

The Molecular Bronchoscope: a Novel Tool for Measurement of Spatially Dependent CO₂ Concentrations in the Lungs

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Abstract

Respiratory physicians use bronchoscopy for visual assessment of the lungs' topography and collecting tissue samples for external analysis. We propose a novel bronchoscope tool that would enable spatially dependent measurements of the functioning of the lungs by determining local concentrations of carbon dioxide, which will be produced by healthy parts of the lung at rates which are higher than from portions where gas exchange is impaired. The gas analyser is based on a compact laser absorption spectrometer making use of fibre optics for delivery and return of low intensity diode laser radiation to and from the measurement chamber at the distal end of a flexible conduit. The appropriate optical wavelength was chosen such that light is selectively absorbed only by gaseous CO₂. The optical absorption takes place over a short path (8.8 mm) within a rigid, 12 mm long, perforated probe tip. Wavelength modulation spectroscopy

was adopted as the analytical technique to reduce the noise on the optical signal and yield measurements of relative CO₂ concentration every 180 ms with a precision as low as 600 part-per-million by volume. The primary objective of such a device is to see if additional spatial information about the lungs functionality can be gathered which will complement visual observation.

Introduction

Since its introduction in the late 1960s, bronchoscopy has become a central tool in respiratory medicine along with X-ray and magnetic resonance methods for the diagnosis and treatment of many lung disorders. This technique involves the insertion of a flexible endoscopic instrument (bronschoscope) into the airways and further down into the bronchopulmonary segments of the lungs, allowing visual inspection of the lung tissue.¹ For the purpose of removing specimens for external analysis, various ancillary tools have been developed such as biopsy forceps and cytology brushes, which can be inserted down the instrumentation channel of a bronchoscope.²

What however is rarely attempted is to corroborate the topographic observation with a concurrent assessment of the physiological function of the lungs, namely taking up oxygen and releasing carbon dioxide. Improvements in the diagnosis and surgical treatment of various pulmonary chronic diseases could be brought about by this combined test; for instance, patients with severe emphysema may be candidates for lung volume reduction by isolation of the target region using endobronchial valves, but collateral ventilation from adjacent lung compartments often reduces the efficacy of this treatment.^{3,4} The ability to evaluate the degree of pulmonary gas exchange in a spatially dependent fashion could aid surgeons in their assessment of collateral ventilation before isolation or resection takes place. Here we introduce a novel bronchoscope insert that could render spatially dependent measurements of the lung function possible by providing continuous, real-time monitoring of the local concentration of carbon dioxide (CO₂) directly within the lungs.

Fibre optic-based laser spectroscopy is the core analytical technique of the functioning prototype developed in this work. The system architecture consists of two basic modules, a small-footprint laser absorption spectrometer and a narrow-diameter, flexible, fibre optic probe compatible with standard bronchoscope tool channels. A brief description of the optical design and measurement principle is provided in the next section and followed by assessment of its analytical performance under various experimental conditions. Demonstration of the overall performance of the prototype in a simulated pulmonary environment was carried out by monitoring time-varying profiles of CO₂ both when inserted into a 3D-printed lung model and when directly interfaced to the mouth during breathing.

Materials and methods

The fibre optic probe

The probe is a passive device which contains optical components only, and consists of a flexible conduit with an optical connector at one end and a partially enclosed measurement tip at the sensing end. The optical connector plugs directly into the spectrometer module. The rigid tip, along with the required length (~ 800 mm) of flexible conduit, can pass through the tool channel of a bronchoscope to the target measurement space. The function of the probe is to deliver laser light from the spectrometer module to the measurement tip, to provide a short measurement path along which optical absorption by the gas sample takes place and to return the optical signal carrying the absorption information to the spectrometer module for analysis.

Delivery and return of the optical signal is via a pair of optical fibres (Thorlabs, SM2000) enclosed within the flexible conduit. These fibres were chosen to suit the wavelength selected for optically probing the CO₂ absorption fingerprint ($2.004\ \mu\text{m}$) and to ensure that transmission losses are reasonably immune to mechanical disturbance, including bending. Separate go-and-return fibres are used to ensure that feedback to the laser is minimised and to reduce

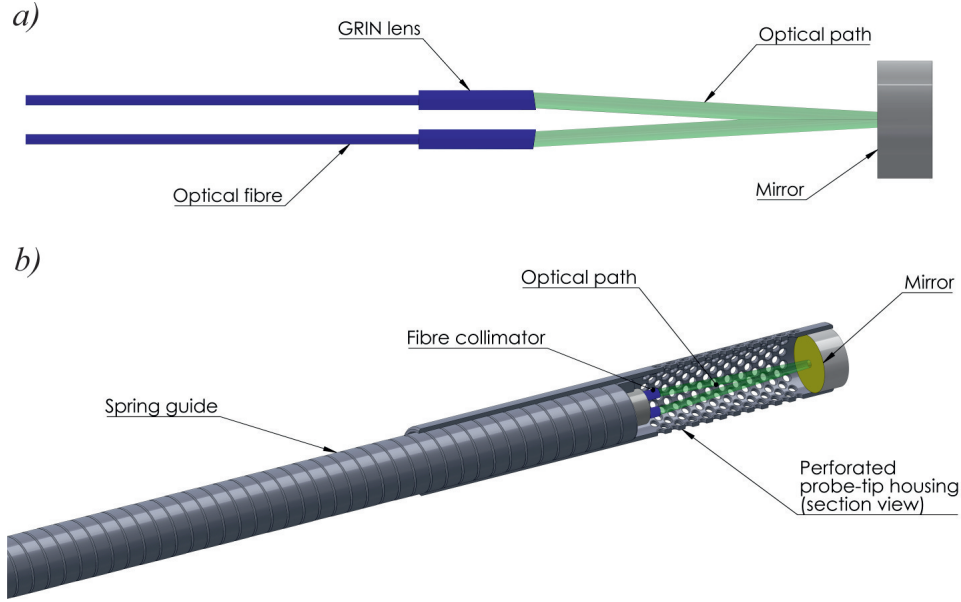


Figure 1: (a) Schematic diagram of the optical arrangement inside the tip. Single-mode optical fibres deliver light to and from the sensing region. The optical path (8.8 mm total length) passes symmetrically from one GRIN lens to the other via a flat mirror. (b) The fibres are enclosed within a spring conduit terminated with a rigid, 12 mm long, perforated tube that ensures a mechanically stable measurement path whilst allowing gas exchange between the measurement volume and the surrounding environment.

the effects of interference between multiple optical paths within the sensor. A duplex optical fibre plug (LEMO, FGG.3K.03A.CLZT76Z) at the spectrometer end provides a stable connection while allowing rapid probe replacement. The two fibres are loosely constrained within the conduit, which allows them to move freely as the conduit bends.

The optical path within the probe tip in Figure 1(a) shows the optical system in which light passes from one fibre to the other via a flat, gold coated, glass mirror (Bern Optics mirror M-75025H-AU-RS02). Each fibre is terminated with a graded-index (GRIN) lens collimator that offers a typical coupling efficiency between the input and output fibres of 30%. The GRIN lenses have angled end faces allowing the use of a single mirror and a symmetrical layout. The total path length through the absorbing medium is 8.8 mm.

The conduit is a stainless steel spring guide (DR Templeman Co., SGF-060-012-018-51) and is typical of guides used extensively for the delivery and control of devices through bronchoscope tool channels (Figure 1(b)). The guide outer diameter of 1.55 mm was selected

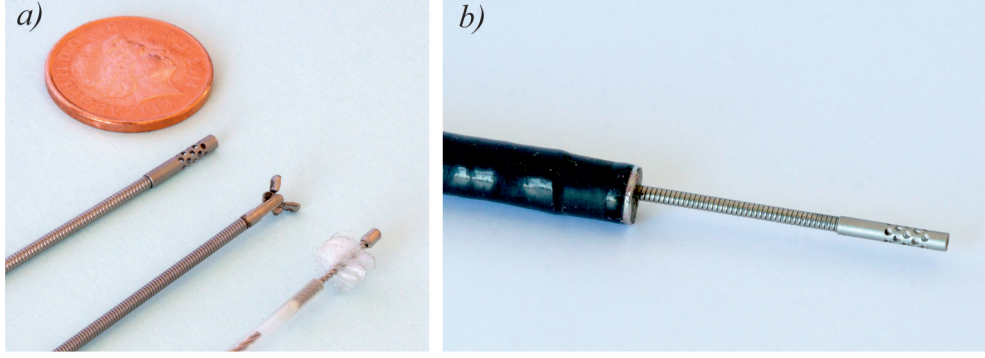


Figure 2: The demonstrator probe **(a)** next to two commercial bronchoscope tools and a 1p coin for size comparison and **(b)** extending beyond the distal end of a flexible bronchoscope.

for compatibility with a 2 mm diameter bronchoscope tool channel. The inner diameter is 0.9 mm, which is large enough to accommodate two fibres and a mechanical support at the probe tip. The guide, although flexible, holds itself straight over a distance of at least ten centimetres when free and is thus reasonably controllable when emerging from the end of a bronchoscope channel.

The probe tip housing is a stainless steel tube, perforated to allow gas exchange between the measurement volume (optical path) and the surrounding lung space. The rigid housing maintains alignment of the optical components and is locked to the spring guide. The perforations in the housing of the demonstrator unit are $700\ \mu\text{m}$ in diameter. For future versions, the perforations will be smaller – estimates suggest that perforations in the range 100 to $200\ \mu\text{m}$ diameter plus a hydrophobic coating on the probe surface will be required to prevent ingress into the measurement volume of liquid in the lungs (which has a surface tension lower than that of water⁵). In the demonstrator device, the tip housing is 12 mm long with an outside diameter of 1.8 mm. There is scope to reduce both the length and diameter of the tip in future versions, which will allow the probe to pass through a smaller radius bend within a bronchoscope.

Photos of the functioning prototype next to a 1p coin (diameter of 20.3 mm) and a pair of commercial bronchoscope inserts for size comparison and inserted through the instrumentation channel of a fibre bronchoscope (Olympus, BF-30) are shown in Figure 2.

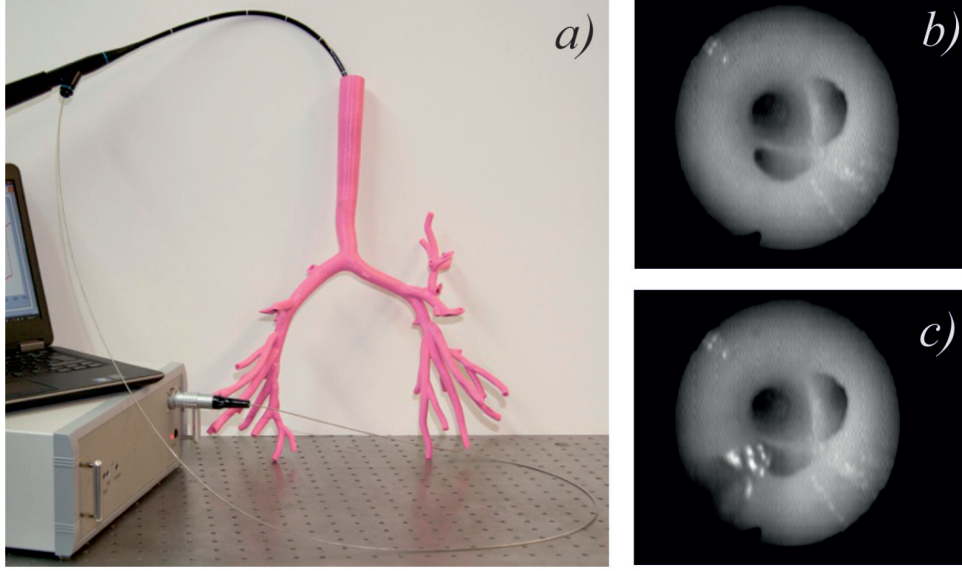


Figure 3: (a) The flexible fibre optic probe and spectrometer modules assembled together and operated in conjunction with a commercial bronchoscope inside a 3D-printed model of the human lungs. (b-c) Images of the bronchial segmentation within the right bronchus collected by the bronchoscope's CCD sensor, which show the probe tip extending beyond the distal end of the insertion tube.

The laser spectrometer

At the spectrometer end, the duplex fibre plug allows direct coupling of the light from a low power (~ 2 mW) pigtailed laser diode (Eblana, EP2000-DM) into the fibre optic probe and back into a photodiode (Hamamatsu, G12183-010K). These two components are housed in a compact rack case together with custom-built electronics for driving the laser and a data acquisition I/O card (National Instrument, NI USB-6361) connected to a laptop via a USB link. Real-time data processing is performed by software written in Labview. Figure 3(a) shows a photograph of the CO₂ probe system integrated with the commercial fibre bronchoscope. The spring catheter enters the flexible insertion tube of the bronchoscope through the access port located next to the control head; together, they were inserted into a 3-D printed, anatomically faithful model of the top portion of a human bronchial tree.⁶ Images of the bronchial segmentation at the level of the right intermediate bronchus illustrated in Figure 3(b-c) were delivered by the fibre bundle to the CCD sensor of the bronchoscope,

and depict the sensing tip of the CO₂ probe extending beyond the distal end of the insertion tube.

The laser spectrometer measures the concentration of CO₂ in the breath sample from the degree to which light is absorbed within the probe tip, in a manner described by the Beer-Lambert law.⁷ According to the principles of tunable diode laser absorption spectroscopy (TDLAS),^{7,8} the quasi-monochromatic light emitted by the single-mode diode laser around 2.004 μm is used to probe a rotationally resolved absorption signature of carbon dioxide, hence offering higher selectivity than more traditional broadband absorption techniques (such as those adopted in capnography). This near-infrared window was selected due to the sufficiently large absorption strength exhibited by the CO₂ ro-vibrational transitions, and to the absence of both structured and unstructured absorption interferences from species occurring in the lungs' environment, most notably water vapour and mucus potentially deposited on the optical components.

The TDLAS variant known as wavelength modulation spectroscopy (WMS) was adopted in this work, as it offers increased sensitivity by encoding the absorption signal into a high-frequency domain, away from the technical (pink, or $1/f$) noise which peaks at low frequency. This is achieved by rapidly modulating (typically at tens of kHz) the laser wavelength as it is swept across the absorption profile, and by using a phase-sensitive demodulator (*e.g.* a lock-in amplifier) to reject most of the technical noise and recover the signal components at harmonics of the modulation frequency. An overview of the theory underlying this technique can be found in a paper by Westberg *et al.*⁹ and references therein. The sensitivity gained by this detection scheme has enabled trace gas measurements in challenging environments that otherwise might have not been accomplished by direct-absorption spectroscopy, with applications spanning from atmospheric gas sensing¹⁰ to combustion diagnostics.¹¹ However, its analytical strength is somewhat offset by two well-known drawbacks, namely the requirement of signal calibration to retrieve the absolute molecular concentration and the dependency of WMS signals on the laser intensity. Immunity from the latter is generally

provided by normalizing the reconstructed n^{th} harmonic of the WMS signal (WMS- nf) to the transmitted intensity (or to WMS- $1f$) so that non-absorption losses such as those introduced by the measurement cell are fully accounted for. To overcome the former problem, *in situ* signal calibration can be performed with a known gas mixture, or more elegant but complex calibration-free forms of WMS^{12,13} can be adopted, although they generally offer poorer sensitivities and are limited to a specific set of experimental conditions.

In this work, direct modulation of the laser injection current at 50 kHz was imposed while periodically ramping the laser wavelength (at 100 Hz) over almost the entire absorption profile; the moderately strong and spectrally isolated $R(18)$ rotational transition belonging to the $2\nu_1 + \nu_3$ vibrational combination band of carbon dioxide was probed around 2.004 μm .¹⁴ The data acquisition I/O card provided both the scan and modulation waveforms, and simultaneously acquired the photodetector signal every 10 ms. Extraction of WMS profiles every 10 ms was performed by a custom-built digital lock-in amplifier and low-pass filter (Labview) at the second harmonic of the modulation frequency, with a integrator time constant of $\sim 250 \mu\text{s}$, and a modulation amplitude such that the optimal WMS signal was observed.

Continuous, real-time retrieval of the fraction of CO_2 in an unknown gas sample was conducted by normalizing each WMS- $2f$ spectrum to the corresponding transmitted signal, averaging consecutive normalized spectra over a 180 ms window, and ultimately fitting the resulting spectrum to a previously calibrated WMS- $2f$ reference spectrum (3% CO_2 /air mixture at 296 K) by means of a linear regression analysis. This protocol resulted in an effective CO_2 measurement rate of approximately 5 Hz.

Results

The analytical performances of the bronchoscope insert were initially assessed by feeding the catheter through the instrumentation channel of the bronchoscope, and then inserting the

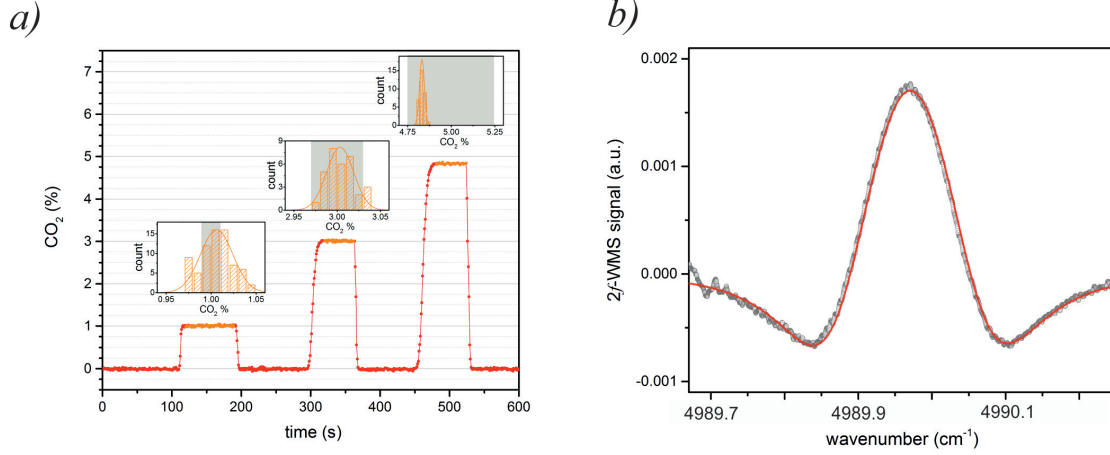


Figure 4: **(a)** Calibration curve obtained by flowing three different calibrated mixtures of CO₂ alternated with air. The data points shown in orange corresponds to the plateau regions, and were used to generate the histogram plots (insets) from which the levels of precision and accuracy of the sensor were determined. The shaded intervals represent the uncertainty range of the nominal amount of CO₂ in the calibrated mixtures. **(b)** Example of the predicted model of the WMS-2f profile (red line) fitted to the experimental spectrum (grey markers) obtained for a 5% CO₂/air mixture.

calibrated sensor in a small flow tube through which various gas mixtures (BOC UK) with a known amount of CO₂ diluted in synthetic air were passed in succession.

The outcomes of this test are reported in Figure 4(a). The histogram plots with Gaussian distribution curves shown in the inset figures summarize the statistics on the three sets of plateau values (orange data points). Each shaded area represents the uncertainty range of the nominal amount of CO₂ in the calibrated mixture ($\pm 1\%$, $\pm 1\%$ and $\pm 5\%$ of the nominal values, respectively). Mean values consistently within the uncertainty ranges and a limit of detection, stated as ± 3 times the standard deviation, below 600 part-per-million by volume (ppmv) were observed, which demonstrated the high levels of accuracy and precision offered by the sensor when operated at ambient conditions.

An example of a WMS-2f spectrum obtained for the 5% CO₂/air mixture is illustrated in Figure 4(b), alongside a predicted model fitted to the experimental data by means of a multiple linear regression analysis. The model is based on the Fourier analysis of the photodetector signal by Kluczynski *et al.*,¹⁵ which allows accounts for any contribution to

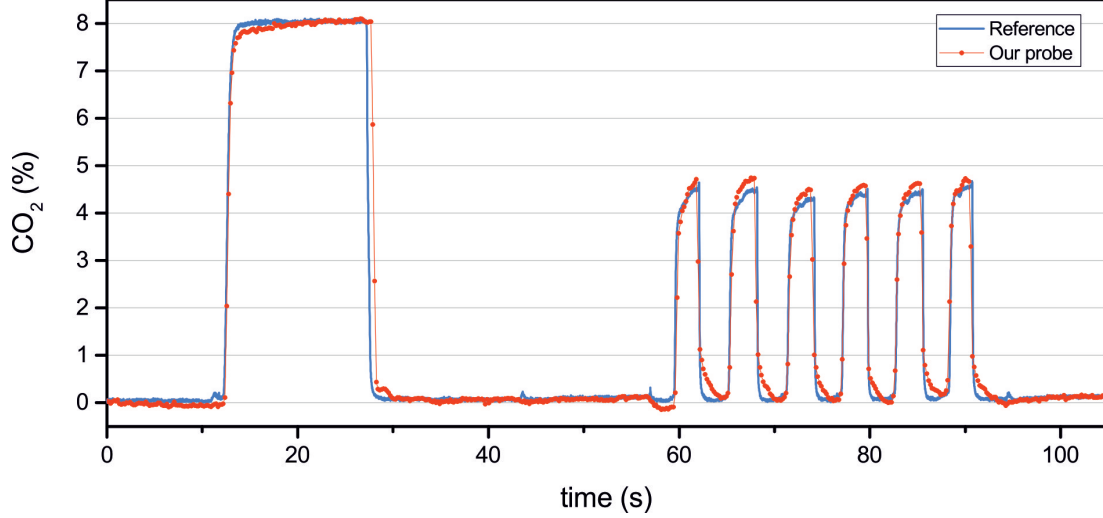


Figure 5: Comparison of the CO_2 content measured in a flow of calibrated mixture and during spontaneous breathing by the bronchoscope probe (red) inserted within the flow tube of a reference capnograph (blue).

the WMS signal from residual laser amplitude modulation.

A similar experiment was also performed where the bronchoscope insert was placed inside the 20 mm diameter flow tube of an in-house developed, mainstream capnograph. The flow tube was heated to 36°C to ensure almost isothermal conditions for the gas sample during breathing. The capnograph measured carbon dioxide also by laser absorption spectroscopy, but with a longer path length (~ 6 cm) and in direct absorption to achieve higher levels of accuracy and sensitivity;¹⁶ it also offered a much faster response time (10 ms) and simultaneous monitoring of the sample temperature by means of a thermocouple probe exposed to the gas flow.

The tube was terminated at one end with a mouth piece for continuously recording the fraction of exhaled CO_2 from a subject breathing through it. As Figure 5 illustrates, a 8% CO_2 /air mixture was initially passed through (data window 15–25 s), followed by synthetic air to flush the flow tube prior to breathing (60–90 s). Good agreement between the outputs of the two devices can be noted, which proves the stability and reproducibility of the probe’s performance under the hot and wet sample conditions mimicking the environment inside the lungs. Additionally, it is clear from the data that the slower response time returned by the

probe (180 ms) is still sufficiently fast to ensure that the changes in the exhaled CO₂ fraction during a respiratory cycle can be adequately followed.

Conclusion

We have constructed a flexible bronchoscope insert relying on fibre optic technology and laser absorption spectroscopy for measuring changes in the exhaled CO₂ fraction between different portions of the bronchial tree. The materials and mechanical arrangement of this first demonstrator model have been chosen to meet the requirements of biocompatibility, rigidity, and size for use as a bronchoscope insert.

We have assessed the CO₂ measurement performance of the probe when inserted inside the instrumentation channel of a commercial bronchoscope by using calibrated gas mixtures and during breathing. Satisfactory levels of accuracy ($< 5\%$) and precision (< 600 ppmv) have been demonstrated when operating the sensor both at ambient conditions and in an environment which partially mimicked the experimental conditions inside lungs.

It is worth noting that the use of a reference gas mixture as a signal calibration scheme could introduce an error in the calculated CO₂ fraction, due to the increase in temperature from the reference sample (ambient) to the lungs' environment ($\sim 37^\circ\text{C}$), and subsequent decrease in the total molecular density. This issue can be mitigated by measuring (and maybe conditioning) the temperature of the reference mixture and assuming a constant body temperature to correct for the volumetric thermal expansion of the sample. Alternatively, the use of an appropriate, calibration-free analysis of the WMS signals could completely remove the need of a calibration mixture, but this adds complexity and impracticality to the existing prototype.

Materials compatibility was considered at all stages during the design process but was not fully implemented in the demonstrator. The remaining issues (biocompatibility and behaviour under heat sterilisation) are in the adhesive used during assembly and the fibre

coating. A suitable adhesive such as those approved for implants will be used for future devices when assembly jigs and procedures are updated. The existing fibre primary coating is unsuitable for steam or dry heat sterilisation. High-temperature coatings are available but not yet as standard products for this fibre. In addition, as previously mentioned, the size of the sampling holes in the perforated probe tip will be reduced, and the use of a hydrophobic coating will be introduced to minimize the interaction of fluids with the optical components inside the sensing tip.

We believe these promising results demonstrate the potential of this fibre optic CO₂ probe as a diagnostic tool in bronchoscopy for spatially mapping the functionality of the lungs, and pave the way for further developments in the optical and mechanical design which would allow *in vivo* evaluation of the instrument.

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