Cavity-enhanced optical frequency comb spectroscopy: application to human breath analysis

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Abstract: Broad-bandwidth, high-spectral-resolution optical detection of human breath has identified multiple important biomarkers correlated with specific diseases and metabolic processes. This optical-frequency-comb-based breath analysis system comes with excellent performance in all criteria: high detection sensitivity, ability to identify and distinguish a large number of analytes, and simultaneous, real-time information processing. We demonstrate a minimum detectable absorption of 8 x 10^{-10} cm^{-1}, a spectral resolution of 800 MHz, and 200 nm of spectral coverage from 1.5 to 1.7 µm where strong and unique molecular fingerprints exist for many biomarkers. We present a series of breath measurements including stable isotope ratios of CO_2, breath concentrations of CO, and the presence of trace concentrations of NH_3 in high concentrations of H_2O.

OCIS codes: (300.1030) Spectroscopy; (120.3890) Instrumentation, measurement, and metrology; (140.4050) Lasers and laser optics.

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1. Introduction

To date, researchers have identified over 1000 different compounds contained in human breath. These molecules have both endogenous and exogenous origins and provide information about physiological processes occurring in the body as well as environment-related ingestion or absorption of contaminants [1, 2]. While the presence and concentration of many of these molecules are poorly understood, many "biomarker" molecules have been correlated to specific diseases and metabolic processes. Such correlations can result in non-invasive methods of health screening for a wide variety of medical conditions. Several methods of trace molecular detection have been applied to the problem of breath analysis, including optical detection [3, 4], mass spectrometry [5, 6], and electronic noses [6, 7].

To understand the choice of optical detection as the preferred technique for breath analysis, we first evaluate the available techniques in the context of the system criteria. For instance, mass spectrometry (MS) is extremely sensitive and thus capable of detecting very small quantities of the analyte molecule. However, when several molecules are present, MS has difficulty identifying a single component of the mixture. To remedy this problem, MS is

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often used in conjunction with gas chromatography to separate out various components of a mixture prior to measurement. While these hybrid systems are highly sensitive and accurate for a large number of biomarkers, they are also large, complex, and require a long period of time to perform a measurement [8]. Conversely, electronic nose devices are typically inexpensive and perform measurements rapidly. However, these devices, which are designed to measure volatile organic compounds, have difficulty distinguishing and accurately measuring concentrations of individual molecules from the group they are designed to detect [9]. Optical detection provides a good compromise as a general approach that can be applied to many molecules. The unique absorption spectrum of each molecule allows accurate identification and concentration measurements of a single molecule in the presence of many others. Furthermore, cavity enhancement techniques permit highly sensitive detection in a matter of seconds [10, 11].

As laser technology becomes less expensive, more compact, and more reliable, the number of optical detection systems designed to detect biomarkers has increased. The advent of tunable laser diodes, for instance, has led to systems operating in the near infrared (NIR) that measure the ratio of stable isotopes of carbon to detect Helicobacter pylori, a leading cause of peptic ulcers [3]. Another NIR system detects methylamine to study its correlation with liver and renal diseases [12]. Quantum cascade lasers, operating in the mid-infrared, have been used to detect ammonia for diagnosis of renal failure [13]. These lasers are also used to detect nitric oxide for diagnosing asthma [4]. Finally, both quantum cascade and lead salt lasers have been used to detect ethane which is produced in lipid peroxidation and by some forms of cancer [14, 15, 16]. While all of these systems provide robust and highly sensitive detections of their analyte molecules, many operate in relatively narrow spectral regions. Others require long times to perform sensitive detections over a large spectral region. Therefore, the number of molecules that can be studied or detected by a single system is rather limited.

Recent approaches to trace detection that use broad bandwidth optical frequency combs have attempted to address this problem by creating parallel detection schemes that in a single shot record large spectral bandwidths [17, 18, 19, 20, 21]. Frequency-comb-based systems also take advantage of the high peak intensities of their pulsed output to easily access any spectral region from UV to far infrared via nonlinear conversion [22, 23, 24]. Furthermore, mode-locked femtosecond fiber lasers now produce robust frequency combs capable of continuous operations without user intervention [25]. In this work, we couple the broad spectrum of a mode-locked fiber laser to an optical enhancement cavity to greatly enhance the detection sensitivity of breath samples. High spectral resolution is achieved within the entire 1.5 - 1.7 µm spectral region with the use of a virtually imaged phased array (VIPA) detector [26, 20]. The relevant spectrum covers many biomarkers, such as ethane 1.68-1.7 µm, acetone 1.67-1.68 µm, methane 1.63-1.69 µm, ethylene 1.62-1.66 µm, carbon dioxide 1.54-1.64 µm, carbon monoxide 1.56-1.6 µm, ammonia 1.5-1.54 µm, methylamine 1.5-1.53 µm.

2. Cavity-enhanced comb spectrometer

The cavity-enhanced optical frequency comb spectrometer for a proof-of-principle set of breath measurements (Fig. 1) consists of two subsystems. A continuous-flow gas system delivers breath samples, standard gases for calibration, and an absorption free reference gas (N_2) to the detection chamber. An optical subsystem records absorption features that are used to determine molecular concentrations. The gas handling system is operated under a condition of continuous flow created using a low pressure regulator and a scroll pump with a choke valve. Continuous flow of gas is used to minimize the effect of adsorption while maximizing the repeatability of absorption measurements and the throughput of the measured gas. The regulator provides a constant pressure inside the cavity while the scroll pump and choke valve allow control over the gas flow rate. In this configuration, flows of .1 to 10 liters/minute at pressures ranging from 100 to 400 torr are achievable. Both the Tedlar sample bag and the

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