Disrupting Blood Gas Analysis, Path to Rapid, Gentle and Continuous Monitoring - DBGA

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ABSTRACT
For prematurely born children, yearly amounting to 15 million, monitoring of CO_2 content in the blood is vital. Clinically, either a blood sample is taken, limiting the number of measurements and delaying the information, or a method detecting the gas escaping through the skin on heating it, is used. The latter poses severe risks of injury either by the heat itself or from skin rupturing on removing the sensor. Here, a truly non-invasive concept has been fully prototyped and benchmarked. It allows for continuous, non-lagging, measurements of a quality seemingly outperforming state-of-the-art equipment, also on body parts previously considered disqualified.

Keywords: Blood gases; transcutaneous monitoring; microplasma, emission spectroscopy.

1. INTRODUCTION

Each year, about 15 million children are born prematurely. About 1 million of them die, many more get life-long impairments. The World Health Organization has estimated that 75% could be saved if given adequate care. The reason they do not is mainly the complexity and cost of modern neonatal care that make it exclusive to the wealthy part of the world, while most premature births occur in developing countries. Hence, the world needs safer, simpler and less costly care, which is exactly what this project aims for. More precisely, the project has investigated a new technology for transcutaneous blood gas monitoring (TBM), which is a common way of monitoring the health of prematurely born children despite the fact that current technology is associated with major problems [1]. We aim to solve these problems by using technology originally developed to look for signs of life on Mars.

On adults, blood gas levels are measured by blood sampling, but this does not work on neonates, since they have too little blood to give. Instead the measurement is done by analysing the minute amount of gas that diffuses from the blood through the skin. To make the diffusion rate high enough for the measurement to work, the skin must be heated, which is a major problem since neonates have very sensitive skin. Generally, the heating causes harmful skin burns within an hour, and to protect the patient, the TBM sensor has to be removed before that. This is time consuming and potentially dangerous, since the skin might tear because of the strong adhesives the sensor is attached with. At best, this makes the monitoring intermittent, but sometimes termination is necessary. The caregivers, of course, want continuous information.

The technology proposed here, enables measurement without heating, which provides simpler, safer, and, most importantly, truly continuous TBM for the first time. Hence, it could offer substantial improvements in the quality of European neonatal care, even outside the most advanced neonatal intensive care units (NICUs).

In this project, a novel TBM system has been developed and investigated. The system has a sensor that analyses the blood gases and a gas collector that interfaces with the skin. Both the scientific foundation and the technology readiness level (TRL) of these have been thoroughly advanced during the project by, e.g., machine learning algorithms, and the system has been benchmarked with a commercial TBM system, showing very favourable performance.

2. STATE OF THE ART

Blood gases refer to the content of CO_2 and O_2 in the blood of a patient, the concentrations of which are important measures of a neonate's health, giving vital information on their, often not fully developed, respiratory and circulatory systems [1]. Today, these gas concentrations have to be sampled through the skin, since ordinary blood drawing is unfeasible due to the patient's low blood volume. The measurement is performed by gluing a stiff, 20-mm diameter probe with an internal gas cavity to the patient, and letting gas diffuse though the skin until the concentrations in the cavity is at equilibrium

with the body. To shorten the time to equilibrium to about 10 min, the skin has to be heated to 43-45ºC, which increases the diffusion rate. Still, this is longer than the caregivers want.

This heating, together with the delicate skin of neonates and their high sensitivity to infections, constitute a major problem. Generally, the heating causes harmful burns to the skin within an hour. This leaves the caregivers with the choice of either aborting the monitoring or moving the probe to another part of the body. The latter implies a significant risk, since the probe is glued to the skin with a strong adhesive to prevent leakage, and skin easily tears and becomes infected. Furthermore, current systems have to be calibrated each time they are reattached, taking both time and labour. The recurring movement of the probe also prevents continuous monitoring, making it intermittent at best, and sometimes even necessitates blood drawing. However, despite the fact that TBM is often dreaded by caregivers due to the major problems and risks, it is still used on almost 75% of all patients at modern NICUs due to the vital information it provides.

3. BREAKTHROUGH CHARACTER OF THE PROJECT

The major breakthrough sought by this project is to create a TBM system capable of transcutaneous, i.e., through-the-skin, monitoring without heating. Given that the main purpose of the heating is to increase the transcutaneous gas flow [1], this requires a technology that can perform reliable measurements on much smaller flows.

This project utilizes an optical sensor concept originally developed at the Ångström Space Technology Centre of Uppsala University, Sweden, aimed at applications in planetary exploration, more precisely to look for signs of past or present life on Mars [2]. The sensor is based on a method called microplasma emission spectroscopy, where the gas content of a sample is quantified by ionizing it in a microplasma source and studying the light emitted with a spectrometer. The key to its usefulness in TBM is the unique embodiment of the plasma source – a miniaturized concept called a stripline split-ring resonator [3] – that makes it capable of analysing truly minute amounts of sample [4]. In preliminary tests running up to this project, we had shown that the sensor seemed to be sensitive enough to perform TBM without heating. This has now been confirmed.

During the project, we have also developed a novel gas collector that brings gases from the skin to the sensor. In contrast to current TBM systems, this collector is not hermetically sealed to the skin. It relies on measuring the diffusion gradient across the skin rather than the gas concentration equilibrium. This makes it much faster and, more importantly, it doesn't rely on adhesives. This reduces the risks, and makes the handling of the monitoring by the caregiver much less complex.

Combining these achievements, tab. 1, the breakthrough nature of this project becomes evident.

Tab. 1. Comparison between a commercial state-of-the-art TBM system and the prototype investigated here.

	Commercial state-of-the-art	This project
Requires heating	*Yes*	*No*
Requires strong adhesives	*Yes*	*No*
Continuous monitoring	*No*	*Yes*
Time to first measurement [min]	10	1
Attachment process	*Clean skin -> Glue on attachment ring -> Calibrate sensor -> Apply contact fluid -> Attach sensor*	*Clean skin -> Attach sensor*

4. PROJECT RESULTS

Four major investigations have been conducted: 1.) The physical and chemical plasma processes that are the foundation of the sensor principle have been studied in more detail, 2.) Building on this, machine learning algorithms have been developed and implemented to improve the performance of the sensor, 3.) A novel gas collector system has been developed and tested, and 4.) A prototype of a complete TBM system has been prototyped and benchmarked with the state of the art. This has led to three scientific journal manuscripts [5-7].

Plasma physics and chemistry

An important aim of this study was to understand the plasma processes that generate the utilized spectroscopic signal in general, and how it is affected by power and the presence of chemical species, e.g., oxygen. To this end, the sample composition was studied by emission spectroscopy and a residual gas analyser (RGA) simultaneously.

A major finding was that the 560-nm emission from CO could be used to precisely quantify CO_2. This is shown in fig. 1, where the CO_2 content measured by RGA and the CO content measured by emission spectroscopy correlate linearly with R^2>0.99 for relative CO_2 contents below 10%, being the range relevant here. [5]

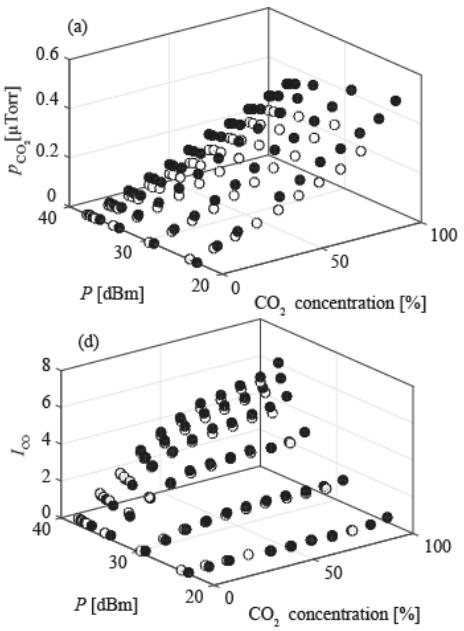

Fig. 1. CO_2 concentration acquired by RGA (top) and CO concentration acquired by emission spectroscopy (bottom) vs plasma power and mixing ratios in air (black markers) and N_2 (white markers).

Machine learning

The first study was promising, but revealed the need for improving accuracy, precision and stability. So far, only ~1.5% of the recorded spectrum had been utilized. To make better use of the data, the second study investigated the use of machine learning algorithms, which soon proved to be beneficial, particularly increasing the precision. Fig. 2 shows an example of the performance achieved with respect to linearity, accuracy and precision. [7]

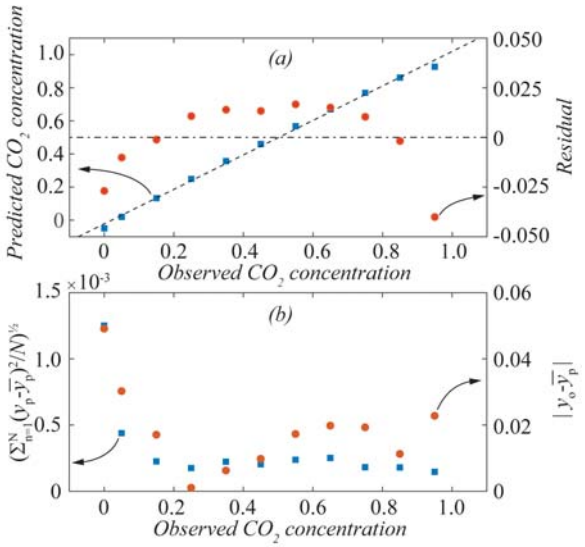

Fig. 2. Linearity (top), and precision (bottom, left y axis) and accuracy (bottom, right y axis) of one of the models developed, for samples of CO_2 mixed with air at ratios between 0 and 95%.

Gas collector

The third study focused on the other part of the system, i.e., the gas collector, and demonstrated the first flexible TBM skin interface, fig. 3. Due to stiffness, state-of-the-art sensors can only be attached to flat surfaces of the neonate's skin (typically the torso), whereas our interface can also be attached to arms or legs where it does not to compete with, e.g., ECG electrodes.

Fig. 3. A compliant, 10-mm diameter gas collector.

However, the flexible interface, which consists of polydimethylsiloxane with small channels that conduct the blood gases to the sensor, could also be a problem if its deformation affects the measurement. Therefore, it was investigated how the collector behaves under mechanical loads. Fig. 4 shows an example, where collectors with different channel widths were subjected to increasing loads, and that the wider channels withstood loads of 3 N, which is more than enough. [6]

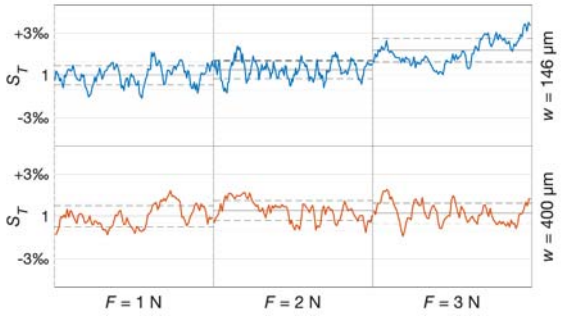

Fig. 4. Effect of mechanical loading on the TBM signal, S_T, for gas collectors with 164 μm (blue) or 400 μm (red) wide channels. See [6] for details.

Prototype and benchmarking

Finally, the sensor and gas collector were integrated with, e.g., pump and valves and power supply into a fully functional TBM prototype, fig. 5.

Fig. 5. Rendition of the 300 x 250 x 150 mm large prototype.

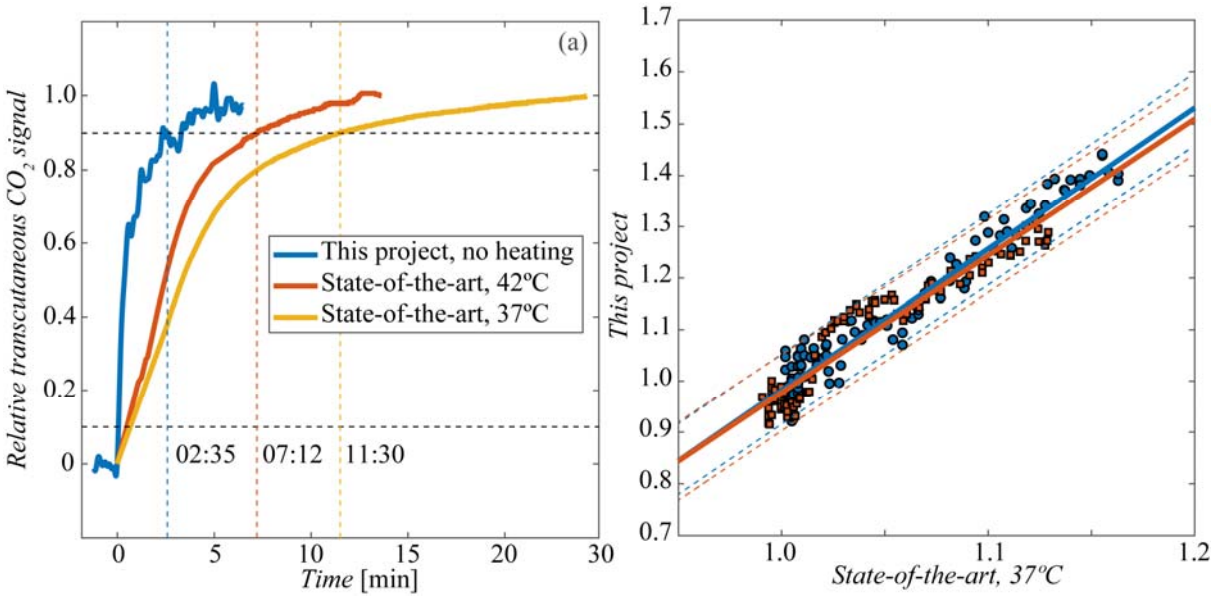

Fig. 6. Benchmarking of the prototype with the state-of-the-art equipment, showing rise times (a) of the CO_2 signal when attaching the device to the arm of an adult subject, and relative signal change (b) when occluding the blood flow to the arm [6]. The slope of the linear fits in the latter is ~2.7, indicating that the prototype exhibits correspondingly higher sensitivity. See [6] for details.

On benchmarking with a state-of-the-art TBM, the prototype stabilized up to 10 min faster, and also proved to be almost 3 times as sensitive, fig. 6 [6]. Whereas the state-of-the-art equipment collects gas and waits for equilibrium, the prototype allows air to mix with the blood gas to set up a concentration gradient. This probably explanes why the prototype is much faster, but the fact that it is more sensitive must be attributed to the excellent performance of the sensor.

5. FUTURE PROJECT VISION

5.1. Technology Scaling

The strategy for scaling the TRL of our prototype varies somewhat between the different subsystems. Among those, the sensor is the most mature and has already reached TRL 5. To continue to TRL 6 and beyond, it requires clinical testing and validation, preferably in collaboration with experts in the field. The gas collector is less mature, even though proof of concept and initial validation have been achieved. In a clinical setting, the collector will be regarded as a disposable and, hence, be discarded between measurements. To facilitate this, manufacturing must be made compatible with high-volume production to reach a higher TRL. To reach TRL 8-9, the whole system has to go through CE marking, MedTech certification, and a full clinical study.

5.2. Project Synergies and Outreach

In order to advance the whole system to TRL 5-7, clinical expertise, preferably both from industry and NICUs, and experience in the regulatory requirements of MedTech products are needed. We have already begun work on reinforcing our consortium in this way by building strong relationships with Uppsala University Hospital, which has one of Europe's leading NICUs, and one of the major companies in the blood gas market. At this point, we have no immediate plans to cluster with other ATTRACT Phase 1 projects.

During Phase 1, we have been fortunate not only to write three scientific manuscripts that have been, or will soon be published in open access journals, but also filed for two patents. Hence, we believe that we have worked both open for the public, and for future commercialization of our innovation. We would aim to continue with his during Phase 2.

5.3. Technology application and demonstration cases

For the first time in a century, the fraction of preterm births is increasing in Europe. This probably has several explanations, like more stress and increased average age of first-time parents [8]. Regardless of the cause, neonatal care will be increasingly important in our future healthcare system. Phase 2 would give our innovation a great leap closer to actually being used in European healthcare. Once there, it will offer great improvements on the quality of neonatal care as detailed in this report.

5.4. Technology commercialization

The commercial partner of the consortium – the start-up Fourth State Systems – has already been approached by investment stakeholders like business angels, and companies in the market, but not yet taken an investment. We see two principal roads to commercialization: 1.) Teaming up with an already established MedTech company by joint-venture, licensing or acquisition, or 2.) Taking the innovation to market ourselves backed by venture capital. A decision on which road to take is still to be made.

5.5. Envisioned risks

In MedTech, the process of getting though TRL 5-7 is often referred to as the "Valley of death", due to the immense regulatory requirement put on a medical product, making the process both expensive and very time consuming. We aim to mitigate this risk by adding more experience to the consortium.

5.6. Liaison with Student Teams and Socio-Economic Study

We have long experience in supervising MSc students within the consortium, and would have lots of opportunities to create meaningful projects for them during Phase 2. Moreover, we would be happy to contribute to studies aimed at developing the European innovation landscape.

6. ACKNOWLEDGEMENT

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