680 Torr. The modulation depth of CH_4 gas ranges from 5 mV to 40 mV, while the modulation depth of CO_2 gas ranges from 25 mV to 60 mV. The peak signal for CH_4 reaches its highest value at 680 Torr and 35 mV, while the peak signal for CO_2 is highest at 600 Torr and 50 mV. Although the individual optima were 680 Torr for CH_4 and 600 Torr for CO_2, we finally chose to measure both gases simultaneously at 680 torr because the CO_2 signal loss at 680 Torr was negligible relative to 600 Torr.

The PAS second harmonic signals of the two gases measured under optimal conditions are shown in Fig. 6. The peak signal for CH_4 is 410 μV. Considering the 1σ noise level of 0.262 μV, the signal-to-noise ratio (SNR) is approximately 1560 at a concentration of 500 ppm, and the minimum detection limit at SNR = 1 is ~320 ppb. The optimal peak signal for CO_2 is 26 μV. Considering the 1σ noise level of 0.233 μV, the SNR is approximately 111.6 at a concentration of 5%, and the minimum detection limit at SNR = 1 is ~450 ppm.

To validate the performance of the PAS sensor, we measured the signals of different concentrations of CO_2 and CH_4. Initially, we conducted measurements with varying concentrations of CO_2, prepared using a gas dilution system to create CO_2:N_2 mixtures (ranging from pure 1–5% CO_2). By locking the emission wavelength of the laser 2 to the peak absorption line of CO_2, we collected data. For each CO_2 concentration, 200 data points were gathered, which are shown as a function of time in Fig. 7a. b displays the linear fitting of the variation of PAS peak signal with the CO_2 concentration.

Next, we measured CH_4 at different concentrations, again using a gas dilution system to prepare CH_4:N_2 mixtures (ranging from 50 to 500 ppm of CH_4). By locking the emission wavelength of the laser 1 to the peak absorption line of CH_4, data collection was performed. For each CH_4 concentration, 200 data points were collected, which are shown as a function of time in Fig. 8a. b displays the linear fitting of the variation of PAS peak signal with the CH_4 concentration.

After conducting operating parameters optimization and sensitivity testing, we first performed real-time detection of CO_2 and CH_4 in the exhaled breath of a healthy volunteer to validate the effectiveness of the system. In the experiment, the volunteer exhaled through a custom exhaled gas detection device into the photoacoustic chamber. To prevent water vapor from interfering with the measurement of the exhaled gas signals, a drying tube was added at the inlet. During the entire exhalation process, the pump at the exhaust end remained open. By adjusting the needle valve switches at both the inlet and exhaust, the flow rate was kept constant (50 sccm), ensuring that the pressure inside the photoacoustic chamber remained balanced throughout the process. The output wavelength of laser 1 is fixed at the CH_4 absorption line, and the output wavelength of laser 2 is fixed at the CO_2 absorption line.

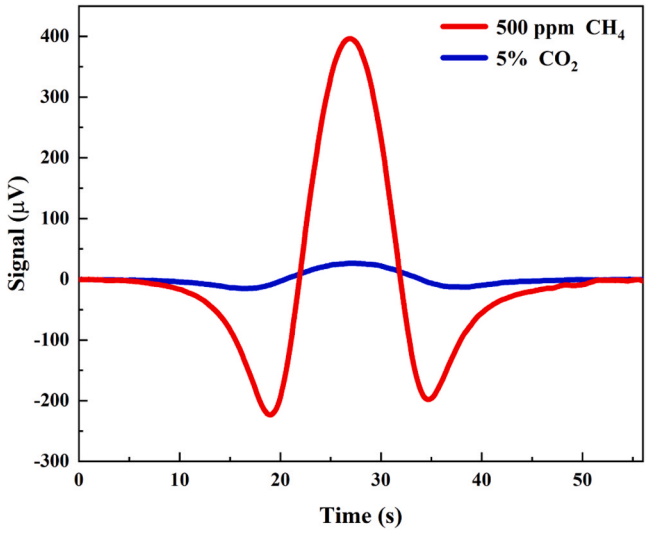

Fig. 6. Second harmonic Signal of 500 ppm CH_4 (red line) and 5% CO_2 (blue line) in nitrogen.

From Fig. 9, we can see that the system can simultaneously detect CO_2 and CH_4 in the exhaled breath. It can be seen from the figure that the signal rise time and fall time, defined as the time to reach the plateau or the background value, fall in the 6–7 s range, while the stable phase lasts a bit longer (about 10 s). Prior to each volunteer's test, baseline calibration was performed using pure nitrogen (N_2, purity ≥ 99.999%) at a constant flow rate of 50 sccm for 5 min to stabilize the system and eliminate baseline drift. The average concentrations of carbon dioxide and methane measured during the stable phase were 4.6% and 2.5 ppm, respectively, both of which are within the normal range for healthy human exhalation. To ensure the consistency and reliability of multi-volunteer data, all subsequent participants followed standardized sampling protocols: they fasted from gas-producing foods for 12 h and were tested in the fasting state, using continuous steady exhalation for sampling. Subsequently, we monitored the exhaled CO_2 and CH_4 concentration in three healthy volunteers. The results are presented in Fig. 10a and b, respectively. The same criterion as in Fig. 9 was applied to measure the mean CO_2 and CH_4 concentrations for the three volunteers which resulted to be 4%, 4.5%, and 4.6%, for CO_2 and 2.1 ppm, 1.7 ppm, and 2.6 ppm for CH_4, all within the typical range for healthy individuals. The stable detection results in healthy volunteers confirm the system's practicality for clinical use, laying the foundation for subsequent patient cohort validation.

The experiment demonstrates that the detection platform can simultaneously monitor CO_2 and CH_4 in exhaled breath in real-time, and that high concentrations of CO_2 do not interfere with the real-time detection of CH_4. This platform can provide valuable pathological analysis reference data for multiple exhaled gases, offering early warning for health issues. Although further diagnosis and pathological analysis of conditions such as SIBO may require reference to the concentrations of hydrogen (H_2) and CH_4 in the exhaled gases, when the CH_4 concentration exceeds 10 ppm or higher, it is advisable to seek further medical examination for early prevention or intervention [23].

4. Conclusions

This paper presents the design and construction of a PAS-based system for the online and synchronous monitoring of multi-gas component in exhaled breath. The system uses a differential photoacoustic cell as the core detection unit and targets the CH_4 absorption line at 6046.97 cm^{-1} and the CO_2 absorption line at 6361.24 cm^{-1}. By designing a small-volume differential photoacoustic cell and optimizing experimental parameters such as working pressure and laser modulation depth, the system achieves a minimum detection limit of 320 ppb for CH_4 and 450 ppm for CO_2 with a response time of 1 s. These concentrations are more than sufficient to meet the sensitivity requirements for measuring CH_4 and CO_2 in the exhaled breath of healthy subjects. Real-world tests conducted with multiple volunteers demonstrate that the system fully meets the application requirements for online exhaled gas sensing in the medical field. The exceptional performance of the described device lies in its ability to perform synchronous measurements of multiple components with concentration differences spanning up to four orders of magnitude, using a single photoacoustic cell. This design demonstrates high efficiency and flexibility in complex gas environments. Compared to traditional single-gas detection methods, this system not only enhances detection efficiency but also provides a practical solution for simultaneous multi-gas monitoring in exhaled breath analysis, supporting clinical non-invasive diagnosis. This design opens up broad application prospects for PAS systems in human breath analysis, enabling faster and more accurate gas concentration monitoring to support clinical diagnosis. The current PAS-based exhaled multi-gas detection system is still at the stage of technical validation for medical

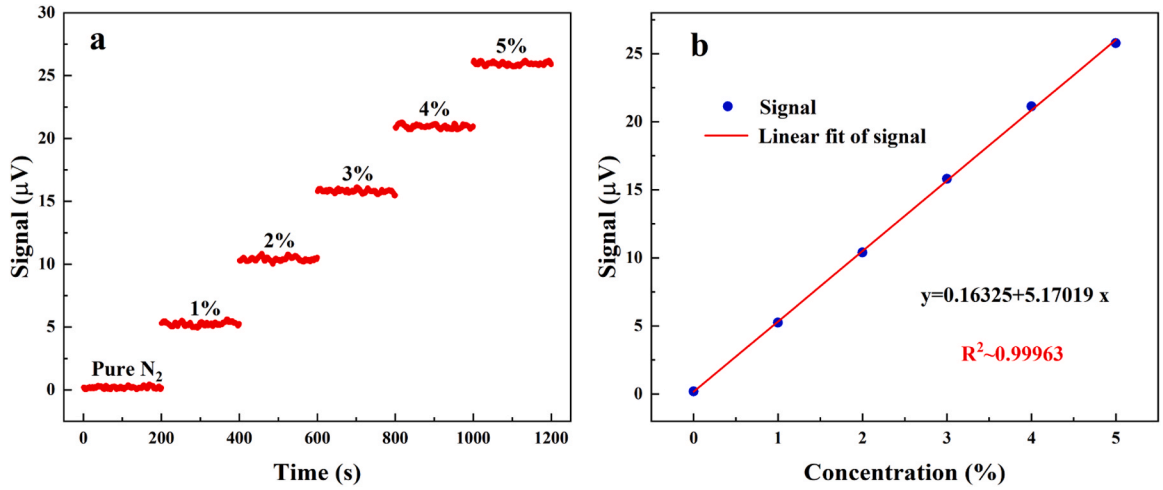

Fig. 7. (a) Photoacoustic signals at different CO_2 concentrations. A total of 200 data points were collected at each concentration; (b) Linear fitting graph of different CO_2 concentrations.

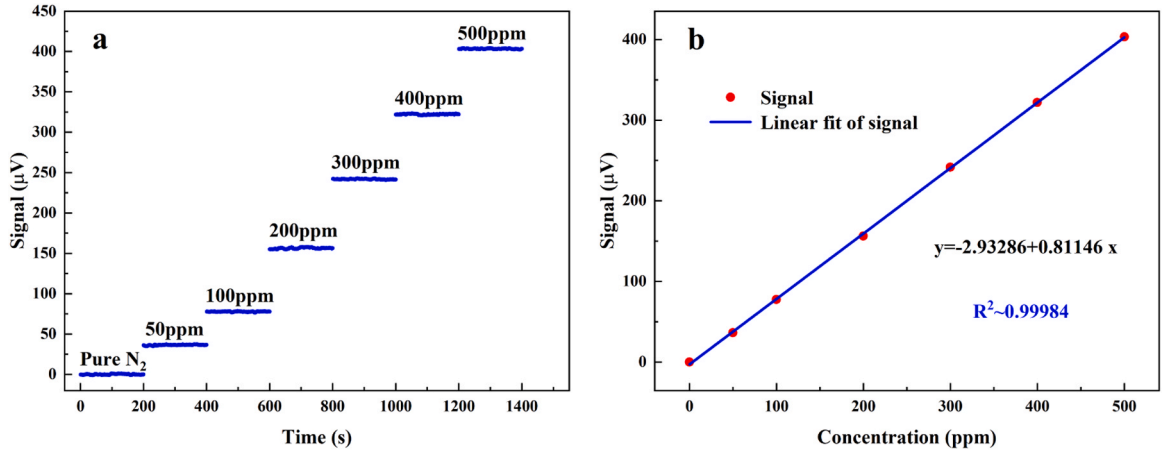

Fig. 8. (a) Photoacoustic signals at different CH_4 concentrations. A total of 200 data points were collected at each concentration; (b) Linear fitting graph of different CH_4 concentrations.

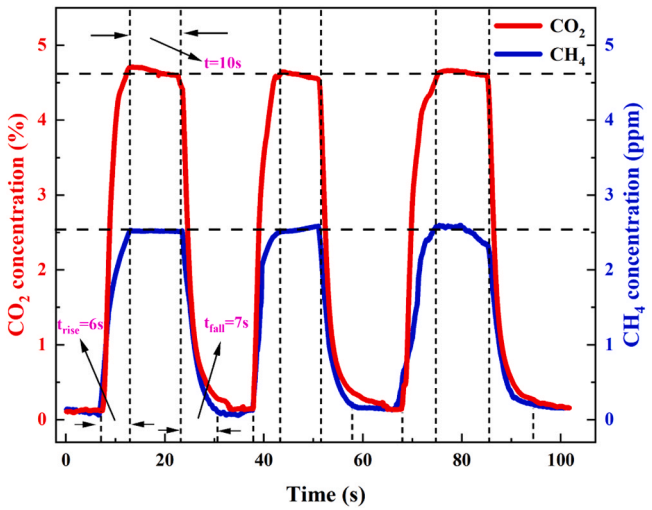

Fig. 9. The simultaneous detection of CO_2 and CH_4 in exhaled human breath.

applications. At present, spectral interference analysis is mainly based on typical breath compositions of healthy individuals, and further evaluation under complex pathological conditions is required. In addition, the detection sensitivity can be further improved through optimization of absorption line selection and system parameters. Future work will focus on extending interference verification to broader breath compositions and conducting patient-based studies to continuously refine system performance.Thanks to the wavelength-independent nature of PAS, future improvements can be achieved by changing the excitation light source, enabling high-precision online monitoring of a broader range of exhaled gases. Additionally, the system's sensitivity can be further enhanced by using mid-infrared light sources targeting stronger absorption line intensities, potentially achieving order-of-magnitude improvements in sensitivity.

CRediT authorship contribution statement

Ruyue Cui: Formal analysis. **Lina Shi:** Validation. **Hongpeng Wu:** Conceptualization. **Lei Dong:** Writing – review & editing, Validation, Supervision. **Xiaogang Xie:** Validation. **Xukun Yin:** Resources, Project administration. **Chaofan Feng:** Software. **Vincenzo Spagnolo:** Writing – review & editing, Supervision. **Xiaowen Shen:** Data curation. **Liantuan Xiao:** Writing – review & editing, Visualization, Supervision. **Chunyan Wang:** Visualization, Validation. **Pietro Patimisco:** Writing – review & editing, Supervision. **Chaofeng Sun:** Writing – original draft. **Angelo Sampaolo:** Writing – review & editing, Supervision. **Yaoxin**

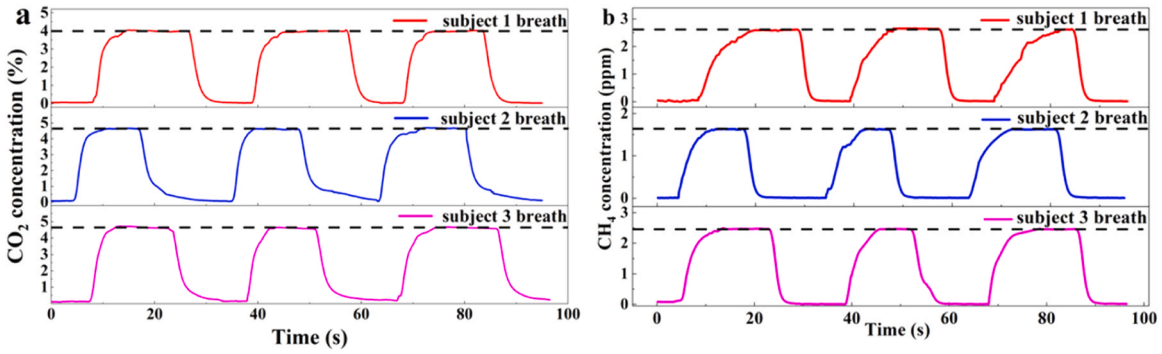

Fig. 10. (a)The online monitoring of exhaled CO_2 gas in three healthy volunteers; (b) The online monitoring of exhaled CH_4 gas in three healthy volunteers.

Wang: Investigation. **Jialiang Dai:** Methodology. **Marilena Giglio:** Resources, Methodology, Investigation.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data Availability

Data will be made available on request.

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