DETECTION OF DISSOLVED CO_2 GAS USING AN RF RESONANT SENSOR

A Thesis by

Luke Richardson

Bachelor of Science in Biomedical Engineering, Wichita State University, 2020

Submitted to the Department of Biomedical Engineering
and the faculty of the Graduate School of
Wichita State University
in partial fulfillment of
the requirements for the degree of
Master of Science

May 2022

DETECTION OF DISSOLVED CO_2 GAS USING AN RF RESONANT SENSOR

The following faculty members have examined the final copy of this thesis for form and content and recommend that it be accepted in partial fulfillment of the requirement for the degree of Master of Science with a major in Biomedical Engineering.

Kim Cluff, Committee Chair

Nils Hakansson, Committee Member

Gamal Wehaba, Committee Member

DEDICATION

To my friends and family

“There is an art to flying, or rather a knack. The knack lies in learning how to throw yourself at the ground and miss.” - Douglas Adams

ACKNOWLEDGEMENTS

I would like to thank my advisor Dr. Kim Cluff for his guidance and support- from helping to get me interested in BME on the first day I came to tour Wichita State through teaching me in the classroom and lab. I would also like to thank Dr. Nils Hakansson for his counsel as an advisor during my undergraduate years and beyond. Thanks also to Dr. Gamal Wehaba and Dr. Nils Hakansson as well for their teaching and support as members of my thesis committee.

I also want to thank my fellow members of the BioME lab for their friendship and assistance in helping me learn and grow as a member of the lab: Bernardo, Suhaib, Subash, Noor, and everyone else who helped build up this foundation.

Thanks as well to my family and friends for supporting me throughout my time in college in more ways than I could count. In particular, thanks to my parents Dana and Sharon, without whom none of this would be possible, for all of their love and support.

ABSTRACT

Carbon dioxide (CO_2) in the blood has the potential to cause severe health detriments as well as milder cognitive effects if its concentration increases to unsafe amounts- typically either through environmental exposure or conditions affecting the respiratory system in one way or another. Astronauts, in particular, are prone to this exposure due to high ambient CO_2 levels aboard spacecraft and have reported some symptoms due to CO_2 exposure which aren't always able to be identified as such without blood CO_2 monitoring. Current state-of-the-art monitoring methods like arterial blood gas analysis and capnography are limited mostly to clinical settings due to requiring invasive procedures, operator training, or bulky equipment- and aren't practical for use aboard spacecraft. Recent studies have investigated the usage of radiofrequency (RF) resonant sensors to measure health diagnostics noninvasively- and such a sensor could potentially address this gap quite well. This thesis focused on determining if a spiral resonator would be capable of detecting changes in dissolved gas CO_2 due to the gas's effect on the electromagnetic properties of water. In order to do this, a benchtop model was developed to control the amount of CO_2 gas dissolved in water which was then measured using the spiral resonator sensor. A significant correlation between negative shifts in the sensor's resonant frequency and an increase in dissolved CO_2 gas was measured, with an R^2 value of 0.923. While the detection of CO_2 in blood will pose other challenges in accounting for factors like pulsatile blood flow and changes in other parts of blood content and discerning their effects from those of CO_2, this work still demonstrates the potential of this methodology to be used as a noninvasive blood gas CO_2 sensor.

TABLE OF CONTENTS

TABLE OF CONTENTS (continued)

LIST OF FIGURES

LIST OF FIGURES (continued)

LIST OF ABBREVIATIONS

CO_2	Carbon Dioxide
EM	Electromagnetic
$NaHCO_3$	Sodium Bicarbonate
RF	Radiofrequency
VNA	Vector Network Analyzer

LIST OF SYMBOLS

S_{11}	Reflection Coefficient
f	Resonant Frequency
L	Inductance
C	Capacitance
π	Pi
P	Pressure
V	Volume
n	Number of Moles
R	Ideal Gas Constant
T	Temperature
C	Concentration
P	Partial Pressure
K	Henry's Law Constant

CHAPTER 1: INTRODUCTION

1.1 Motivation

When living and working for long periods of time in controlled air environments- such as aboard spacecraft, submersible vessels, some aircraft, and even in certain indoor spaces- there can be a risk of exposure to higher-than-normal levels of carbon dioxide. On the International Space Station, for example, the ambient level of CO_2 is at a partial pressure of 3.8 mmHg on average, compared to just 0.23 mmHg on Earth [James & Zalesak, 2013]. While this level isn't inherently dangerous, it means that when an area of the space station has inadequate air circulation, or when certain situations such as astronauts meeting in one room for long periods of time cause CO_2 levels to increase, they have been exposed to levels high enough to cause adverse physical effects. Some of these symptoms can often be subtle enough that they aren't noticed or attributed to the air- such as lowered productivity, dizziness, or headaches- all of which can impact a person's ability to perform well on a mission [Allen et al., 2016]. However, CO_2 exposure can also have much more severe effects such as seizures and even coma or death [Chapman & Dragan, 2020].

There are several different current methods for measuring the CO_2 content of a person's blood. Chiefly, these include arterial blood gas analysis, capnography, and some trans-cutaneous sensors. Of the three, arterial blood gas analysis is the most accurate and the most widely used in clinical settings- requiring blood to be drawn from the subject and then processed using a specialized machine [Huttmann et al., 2014]. However, since it is invasive and requires bulky equipment and trained personnel for analysis, it's not ideal for some situations where CO_2 monitoring may be needed- like during space missions where available personnel are limited and weight is especially a concern due to the high costs of space travel. Some other sensing methods are noninvasive, such as using transcutaneous sensors that measure blood gas levels through the skin [Van Weteringen et al., 2020]. These also suffer from similar issues where they either require specialized equipment or training, or instead produce results that aren't reliably accurate. Because of these inadequacies there exists a significant gap for a blood gas CO_2 sensor that is accurate, lightweight, and noninvasive- and can also be operated by people without extensive medical experience to monitor blood CO_2 at a point of care level.

Therefore, the motivation behind this thesis was to determine if an RF skin patch sensor could be developed as a viable alternative to existing CO_2 monitoring techniques. Past research has already confirmed this technology's potential as a noninvasive diagnostic sensor for other key health attributes such as blood flow and intracranial pressure [Cluff et al., 2018; Griffith et al., 2018]. Additionally, existing studies have shown that CO_2 causes changes in the electromagnetic properties detected by the sensor- and should do so as well when dissolved in a liquid [Siefker et al., 2021]. This sensor would be lightweight enough to be used in a point of care setting on spacecraft or anywhere else, easily usable without much training, and noninvasive to not require any additional equipment for drawing blood or risk any infection like arterial blood gas analysis.

1.2 Objectives

The primary objective of this thesis is to investigate the use of an RF resonant skin patch sensor for non-invasively detecting carbon dioxide gas dissolved in the blood for the purpose of identifying and diagnosing excessive CO_2 exposure.

1.3 Thesis Outline

1. Chapter 1 introduces the motivation behind this thesis, as well as the primary objectives to be achieved.
2. Chapter 2 presents a literature review covering the current state of the art in medical technologies measuring CO_2 and other gases in the blood, how the CO_2 present in the bloodstream is composed and how ambient CO_2 levels affect it, the adverse effects of C CO_2 exposure and the situations in which it might arise, and also how an RF sensor could measure dissolved CO_2 and how such a sensor would function.
3. Chapter 3 presents a benchtop model test established to control the amount of CO_2 dissolved in a liquid and determine if there is a correlation between the change in resonant frequency of the sensor and the liquid's CO_2 content. It discusses the results of this test, how this data can be processed, and explores the potential for future advancements in developing a functional RF sensor for detecting blood CO_2 levels.

REFERENCES

[1] J. G. Allen, P. Macnaughton, U. Satish, S. Santanam, J. Vallarino, and J. D. Spengler, "Associations of Cognitive Function Scores with Carbon Dioxide, Ventilation, and Volatile Organic Compound Exposures in Office Workers: A Controlled Exposure Study of Green and Conventional Office Environments," Environmental Health Perspectives, vol. 124, no. 6, pp. 805-812, 2016-06-01 2016, doi: 10.1289/ehp.1510037.

[2] K. Chapman and K. E. Dragan, "Hypercarbia," in StatPearls [Internet]: StatPearls Publishing, 2020. [cited February 30, 2022]

[3] K. Cluff et al., "Passive Wearable Skin Patch Sensor Measures Limb Hemodynamics Based on Electromagnetic Resonance," IEEE Transactions on Biomedical Engineering, vol. 65, no. 4, pp. 847-856, 2018-04-01 2018, doi: 10.1109/tbme.2017.2723001.

[4] J. Griffith et al., "Non-invasive electromagnetic skin patch sensor to measure intracranial fluid–volume shifts," Sensors, vol. 18, no. 4, p. 1022, 2018.

[5] S. E. Huttmann, W. Windisch, and J. H. Storre, "Techniques for the Measurement and Monitoring of Carbon Dioxide in the Blood," Annals of the American Thoracic Society, vol. 11, no. 4, pp. 645-652, 2014-05-01 2014, doi: 10.1513/annalsats.201311-387fr.

[6] J. T. James, "Surprising effects of CO_2 exposure on decision making," in 43rd international conference on environmental systems, 2013, p. 3463.

[7] Z. A. Siefker et al., "Manipulating polymer composition to create low-cost, high-fidelity sensors for indoor CO_2 monitoring," Scientific Reports, vol. 11, no. 1, 2021-12-01 2021, doi: 10.1038/s41598-021-92181-4.

[8] W. Van Weteringen et al., "Novel transcutaneous sensor combining optical tcPO2 and electrochemical $tcPCO_2$ monitoring with reflectance pulse oximetry," Medical & Biological Engineering & Computing, vol. 58, no. 2, pp. 239-247, 2020-02-01 2020, doi: 10.1007/s11517-019-02067-x.

CHAPTER 2: LITERATURE REVIEW

In this literature review, background information about how CO_2 is carried in the blood, the effects it can have on the body, and situations in which it needs to be monitored will be provided as a basis for the need for a device capable of easily measuring it in the blood. The current state-of-the-art in CO_2 blood monitoring technology will be explored, along with the drawbacks of these current technologies and gaps where improvement is needed. Finally, the feasibility of using an RF sensor to measure blood CO_2 content will be examined, along with the fundamentals behind how such a sensor could work and respond to these changes and how its data could be processed.

2.1 Carbon Dioxide in the Blood

Carbon dioxide, or CO_2 for short, is a gas which naturally occurs in the atmosphere and is also present in many different biological processes, and which is carried in the bloodstream. CO_2 enters the blood primarily through one of two ways- either as a product of biological processes in the body or through inhalation. In the first case, most CO_2 produced by the body is a result of the citric acid cycle, also referred to as the Krebs cycle. This series of reactions is a key function of the mitochondria in releasing energy stored in sources like carbohydrates so that it can be used by the cell. After the CO_2 is produced, it diffuses out from the cell into the bloodstream- where it will later then flow into the lungs. Upon entering the pulmonary capillaries, it diffuses into the air in the alveoli- provided that the CO_2 concentration of the inhaled air is lower than that of the blood- and then is exhaled. If the inhaled air contains higher than normal concentrations of CO_2, the process can wind up reversed- with CO_2 diffusing from the inhaled air into the blood as it follows the gradient in partial pressure of CO_2 across the barrier. Moderately high levels of CO_2

in the inhaled air can also prevent the CO_2 produced by the body from being able to diffuse out properly, causing it to build up in the blood.

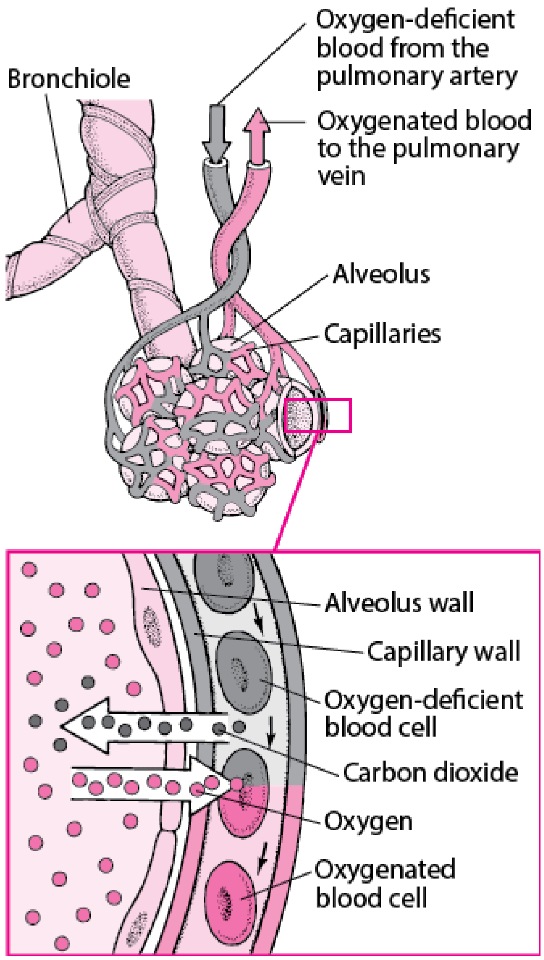


Figure 2.1: Diagram of blood flow into the alveoli and typical gas exchange from inhaled air into the blood [Dezube, 2019]

While its transport by the blood is an important biological function, the actual amount of CO_2 is comparatively quite small compared to the overall composition of blood- a small fraction of a percent. Additionally, while CO_2 initially enters the blood as a dissolved gas, most of it doesn't stay that way. Instead, most of the CO_2 dissolved in the blood becomes and is stored as carbonic acid and bicarbonate, with only roughly 5% actually remaining as a physically dissolved gas. The CO_2 is converted into carbonic acid through a reaction aided by the carbonic anhydrase enzyme found in red blood cells- which help to carry the CO_2 much like they do oxygen. The balance of dissolved CO_2, carbonic acid, and bicarbonate is maintained in a complex buffer system which is affected by various external conditions like the presence of hydrogen ions and the availability of hemoglobin- with the reaction continuously taking place along the formula in equation (1).

$$CO_2 + H_2O \leftrightarrow \underset{\text{(carbonic acid)}}{H_2CO_3} \leftrightarrow \underset{\text{(bicarbonate)}}{HCO_3 + H^+} \tag{1}$$

This buffer system allows for the blood to carry a greater amount of CO_2 without it being in a regularly dissolved form. This is quite important to the health of the body, as one significant effect that this dissolved CO_2 has is on the pH level of the blood, making it more acidic as the concentration of CO_2 increases [Chapman & Dragan, 2020]. Increases in blood acidity (and therefore decreases in pH) are the main cause of the symptoms that are typically associated with hypercapnia- a term which covers the general condition of high blood CO_2 levels, over a partial pressure of 35-45 mmHg, though the syndrome itself has many causes ranging from environmental conditions, chronic diseases, and more acute conditions such as respiratory failure. The exact symptoms resulting from hypercapnia can vary in severity and nature depending on the degree of hypercapnia and the patient, but some of the most common ones that are associated with it are headaches, dizziness, nausea, fatigue, and vomiting [Ismaiel & Henzler 2011]. In more severe cases, where the hypercapnia is excessively severe or persists at a significant level for long periods of time, more serious and potentially life-threatening symptoms may present as well. These can include fainting, confusion, palpitations, seizures, coma and even death if severe and untreated. While severe cases of hypercapnia are treated with intubation and ventilation, most of the time the underlying medical or environmental condition causing the excessive build-up of CO_2- either from high ambient levels or the body's inadequacy in eliminating the CO_2 through the lungs on its own- are what must be treated instead.

2.2 Hypercapnia: Medical and Environmental Causes and Outcomes

While it's been established that there can be significant health effects of hypercapnia, these aren't typically of too much concern to the average person in most situations. In circumstances when blood CO_2 levels are at risk of rising to subtly or severely impactful levels, there are two main types of causes: medical conditions impacting the ventilation ability of the lungs, and environmental conditions which create insufficient air circulation or otherwise result in a higher-than-normal level of ambient CO_2.

In the case of the former, there are many different conditions which can affect a person's ability to breathe properly and eliminate CO_2 through their lungs and exhalations. One of the first to be widely discovered, and which has led to a lot of the historical development of blood CO_2 measurement, was poliomyelitis (or just polio, as it is commonly referred to). During the polio epidemic of the 1950s, it was found that the greatest cause of mortality within polio patients was respiratory failure due to the weakness and paralysis of the intercostal muscles and diaphragm [Walley, 1959]. These muscles are essential to moving the chest wall and enabling the lungs to expand and contract during ventilation, and their paralysis can cause general respiratory failure. In some cases, even despite the administration of oxygen to help the patient breathe they still experienced respiratory acidosis due to the buildup of CO_2 in their blood, which lead to more common usage of CO_2 testing in hospitals to help understand this condition. And in general, for other types of respiratory failure as well, an increase in blood CO_2 levels is seen as a significant indicator of failure in the ventilation capability of the lungs [Roussos & Koutsoukou, 2003].

Aside from polio, acute hypercapnia related to respiratory failure can be a symptom of acute kidney failure, drug overdose, stroke, and many other conditions. Severe cases of COVID-19, to give a recently relevant example, can result in respiratory failure causing hypercapnia, though hypoxemia (low levels of oxygen in the blood) is a more common threat in most of those cases [Wilcox, 2020]. Acute hypercapnia can also be prevalent when a person is exposed to significant levels of CO_2 in the air that they're breathing, preventing their lungs from eliminating the CO_2 produced as waste by cellular processes and potentially introducing even more CO_2 with every breath.

While acute hypercapnia produces the most immediately significant symptoms, experiencing longer-term but more subtly elevated levels of blood CO_2 can have a range of detrimental effects as well. The most common disease in which this type of persistent hypercapnia is found is chronic obstructive pulmonary disease, or COPD for short- though there are other conditions capable of causing it as well such as neuromuscular disorders, asthma or even obstructive sleep apnea. In the case of COPD, long-term damage to the air sacs of the lungs and the inflammation of the bronchi inhibits both breathing and the transfer of oxygen and CO_2 between inhaled air and the bloodstream. As a result, one study found that about 39% of COPD patients experienced significant levels of hypercapnia [Zainab et al., 2014]. Additionally, a number of patients also experienced hypocapnia instead- or a lower-than-normal level of CO_2. In both cases, whether the patients' blood CO_2 levels were higher or lower than the typical averages, the study found an association with an increased chance of mortality associated with the disease as shown below in Figure 2.2. This emphasizes the importance of blood CO_2 monitoring with this condition to help evaluate the overall health of the patient.

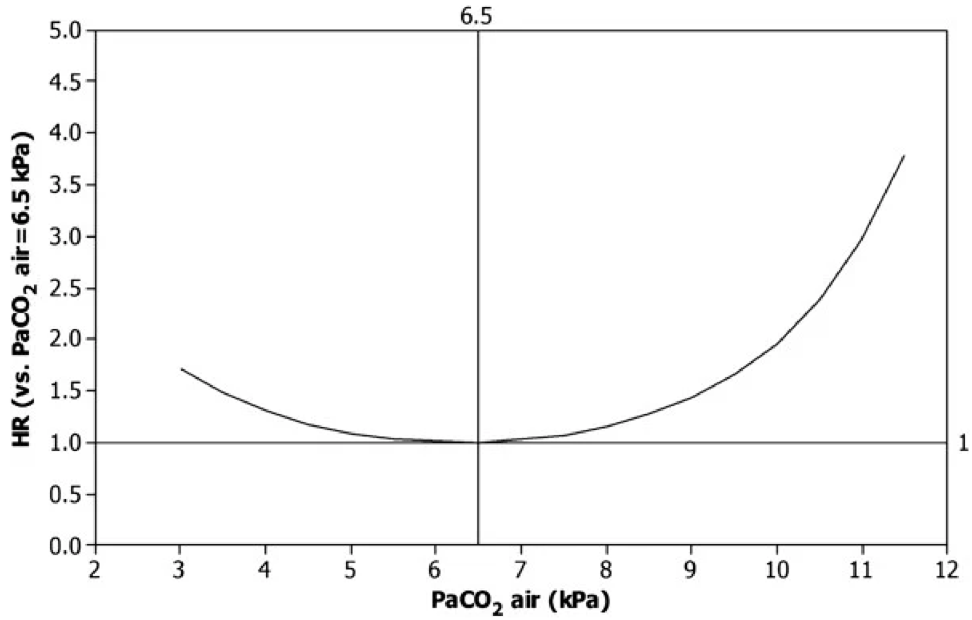


Figure 2.2: Hazard ratio of different levels of capnographically-measured CO_2 concentrations in exhaled air among COPD patients compared with the average level of 6.5 kPa [Zainab et al., 2014]

While certain health conditions are known to produce a risk of hypercapnia, there are different environments that can lead to the condition as well. Typically, this results from either a heightened ambient level of CO_2 in the air being breathed, or inadequate ventilation or circulation in an environment causing the CO_2 exhaled by people within that environment to build up to abnormal levels. One common environment where excessive CO_2 exposure may occur is in the office workplace. In an indoor location like that where a lot of people are close together, the CO_2 they exhale can build up to higher-than-normal levels if there is insufficient ventilation and air circulation around the building. While there are some health and safety regulations in place to ensure proper ventilation for workers, they still allow up to 1,400 ppm of CO_2 in the air- which is a few times higher than typical outdoor levels and can be enough to produce some adverse effects [Allen et al., 2016].

Heightened ambient levels of CO_2 are also found in controlled air environments sealed off from any outside circulation. One place where this is especially of concern is aboard spacecraft. Aboard the International Space Station (ISS), for example, there are many complex systems in place to circulate air throughout the station and provide astronauts with fresh oxygen to breathe. Despite this, the ambient concentration of CO_2 is still much higher than it is on Earth- at least 3000 ppm and sometimes higher, compared with only 400 ppm at sea level on Earth [Georgescu et al., 2020]. Additionally, in some areas aboard the ISS and spacecraft in general there may be pockets where the air doesn't circulate properly due to insufficient ventilation, creating especially high CO_2 levels in those areas. As a result, astronauts are especially prone to experiencing hypercapnia. Typically, NASA astronauts undergo training before flights where they are exposed intentionally to heightened (but not dangerous) levels of CO_2 so that they can learn the warning signs of excessive CO_2 exposure- which could be very serious in space in the case of failing life support systems [Law et al., 2017]. However, hypercapnia often also presents itself at lower levels which are less obvious to even trained personnel but still can have a significant impact on a person's health and cognitive function. Headaches attributed to high CO_2 levels are a fairly common occurrence on the ISS and have been correlated directly in previous studies with ambient CO_2 levels. One study found that headache incidences among crew members doubled for each increase of 1 mmHg in the partial pressure of ambient CO_2 [Law et al., 2014]. These sorts of headaches are also frequently reported when crew members are all gathered together for long periods of time- presumably due to CO_2 increases from their combined breathing. Aside from the headaches, which are still a concern to crew comfort, CO_2 exposure at even mild levels can have another potentially serious detriment in the form of decreased cognitive abilities- which might not even be noticed or realized as an effect of CO_2. A study examining the effects of different CO_2 levels on office workers found significant decreases at higher CO_2 levels in several test scores evaluating different cognitive functions as shown below in Figure 2.3 [Allen et al., 2016]. NASA themselves have investigated this phenomenon as well- finding clear detriments to decision-making caused by CO_2 and some anecdotal reports of more difficulty with the same sorts of complex tasks in space compared with their training on Earth [James and Zalesak 2013]. This sort of decreased cognitive function is already detrimental enough when it takes place on Earth due to the potential to affect things like productivity in the workplace. But aboard spacecraft during mission-critical situations where decision-making and mental clarity are paramount, it could potentially affect mission outcomes or even astronaut safety. Therefore, there is a need for the monitoring of blood CO_2 levels to help identify when this subtle hypercapnia is taking place so that corrective measures can be taken to ensure proper ventilation and peak astronaut performance.

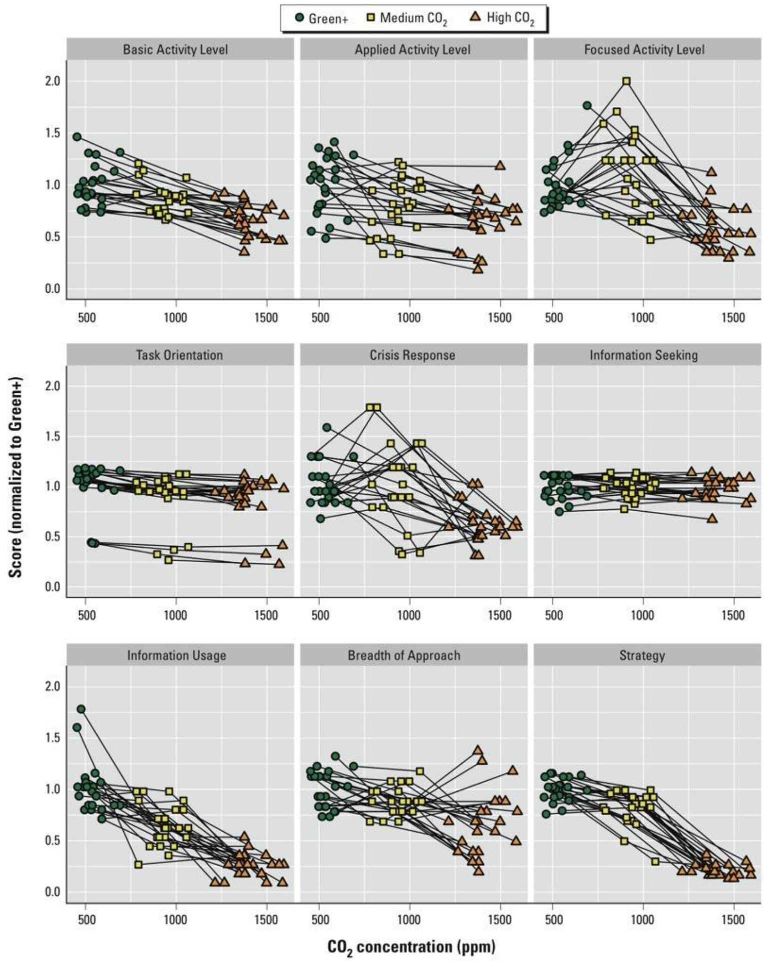


Figure 2.3: Cognitive test scores of workers subjected to different levels of CO_2, with “Green+” targeting 550 ppm, “Medium” targeting a level of 945 ppm, and “High” targeting 1400 ppm [Allen et al., 2016]

2.3 Measurement Methods and State-of-the-art

A variety of methods have been developed over the years to measure the CO_2 content of the blood in different applications. Initially, it was done indirectly by estimating it based off the pH of the blood instead, but as technology advanced it became possible to evaluate the level of CO_2 more directly. The current methods employed to do this include two main techniques: either measuring through some form of direct contact with the blood itself, or by inferring the CO_2 concentration by using the partial pressure of CO_2 in the air exhaled by a patient. Either way, these results are typically represented as $PaCO_2$, or the partial pressure of carbon dioxide present in either the blood or exhaled air.

The latter method, known primarily as capnography, is commonly used in surgical, emergency room, and intensive care settings. In these situations, it can be essential to ensure that the patient is properly exhaling out CO_2 while under assisted ventilation, during a surgical procedure, or in other scenarios in which their breathing must be carefully monitored. The most common and economical capnography method is via infrared sensors integrated into hospital ventilator systems, measuring the CO_2 of exhaled air as it flows through either the breathing circuit or an attached sampling tube. As shown in Figure 2.4 below, capnography both provides insight into the CO_2 exhaled by a patient, as well as the waveform of the CO_2 in the air they exhale over time. This can provide information about their breathing patterns and how well the gas is exchanged within the alveoli of their lungs allowing them to alter breathing assistance or better assess the patient's condition. Some other methods of analyzing the data from capnography exist as well- presenting the data relative to the volumetric changes in the air being breathed and giving insights into how well the lungs are eliminating CO_2 from the body [Kodali 2013]. However, this methodology overall does have some drawbacks. There is a delay of a few seconds between the patient's breathing and the measurements, as it takes time for the CO_2 to reach the sensor through the ventilation system. The disconnect of measuring exhalations instead of the blood also means that the measurements may be misleading. And one other large limitation is that capnography typically requires the patient to be intubated and breathing through a ventilator, requiring a lot of equipment and a trained practitioner- which limits its practical use mostly to hospital settings.

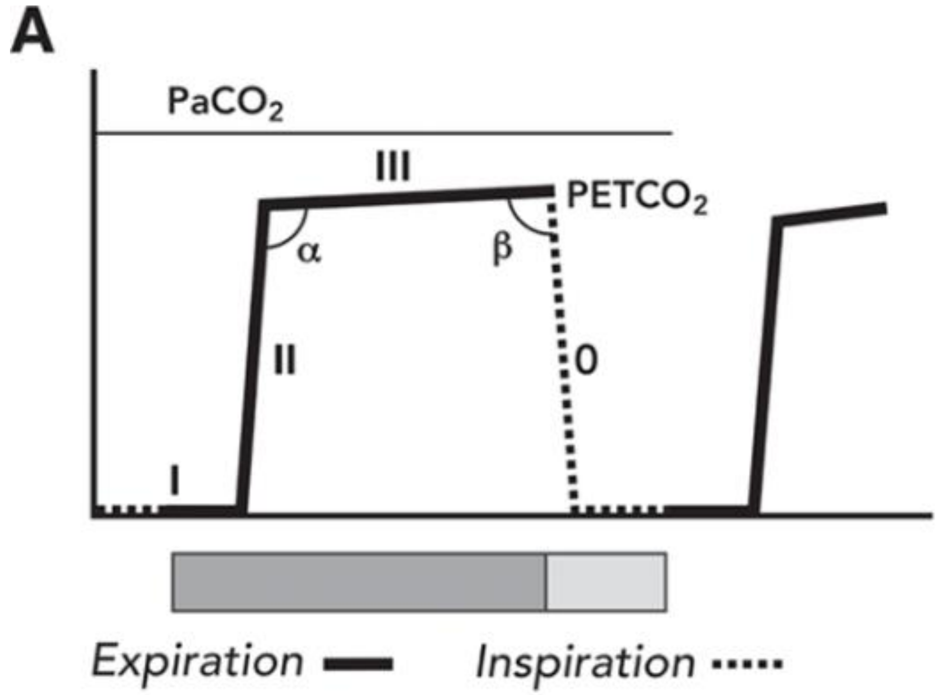


Figure 2.4: Capnograph showing the typical waveform of CO_2 content in a patient's exhaled air over time [Kodali 2013]

The most commonly used method for blood CO_2 evaluation in a clinical setting is arterial blood gas analysis (ABG). ABG allows for an accurate measurement of both the partial pressure of CO_2 in a patient's blood along with the partial pressure of oxygen- generally to within a fraction of 1 mmHg. In both cases, the result is obtained by analyzing a blood sample taken either through a puncture or from an existing catheter. Typically, the blood is drawn from the radial artery in the forearm- provided that there is sufficient circulation to the upper extremities. For some patients whose conditions may be causing circulatory issues, blood must be taken from elsewhere like the femoral artery instead [Castro et al., 2021]. The sample is then processed in a machine which returns information about its dissolved gas content, as well as the pH and other information like the bicarbonate content that helps provide insight into the overall CO_2 content. While the information provided by an ABG is generally very accurate and is important for many healthcare situations, much like capnography its usefulness is rather limited outside of clinical settings. It can still provide point-of-care information in hospitals and clinics that have access to it, but the bulky equipment required to process the blood samples makes it impractical for continuous monitoring or usage in areas with limited resources. Additionally, the fact that it requires an invasive procedure in drawing the blood poses other risks such as infection and makes it necessary to have the person performing the test be trained in venipuncture.

Besides capnography and ABG, there are a couple of other techniques being studied for use in measuring blood CO_2, but the most significant by far is by transcutaneous means- measuring the CO_2 that diffuses into the skin through the capillaries. In order to achieve this, an electrode is placed against the skin- which is heated slightly to encourage the gas's movement through the layers of the skin. The CO_2 within the skin then slowly diffuses into a CO_2-permeable membrane placed against the electrode, which then measures the change in pH of this membrane- yielding an estimation of the amount of CO_2. The measured amount is typically higher than the actual concentration in the blood due to its diffusion through the skin and the metabolism of cells in the skin producing excess CO_2- though the amount in the blood can still be estimated based on this value. Due to this difference, though, there can be some inaccuracies in transcutaneous blood CO_2 measurement- and while recent improvements have helped to reduce this gap it can still cause issues in certain situations. Different skin thickness in different patients, drugs which affect the diffusive properties of the skin, and conditions which may cause vasoconstriction and impair circulation can all impair the accuracy of transcutaneous CO_2 measurement [Nassar & Schmidt, 2017]. Generally, transcutaneous measurement isn't accurate enough to be clinically acceptable (within 7.5 mmHg of variance) [Conway et al., 2019]. Additionally, the skin is slower to respond to changes in the blood CO_2 levels compared with other methods- and the electrode heating required to help the CO_2 diffuse can also be a bit uncomfortable for patients and use more power.

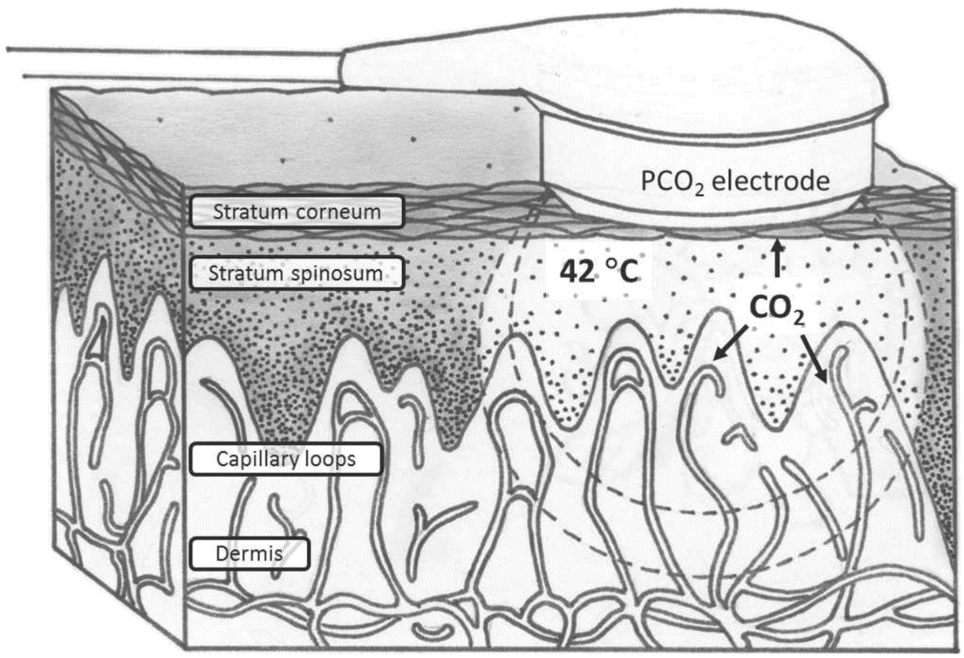


Figure 2.5: Display of how CO_2 diffuses from the capillaries through the skin and is measured by a transcutaneous CO_2 monitoring electrode [Nassar & Schmidt, 2017]

Overall, current methods of blood CO_2 evaluation are sufficient in most areas for hospital-based situations in the operating room or ICU where careful monitoring of blood gases is important to ensuring patient health. However, options for CO_2-monitoring are more limited when it comes to point-of-care applications or situations in which continuous monitoring would be helpful outside of a clinical setting. Additionally, in a situation like spaceflight there are extra limitations on the availability of trained personnel to operate monitoring devices as well as a limitation on the potential mass of a sensor due to the high cost to weight ratio of putting anything into orbit. Therefore, there exists a significant gap for a blood CO_2 sensor that is lightweight, portable, noninvasive, and which doesn't require much operator training- while still being accurate enough to detect subtle changes in blood CO_2 that may cause negative health and cognitive effects. This would allow for the point-of-care monitoring of people at risk of CO_2 exposure in settings such as spaceflight, or in some cases for continuous monitoring patients with conditions that may cause hypercapnia.

2.4 RF Resonator Sensing Methodology and Dissolved Gas Detection

One type of sensor which could potentially fill this gap would be a radiofrequency-based sensor that utilizes electromagnetic fields. By measuring the changes in electromagnetic properties of the blood using an interrogating electromagnetic field, the associated changes in blood CO_2 content could be discerned. This sort of sensing methodology operates based on the dielectric permittivity of the measurand- or the degree to which the molecules of a material are polarized by an electromagnetic field. In the case of an RF sensor, the electromagnetic field produced by the sensor is perturbed to a degree by the material it passes through, depending on that dielectric permittivity. While the overall effective relativity depends on a number of factors affecting the electromagnetic field as a whole, each material has a specific characteristic which affects its ability to be polarized. This dielectric constant of the material varies from one material to another and also depends on the temperature (and in the case of gases, the pressure as well). Based on how much of the power of the produced electromagnetic field is reflected back to the sensor, inferences can be made about the surrounding area within that field. RF sensors based off of this sensing methodology have been used to measure volumetric shifts and changes for various applications [Wylie et al., 2006; Li et al., 2014] but have not been explored to as much of a degree for the purposes of evaluating chemical changes or dissolved gases. However, it still stands to reason that a significant change in carbon dioxide content should have an effect on the permittivity of blood that would produce a measurable effect in an RF sensor.

Carbon dioxide, at room temperature, has a dielectric constant of roughly 1.01 to 1.1 depending on the pressure [DDBST GmbH, 2021]. By contrast, water, the main component of blood, has a much higher dielectric constant around 77 near room temperature [Anderson et al., 2000]. When CO_2 (or any gas, for that matter) dissolves into water, the gas molecules occupy the small spaces in between the water molecules without significantly increasing the volume of the water- as long as the amount of CO_2 stays below the saturation level at which the CO_2 would begin to bubble out. Therefore, the CO_2 molecules should produce a change in the overall effective permeability of the liquid as a whole- which could be detected by an RF sensor. Additionally, as mentioned previously, CO_2 in the blood is carried both as a dissolved gas and in other chemical forms, such as carbonic acid (H2CO3) and bicarbonate (HCO3). While the dissolved gas form would be more quickly sensitive to changes in the overall levels of CO_2 in the blood, it only makes up a relatively small portion of the overall amount- and thus being able to measure the other two forms would be useful as well for easier diagnostics. The exact dielectric properties of carbonic acid and bicarbonate, however, are not very well studied- but they could still potentially be different enough from that of blood overall that a change in their concentrations could still be detected. Some studies have tested RF resonant sensors for biochemical applications a bit as well, helping to prove the viability of the concept. One study that tested a proposed RF resonant biochemical sensor found significant differences in the sensor's resonant frequency that depended on the chemical being measured, allowing for them to be measured and discerned from one another nonintrusively as shown below in Figure 2.6 [Pandit et al., 2020]. While the difference between the effective permittivity of the biochemicals measured in this study may be greater than the difference in the effective permittivity of regular blood and blood with an increased concentration of CO_2, a sensor which is sufficiently sensitive should still be able to measure some degree of shift.

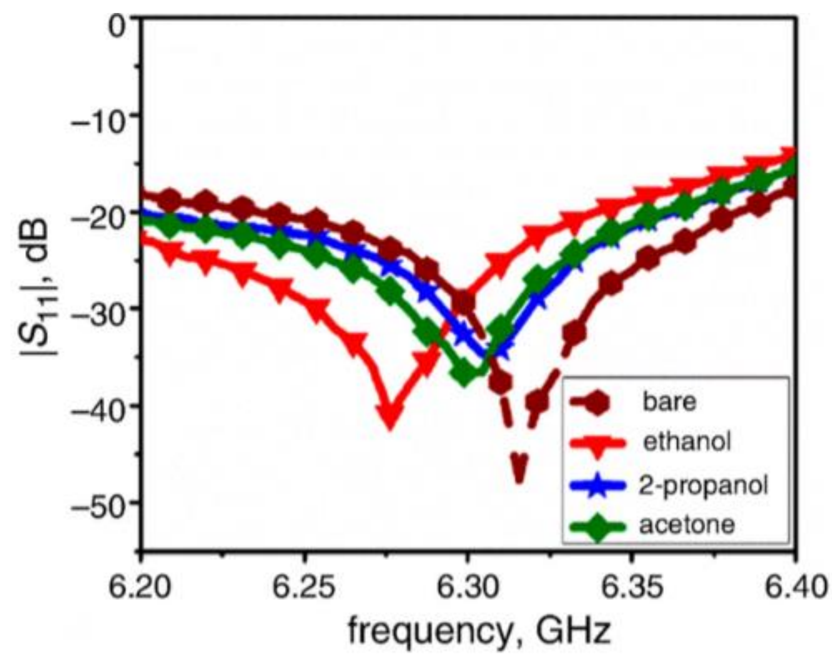


Figure 2.6: Recorded resonant frequencies of an RF sensor across a sweep of frequencies for different biochemicals [Pandit et al., 2020]

While their usage across a variety of industrial applications has been more established in the past, RF resonant sensors have recently begun to be explored in a number of medical applications as well. One 2015 study, for example, utilized an array resonator (and also tested a couple of other types as well) placed on the wrist to measure the heart rate of sleeping subjects in order to evaluate changes in cardiac activity through the night due to conditions such as sleep apnea [Kim et al., 2015]. The sensor was able to accurately measure heart rate, even through the barrier of the patients' clothing and despite their tossing and turning through the night. A more recent study investigated the possibility of using cylindrical resonators to detect blood glucose levels as an alternative to more invasive measurement methods [Turgul & Kale, 2019]. It identified a number of significant challenges, though, which would have to be overcome with the fairly weak sensor design that was considered in order to make this a feasible measurement method- many of which will need to be considered in order to facilitate the measurement of blood CO_2 as well. Array and cylindrical resonators are just a couple of designs capable of making these sorts of measurements using an electromagnetic field, though- and many different designs of resonators and antennas exist with the potential for use as a sensor. Spiral resonators, in particular, are used regularly in a variety of electronics applications- quite often as bandpass filters for wireless communications- but have been tested for use as RF sensors in biomedical applications as well. Their usage as sensors for different medical diagnostics such as heart stroke volume, limb blood dynamics, and intracranial pressure [Alruwaili et al., 2018; Cluff et al., 2018; Griffith et al., 2018]. The same sorts of spiral resonator sensor designs were also examined for usage in sensing material changes rather than volumetric shifts- such as differentiating between healthy and malignant skin tissue in order to screen suspicious moles for skin cancer. The proven capability of this spiral resonator sensor to detect these types of differences could potentially make it a good candidate for detecting dissolved gas CO_2 in the blood as well.

Typically, the type of spiral resonator used as a sensor for these sorts of applications would be composed of a single trace of copper in a flat spiral pattern. This would make it quite lightweight and able to be used directly as a skin patch sensor. The spiral resonator is surrounded by a loop antenna which interrogates it. As an alternating current flows through the loop antenna, it produces an electromagnetic field which inductively couples with the spiral resonator, inducing a current within it as well and enabling power to be transferred between them. A second electromagnetic field is produced by the spiral resonator as a result, causing it to act as an antenna and penetrate the area of interest around the sensor- with the produced radiation pattern depending on the design of the resonator. Measurements are then made based from the changes in the electromagnetic field due to the relative permittivity of the area affected by that field. The sensor is powered and its results analyzed by a vector network analyzer (or VNA). The VNA delivers an alternating current through a port which is connected to the loop antenna, transferring power to the system as a whole. It performs a sweep that alternates the current across a range of frequencies which can be controlled. The VNA also records the output of the sensor by returning a number of impedance and scattering parameters. The main one of interest in analyzing the results of the sensor is the S_{11} parameter- which describes the proportion of power reflected back by the sensor. At certain resonant frequencies, which spiral resonators have multiple of, the S_{11} coefficient reaches a peak value where the maximum amount of power is transferred and absorbed by the sensor's surroundings, and the minimum amount is reflected back. By evaluating changes in these peak values as a result of the changing relative permittivity of the area being measured by the sensor, conclusions can be made about volumetric shifts or material changes which could affect the dielectric constant of the area of interest. Through these means, it could be possible to measure the change in permittivity of blood due to increases in dissolved CO_2 content. Proper data analysis and spiral resonator design could potentially yield results as accurate as current clinically-used measurement methods.

REFERENCES

REFERENCES

Z. Ahmadi, A. Bornefalk-Hermansson, K. A. Franklin, B. Midgren, and M. P. Ekström, "Hypo- and hypercapnia predict mortality in oxygen-dependent chronic obstructive pulmonary disease: a population-based prospective study," Respiratory Research, vol. 15, no. 1, p. 30, 2014-12-01 2014, doi: 10.1186/1465-9921-15-30.

J. G. Allen, P. Macnaughton, U. Satish, S. Santanam, J. Vallarino, and J. D. Spengler, "Associations of Cognitive Function Scores with Carbon Dioxide, Ventilation, and Volatile Organic Compound Exposures in Office Workers: A Controlled Exposure Study of Green and Conventional Office Environments," Environmental Health Perspectives, vol. 124, no. 6, pp. 805-812, 2016-06-01 2016, doi: 10.1289/ehp.1510037.

F. Alruwaili, K. Cluff, J. Griffith, and H. Farhoud, "Passive Self Resonant Skin Patch Sensor to Monitor Cardiac Intraventricular Stroke Volume Using Electromagnetic Properties of Blood," IEEE Journal of Translational Engineering in Health and Medicine, vol. 6, pp. 1-9, 2018-01-01 2018, doi: 10.1109/jtehm.2018.2870589.

G. S. Anderson, R. C. Miller, and A. R. H. Goodwin, "Static Dielectric Constants for Liquid Water from 300 K to 350 K at Pressures to 13 MPa Using a New Radio-Frequency Resonator," Journal of Chemical & Engineering Data, vol. 45, no. 4, pp. 549-554, 2000-07-01 2000, doi: 10.1021/je9903092.

D. Castro, S. M. Patil, and M. Keenaghan, "Arterial blood gas," in StatPearls [Internet]: StatPearls Publishing, 2021. [cited February 30, 2022]

K. Chapman and K. E. Dragan, "Hypercarbia," in StatPearls [Internet]: StatPearls Publishing, 2020. [cited February 30, 2022]

K. Cluff et al., "Passive Wearable Skin Patch Sensor Measures Limb Hemodynamics Based on Electromagnetic Resonance," IEEE Transactions on Biomedical Engineering, vol. 65, no. 4, pp. 847-856, 2018-04-01 2018, doi: 10.1109/tbme.2017.2723001.

A. Conway et al., "Accuracy and precision of transcutaneous carbon dioxide monitoring: a systematic review and meta-analysis," Thorax, vol. 74, no. 2, pp. 157-163, 2019-02-01 2019, doi: 10.1136/thoraxjnl-2017-211466.

L. Da Silva Araujo and A. J. Belfort De Oliveira, "The square spiral resonator: Investigating its electromagnetic performance for filter design," in 2015 SBMO/IEEE MTT-S International Microwave and Optoelectronics Conference (IMOC), 2015-11-01 2015: IEEE, doi: 10.1109/imoc.2015.7369227.

DDBST GmbH. Dielectric Constant of Carbon Dioxide, DDBST GmbH, 2021 [cited March 12, 2022]

R. Dezube, "Exchanging Oxygen and Carbon Dioxide," Merck Manuals, 2019.

M. Ganter and A. Zollinger, "Continuous intravascular blood gas monitoring: development, current techniques, and clinical use of a commercial device," British Journal of Anaesthesia, vol. 91, no. 3, pp. 397-407, 2003-09-01 2003, doi: 10.1093/bja/aeg176.

M. R. Georgescu, A. Meslem, and I. Nastase, "Accumulation and spatial distribution of CO_2 in the astronaut's crew quarters on the International Space Station," Building and Environment, vol. 185, p. 107278, 2020-11-01 2020, doi: 10.1016/j.buildenv.2020.107278.

J. Griffith et al., "Non-invasive electromagnetic skin patch sensor to measure intracranial fluid–volume shifts," Sensors, vol. 18, no. 4, p. 1022, 2018.

U. Guler, I. Costanzo, and D. Sen, "Emerging Blood Gas Monitors: How They Can Help With COVID-19," IEEE Solid-State Circuits Magazine, vol. 12, no. 4, pp. 33-47, 2020, doi: 10.1109/mssc.2020.3021839.

H. Huang, "Flexible Wireless Antenna Sensor: A Review," IEEE Sensors Journal, vol. 13, no. 10, pp. 3865-3872, 2013-10-01 2013, doi: 10.1109/jsen.2013.2242464.

S. E. Huttmann, W. Windisch, and J. H. Storre, "Techniques for the Measurement and Monitoring of Carbon Dioxide in the Blood," Annals of the American Thoracic Society, vol. 11, no. 4, pp. 645-652, 2014-05-01 2014, doi: 10.1513/annalsats.201311-387fr.

N. M. Ismaiel and D. Henzler, "Effects of hypercapnia and hypercapnic acidosis on attenuation of ventilator-associated lung injury," (in eng), Minerva Anestesiol, vol. 77, no. 7, pp. 723-33, Jul 2011.

J. T. James, "Surprising effects of CO_2 exposure on decision making," in 43rd international conference on environmental systems, 2013, p. 3463.

S. W. Kim, S. B. Choi, Y.-J. An, B.-H. Kim, D. W. Kim, and J.-G. Yook, "Heart Rate Detection During Sleep Using a Flexible RF Resonator and Injection-Locked PLL Sensor," IEEE Transactions on Biomedical Engineering, vol. 62, no. 11, pp. 2568-2575, 2015-11-01 2015, doi: 10.1109/tbme.2015.2439681.

S. Kodali, Bhavani, "Capnography Outside the Operating Rooms," Anesthesiology, vol. 118, no. 1, pp. 192-201, 2013-01-01 2013, doi: 10.1097/aln.0b013e318278c8b6.

J. Law et al., "Relationship Between Carbon Dioxide Levels and Reported Headaches on the International Space Station," Journal of Occupational and Environmental Medicine, vol. 56, no. 5, pp. 477-483, 2014, doi: 10.1097/jom.0000000000000158.

J. Law et al., "Carbon Dioxide Physiological Training at NASA," Aerospace Medicine and Human Performance, vol. 88, no. 10, pp. 897-902, 2017-10-01 2017, doi: 10.3357/amhp.4552.2017.

C. Li et al., "A noncontact wireless passive radio frequency (RF) resonant pressure sensor with optimized design for applications in high-temperature environments," Measurement Science and Technology, vol. 25, no. 7, p. 075101, 2014/05/14 2014, doi: 10.1088/0957-0233/25/7/075101.

C. Molnar and J. Gair, "Concepts of biology: 1st Canadian edition," BCcampus: Victoria, BC, Canada, 2015.

B. S. Nassar and G. A. Schmidt, "Estimating Arterial Partial Pressure of Carbon Dioxide in Ventilated Patients: How Valid Are Surrogate Measures?," Annals of the American Thoracic Society, vol. 14, no. 6, pp. 1005-1014, 2017-06-01 2017, doi: 10.1513/annalsats.201701-034fr.

D. P. O'Neill and P. A. Robbins, "A mechanistic physicochemical model of carbon dioxide transport in blood," Journal of Applied Physiology, vol. 122, no. 2, pp. 283-295, 2017-02-01 2017, doi: 10.1152/japplphysiol.00318.2016.

N. Pandit, R. K. Jaiswal, and N. P. Pathak, "Real-time non-intrusive RF biochemical sensor," Electronics Letters, vol. 56, no. 19, pp. 985-988, 2020-09-01 2020, doi: 10.1049/el.2020.1661.

J. Petersson and R. W. Glenny, "Gas exchange and ventilation–perfusion relationships in the lung," European Respiratory Journal, vol. 44, no. 4, pp. 1023-1041, 2014-10-01 2014, doi: 10.1183/09031936.00037014.

C. Roussos and A. Koutsoukou, "Respiratory failure," European Respiratory Journal, vol. 22, no. Supplement 47, pp. 3s-14s, 2003-11-16 2003, doi: 10.1183/09031936.03.00038503.

G. Schmalisch, "Current methodological and technical limitations of time and volumetric capnography in newborns," BioMedical Engineering OnLine, vol. 15, no. 1, 2016-12-01 2016, doi: 10.1186/s12938-016-0228-4.

J. W. Severinghaus, P. Astrup, and J. F. Murray, "Blood Gas Analysis and Critical Care Medicine," American Journal of Respiratory and Critical Care Medicine, vol. 157, no. 4, pp. S114-S122, 1998-04-01 1998, doi: 10.1164/ajrccm.157.4.nhlb1-9.

A. Shrivastava, G. K. Mani, and K. Tsuchiya, "Real Time, Flexible RF Sputtered ZnO Nano-film CO_2 Sensor for Capnographic Applications," in 2019 International Symposium on Micro-NanoMechatronics and Human Science (MHS), 2019-12-01 2019: IEEE, doi: 10.1109/mhs48134.2019.9249267.

Z. A. Siefker et al., "Manipulating polymer composition to create low-cost, high-fidelity sensors for indoor CO_2 monitoring," Scientific Reports, vol. 11, no. 1, 2021-12-01 2021, doi: 10.1038/s41598-021-92181-4.

F. Suarez-Sipmann, S. H. Bohm, and G. Tusman, "Volumetric capnography: the time has come," Current Opinion in Critical Care, vol. 20, no. 3, pp. 333-339, 2014, doi: 10.1097/mcc.0000000000000095.

V. Turgul and I. Kale, "RF/Microwave Non-invasive Blood Glucose Monitoring: An Overview of the Limitations, Challenges & State-of-the-Art," in 2019 E-Health and Bioengineering Conference (EHB), 2019-11-01 2019: IEEE, doi: 10.1109/ehb47216.2019.8970032.

W. Van Weteringen et al., "Novel transcutaneous sensor combining optical tcPO2 and electrochemical $tcPCO_2$ monitoring with reflectance pulse oximetry," Medical & Biological Engineering & Computing, vol. 58, no. 2, pp. 239-247, 2020-02-01 2020, doi: 10.1007/s11517-019-02067-x.

J. J. van Wijk, F. Weber, R. J. Stolker, and L. M. Staals, "Current state of noninvasive, continuous monitoring modalities in pediatric anesthesiology," Current Opinion in Anaesthesiology, vol. 33, no. 6, p. 781, 2020.

R. V. Walley, "Assessment of Respiratory Failure in Poliomyelitis," BMJ, vol. 2, no. 5142, pp. 82-85, 1959-07-25 1959, doi: 10.1136/bmj.2.5142.82.

S. R. Wilcox, "Management of respiratory failure due to covid-19," BMJ, p. m1786, 2020-05-04 2020, doi: 10.1136/bmj.m1786.

S. R. Wylie, A. Shaw, and A. I. Al-Shamma'a, "RF sensor for multiphase flow measurement through an oil pipeline," Measurement Science and Technology, vol. 17, no. 8, pp. 2141-2149, 2006/07/13 2006, doi: 10.1088/0957-0233/17/8/013.

T. Yilmaz, R. Foster, and Y. Hao, "Radio-Frequency and Microwave Techniques for Non-Invasive Measurement of Blood Glucose Levels," Diagnostics, vol. 9, no. 1, p. 6, 2019-01-08 2019, doi: 10.3390/diagnostics9010006.

CHAPTER 3: DETECTION OF DISSOLVED CO_2 GAS USING A RADIOFREQUENCY SPIRAL RESONATOR

3.1 Abstract

Carbon dioxide in the blood can have significant detrimental effects on health and cognitive function, even at lower levels, which can especially be a concern during spaceflight where ambient CO_2 levels are higher than they are on Earth. Current CO_2 monitoring methods are adequate for most clinical settings, but are insufficiently accurate, require invasive procedures, large equipment, or specially trained operators- which make them inconvenient to use outside of a hospital. This study focused on determining whether an RF resonant sensor could identify changes in dissolved gas CO_2 to potentially be used to detect its change in the blood. A spiral RF resonator was used to measure changes in the dielectric properties of water, which had its CO_2 concentrations changed without otherwise altering its chemical composition using a connected reaction flask. Significant changes in the resonant frequency of the sensor were recorded in response to the changes in the CO_2 level of the water. Linear regression analysis showed a correlation between the amount of negative frequency shift and the quantity of CO_2 gas dissolved in the measured water. While many other factors must still be considered and addressed in order to develop a functional sensor for detecting this in the blood, this sensing methodology could potentially be used to develop a lightweight noninvasive sensor for detecting blood gas CO_2 levels.

3.2 Introduction

Carbon dioxide is a gas which occurs naturally in the Earth's atmosphere, and which is also produced in the body as a result of many different biochemical processes. The most significant of these is the Krebs cycle, where oxygen and glucose are used to create energy used by cells in the body and in which carbon dioxide is generated as a waste product. Because of its solubility it is able to be carried as a dissolved gas by the blood after diffusing out from the cells it is produced within in order to be removed from the body. Red blood cells aid in this process by helping to carry and convert carbon dioxide into carbonic acid and bicarbonate, which are maintained in balance with the dissolved gas form of carbon dioxide in the bloodstream's bicarbonate buffer system. After being carried through the body in the blood by means of this buffer system, the dissolved carbon dioxide then diffuses through membranes into the inhaled fresh air stored within the alveoli with each breath, provided that the air has a lower relative concentration of carbon dioxide. The air is then exhaled along with the carbon dioxide it now contains, allowing the breathing cycle to continue.

The process by which CO_2 is eliminated from the body is important to human health because it prevents an excessive build-up of CO_2 in the cells or blood, which would decrease the blood's pH level and create an unhealthily acidic internal environment. However, in the case of certain conditions and diseases, or when the air in the external environment contains too much CO_2 for it to be eliminated at a normal rate, the blood CO_2 levels can build up to an unsafe degree in a condition known as hypercapnia. Chronic conditions in which hypercapnia is common include ones which directly affect or damage the lungs, such as COPD, and other diseases like poliomyelitis and muscular dystrophy which can impact some of the muscles key to breathing like the diaphragm and intercostal muscles [Walley, 1959]. More acute causes of hypercapnia include things like drug overdose leading to respiratory failure as well as certain respiratory diseases such as COVID-19 [Wilcox, 2020]. Hypercapnia can also be a concern to people with otherwise healthy respiratory systems as well, in environments where the air that they're breathing contains higher than normal levels of CO_2- causing the CO_2 in their lungs to not diffuse properly into it due to less of a concentration gradient, or even for it to diffuse from the air into their blood at high enough levels. One common circumstance in which this could potentially occur at mild levels is in the workplace. In an office building containing many employees exhaling CO_2 for long periods of time, it can build up in the air if ventilation is insufficient [Allen et al., 2016]. An environment where air circulation is perhaps the most important is aboard spacecraft- and while life support systems provide adequate oxygen levels, CO_2 concentrations aboard the ISS are much higher than they are naturally on Earth [Georgescu et al., 2020]. Astronauts have reported headaches and other mild symptoms of hypercapnia- which can also lead to subtle impairments in cognitive function which have the potential to seriously affect mission outcomes or astronaut safety. In order to protect astronaut health and ensure that they're doing the best work possible, CO_2 monitoring would be very beneficial in identifying subtle cases of hypercapnia so that astronauts may seek treatment if necessary and ventilation systems can be improved upon.

Current CO_2 monitoring methods are typically used in clinical settings- and especially in operating rooms and ICUs. The most common method used to evaluate blood CO_2, and what is generally considered the current gold standard, is arterial blood gas analysis, or ABG. In ABG, blood is drawn from an artery of the patient and then processed using a blood gas analyzer- which uses electrodes to measure both the amount of dissolved gas CO_2 and the blood's pH to determine the overall level of CO_2 in the blood, bicarbonate included. However, this requires an invasive procedure to draw the blood, a trained professional to carefully carry out the puncture, and a bulky machine to process the blood [Castro et al., 2021]. The other main method used to evaluate blood CO_2 is capnography- which works by measuring the partial pressure of CO_2 in exhaled air. While it can provide useful information about a patient's breathing pattern, it's less accurate than other methods because it’s inferring the blood CO_2 levels indirectly from the air. It also is limited to hospital settings for the most part as current capnography methods require the patient to be breathing through a ventilator which can capture all their exhaled air. There are some other existing methods of measuring blood CO_2 levels as well- such as transcutaneous measurement which uses an electrode to evaluate the CO_2 that diffuses through the skin. However, this is limited in accuracy as well due to the CO_2 produced by cells in the skin creating higher measured values than what’s actually found in the blood. There exists a significant gap for a sensor which can accurately measure blood CO_2 levels, while still being lightweight, noninvasive, and easy to use- which would allow for the convenient monitoring of blood CO_2 levels aboard spacecraft.

One type of sensor which has recently seen more investigation for biomedical purposes and could help fill this gap is a radiofrequency resonant sensor. This type of sensor creates an electromagnetic field which penetrates the material being measured. Based on the changes in the effective permittivity of the material, the resonant frequency of the spiral resonator where the least amount of power is reflected back from its electromagnetic field can change. And by measuring this change in resonant frequency, inferences can be made about the associated change in the material being measured. This methodology has been used for industrial applications as well as some medical ones such as heart rate evaluation [Kim et al., 2015] and preliminary testing on blood glucose evaluation [Turgul & Kale, 2019]. Recent studies have explored using spiral resonators in particular- due to their compact size and properties like having multiple resonant frequencies to examine making them potentially ideal for a non-invasive skin patch sensor. They’ve shown potential for usage in evaluating health diagnostics like heart stroke volume [Alruwaili et al., 2018] and intracranial pressure [Griffith et al., 2018].

A number of other applications for these spiral resonators have shown their capability in measuring other characteristics as well, laying the foundation for further investigation [Alruwaili et al., 2017; Loflin et al., 2020; Mohammed et al., 2019; Rogers et al., 2016]. Therefore, they could also be capable of detecting the changes in permittivity that result from an increase in the CO_2 dissolved in a liquid like blood. The objective of this study was to test the feasibility of using an RF spiral resonator to detect changes in dissolved gas CO_2 in the blood by first seeing if it could detect similar changes in water.

3.3 Materials and Methods

3.3.1 Sensor Fabrication and Design

After some experimentation, it was decided that initial testing would focus on a single sensor design in order to first determine if a change in dissolved gas CO_2 would produce a measurable response in the sensor- with the possibility of further optimization of the sensor design down the line. Thus, for this study, a square spiral resonator was used to conduct measurements. A loop antenna surrounded the spiral resonator which would connect to the measuring device and electromagnetically couple with the sensor when it was powered. The sensor was designed using MATLAB code which generated a custom spiral shape given input parameters like the number of turns and gap width. In order to create the design's shape out of copper, it was first printed onto a copper-clad laminate using a modified Xerox Colorqube 8580 printer- creating a positive mask from the wax in the design of the sensor. After being smoothed in an acetone vapor bath and cut out, the sensor was then chemically etched using ferric chloride (FeCl3). Once the etching process was finished, the completed sensor was removed from the FeCL3 solution, cleaned off, and then connected to a coaxial cable which would connect it to the measuring device.

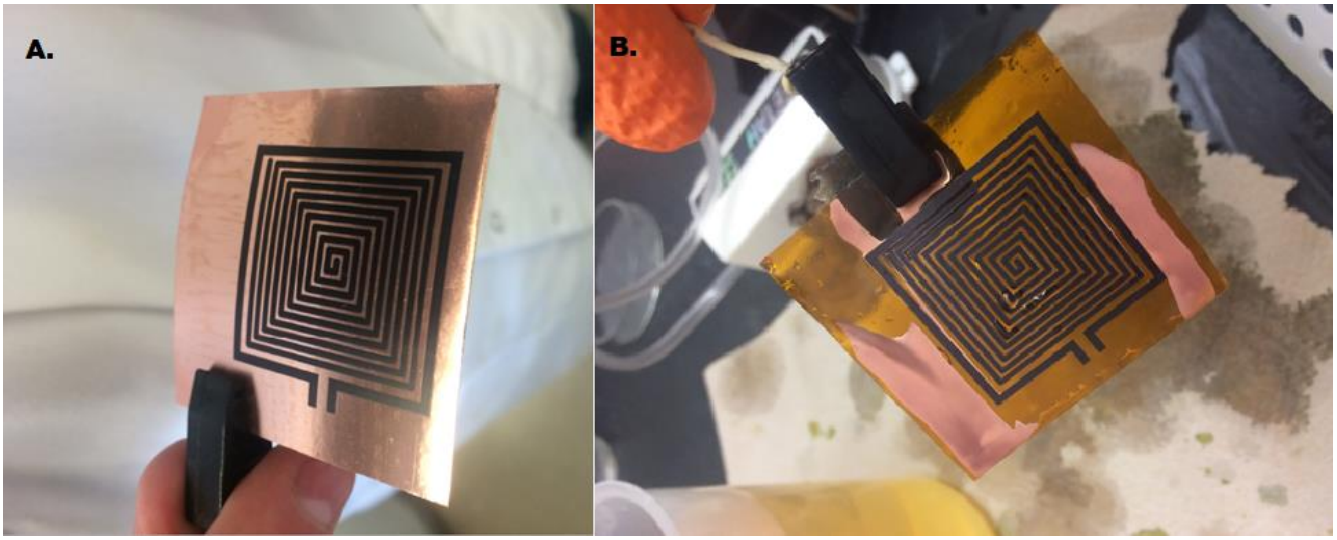


Figure 3.1: Example spiral resonator sensor design on copper-clad laminate before etching (A.) and after the etching process was completed (B.)

The completed sensor which was used in this study, shown below in Figure 3.2, had 10 turns in total and a trace width of about 1.10 mm (that is, the width of the antenna itself throughout the spiral pattern). The gap width between each trace, by comparison, was roughly 0.56mm. These parameters had slight fluctuations due to variance in production, but nothing that would be enough to significantly affect the results.

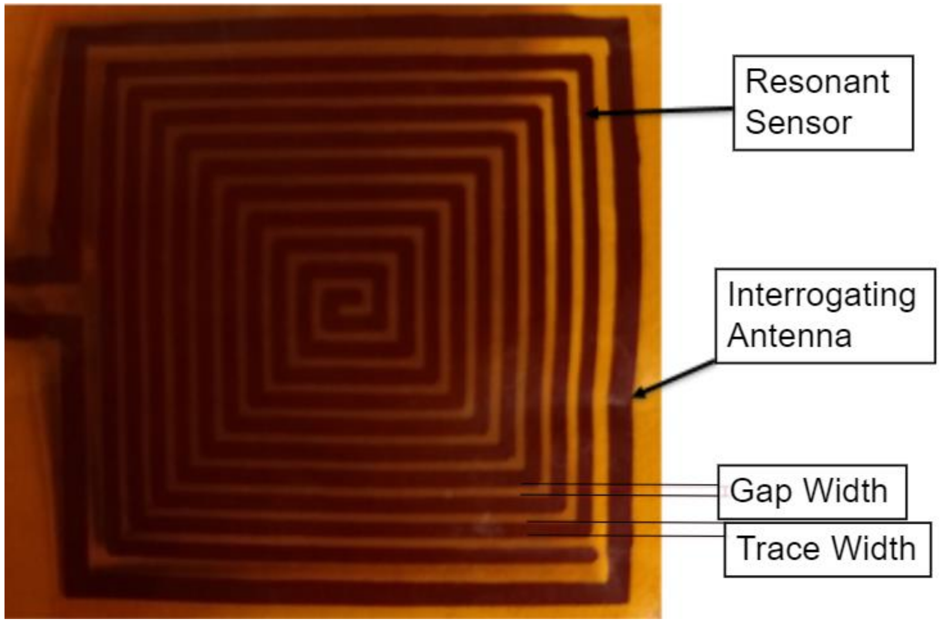


Figure 3.2: Spiral resonant sensor used in the experiment, along with the key parameters of its design: 10 turns, a gap width of 0.56 mm, and a trace width of 1.10 mm

3.3.2 Operating Methodology

The sensor was powered, and its results measured by a vector network analyzer (VNA) which sent an alternating current through the outside loop. For this study, the VNA which was used was the SDR-Kits DG8SAQ VNWA 3- which has an overall frequency range from 1 kHz to 1.3 GHz and was found to have a full-sweep sampling rate of roughly 1.2 Hz based on testing. The VNA sends an alternating current passing through the loop antenna, creating an electromagnetic field around the spiral resonator which couples with it and induces a current within it as well. This current causes the resonator to emit an electromagnetic field of its own, with a radiation pattern specific to the sensor's design. Based on the relative permittivity of the area penetrated by the electromagnetic field, the overall system, which can be represented as a lumped RLC circuit, has its properties affected- primarily in the form of its capacitance. Differences in the dielectric constant of the material being measured, in this case between CO_2 and water, affect the overall relative permittivity and how much energy is absorbed by the material being penetrated. The capacitance of an RLC circuit has an inverse relationship with resonant frequency, as shown in equation (3.1), which causes a decrease in resonant frequency as the capacitance increases. The resonant frequency is also affected by the sensor's parameters such as gap width and number of turns- which change its effective inductance and capacitance and allow for different designs to be tweaked for different applications.

$$f = \frac{1}{2\pi\sqrt{LC}} \tag{3.1}$$

The VNA measures changes in the sensor by analyzing the complex components of the created system- and in particular for measurements with this type of sensor, the S_{11} coefficient is the main feature focused on. The unitless S_{11} coefficient represents the proportion of power put into the system which is reflected back. At an S_{11} of 1, for example, all of the power from the VNA is reflected back to it- while at an S_{11} of 0, all of it is instead absorbed by the sensor's surroundings. The VNA rapidly conducts a sweep during measurements, alternating the current across a range of frequencies and measuring the S_{11} parameter at each to find the resonant frequency at which the peak amount of power is absorbed (and the S_{11} is at its minimum).

3.3.3 Experimental Design

To determine the potential effectiveness of the sensor in measuring dissolved CO_2 gas changes, it was tested in water rather than blood or a blood analogue, as water is the chief component of the blood plasma in which CO_2 is dissolved- and the overall principles of detecting dissolved gas in the two liquids should still be the same. The spiral resonator sensor was placed against the side of a 500 mL flat-bottomed glass beaker, which was filled with 400 mL of deionized (DI) water. This made the water level high enough that the sensor's electromagnetic field wouldn't be significantly affected by any changes in the air above the water line and would only respond to changes in the water itself. Next, the water's CO_2 concentration level had to be changed- which posed the challenge of doing so without introducing any other solvents to the water to ensure that they wouldn't affect its relative permittivity. To do so, the water flask was connected by a tube to a reaction flask with two openings- one connected to the water flask, and the second left open to add the reactants. Both ends of the connection tube used straight inline adapters evenly coated with vacuum grease which would ensure a sealed, air-tight connection. Keck clips were placed to hold the adapters onto the flasks and ensure that the internal pressure would not cause them to move and release any of the trapped gas.

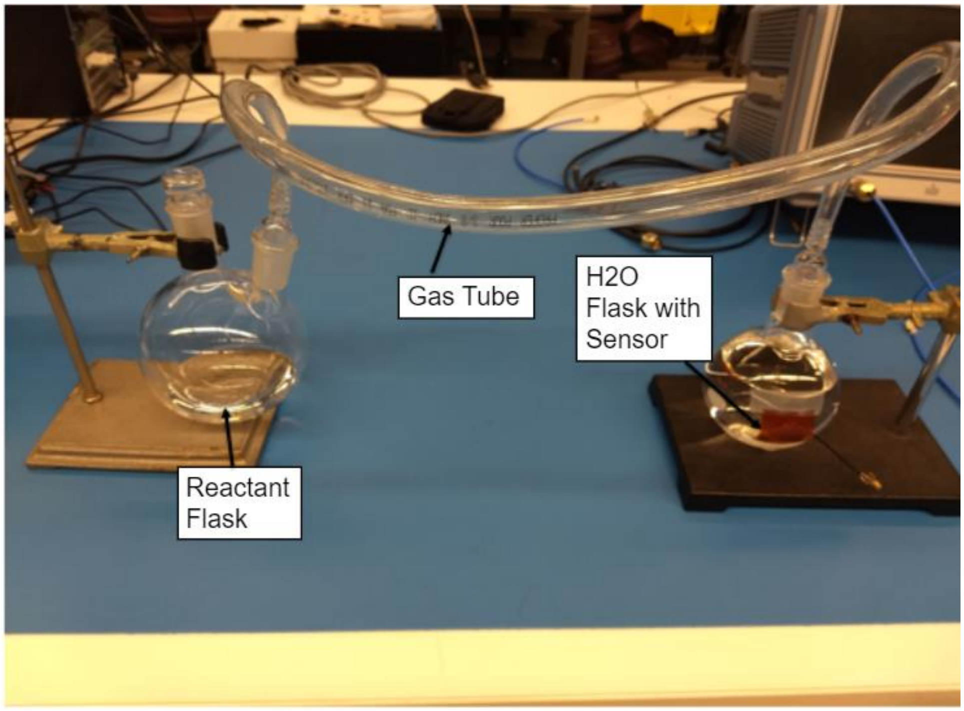


Figure 3.3: Experimental setup showing how the two flasks were connected and the sensor was placed

When conducting the experiment, the reaction flask was filled with an excess amount of acetic acid (CH_3COOH), commonly known as vinegar. Then, through the free opening of the reaction flask, sodium bicarbonate ($NaHCO_3$, or baking soda) was added into the acetic acid at varying amounts depending on the test to create different amounts of CO_2 gas- and the reaction flask was then quickly stoppered off with a vacuum grease-coated plug so that none of the gas could escape. For this experiment, the $NaHCO_3$ was added at five different levels- ranging from 0g to 1g at 0.25g steps. This reaction took place following equation (3.2).

$$NaHCO_3 + CH_3COOH = NaCH_3COO + CO_2 + H_2O \tag{3.2}$$

The resulting CO_2 gas formed by this reaction then flowed from the reaction flask into the water flask until the pressure equalized between them. It should be noted that rough estimates of the produced CO_2 gas were calculated before testing, along with the pressure this would produce inside the system, in order to ensure that the pressure would stay far below the tolerance limits of the glassware used. The heightened partial pressure of CO_2 in the enclosed air then diffused into the water in the flask being measured. Henry's law explains this interaction- stating that the amount of gas dissolved in a liquid is directly proportional to the partial pressure of that same gas in the air above it as shown below in Figure 3.4. Following this principle, the different amounts of sodium bicarbonate added produced different partial pressures of CO_2 gas, and thus different concentrations of CO_2 dissolved in the water. Initial testing determined that it took some time for the CO_2 gas to fully diffuse into the water after the initial reaction- with the system equalizing out after about 30 minutes. At 30 minutes for each sample, a VNA sweep was conducted, and the resulting waveform was measured to determine the change (if any) in resonant frequency or other properties. Based on some initial testing to find the area of interest with the clearest resonant frequency change, the frequency range for the sweep was set to go from 130 to 150 MHz. The entire setup process was repeated, and all containers cleaned and refilled, between each test. This ensured that no contamination from one test would have any chance of affecting another.

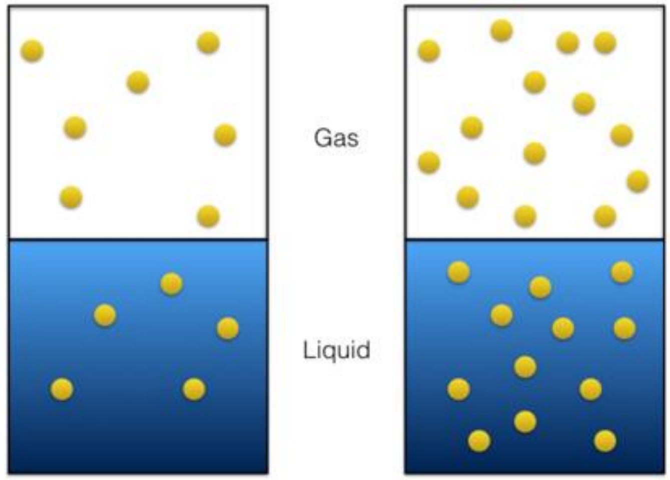


Figure 3.4: Visual representation of Henry's Law, where the concentration of gas dissolved in a liquid is proportional to the partial pressure of the same gas in the air above it.

3.3.4 Data Analysis

The complete sweep across the range of frequencies being measured was recorded for every trial, with five samples taken for each level of CO_2 using the VNWA software associated with the VNA used for the experiment. After being saved and converted into spreadsheet format, each sample was analyzed using Microsoft Excel in order to find the minimum S_{11} value which would identify the resonant frequency. Both the frequency of that resonant peak and the S_{11} parameter at the peak were recorded for each measurement and compared between them- and the overall waveform was plotted against the baseline for a visual comparison as well to see how the resonant frequency and amplitude might be affected by the dissolved gas. The mean for each level of CO_2 was calculated, and any outliers further than 2 standard deviations from the mean within each group were excluded. The potential correlation between resonant frequency shifts and changes in CO_2 concentration were analyzed using linear regression analysis. A one-way ANOVA as well at a significance level of $\alpha = .05$ to determine the significance of the results, with the amount of sodium bicarbonate as the independent variable and the resonant frequency as the dependent variable.

3.4 Results

Initial tests were conducted using the sensor on the experimental setup using the water flask filled with 400 mL of water but with no CO_2 content to establish a baseline. Figure 3.5 below shows the raw VNA reading recorded across the measured area of interest. Because of the potential for environmental changes to affect the sensor's output, the resonant frequency shift in each test was based off of the recorded baseline resonant frequency for that specific test before the CO_2 gas was introduced rather than a single baseline resonant frequency for all tests. In the initial baseline, the principal resonant frequency was found to be at approximately 142.4 MHz at an S_{11} of –4.5 db. For each of the five different amounts of $NaHCO_3$ introduced to the reaction flask, and thus for each level of dissolved CO_2 gas tested, the test was conducted five times- for a total sample size of 25. Initial testing with adding CO_2 to the system also revealed that the resonant sensor changed over time- presumably as the CO_2 diffused into the water more and more. One experimental test with a large amount of sodium bicarbonate found a difference of 0.4MHz in resonant frequency between a measurement 10 minutes and 20 minutes after reaction- but almost no difference between 20 and 30 minutes. The baseline testing also revealed some noise in the signal, including an artifact to the right of the resonant frequency peak.

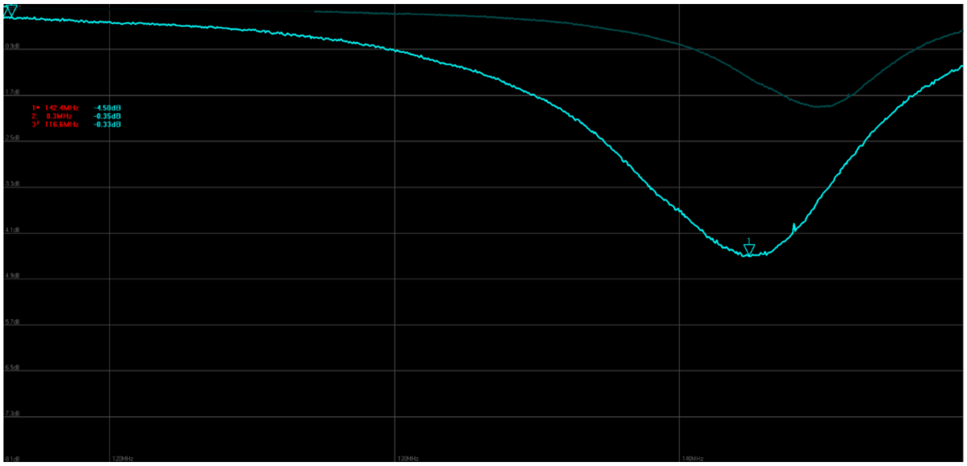
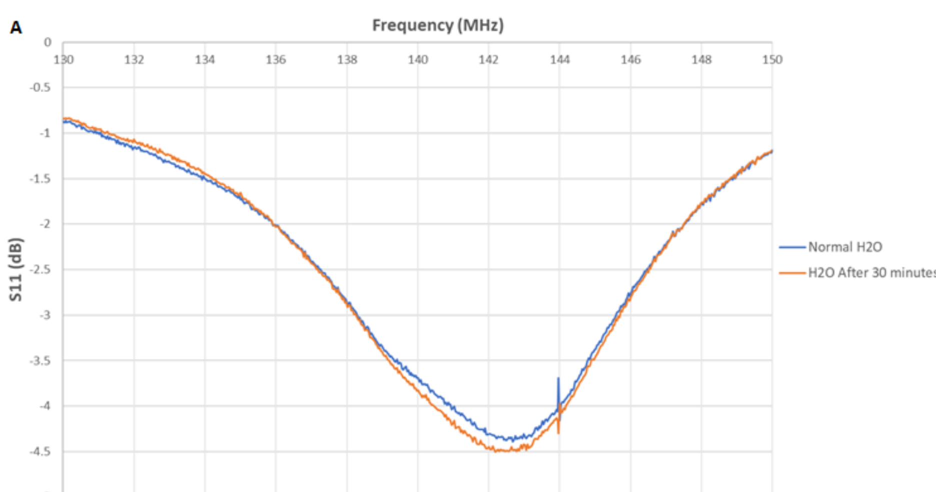
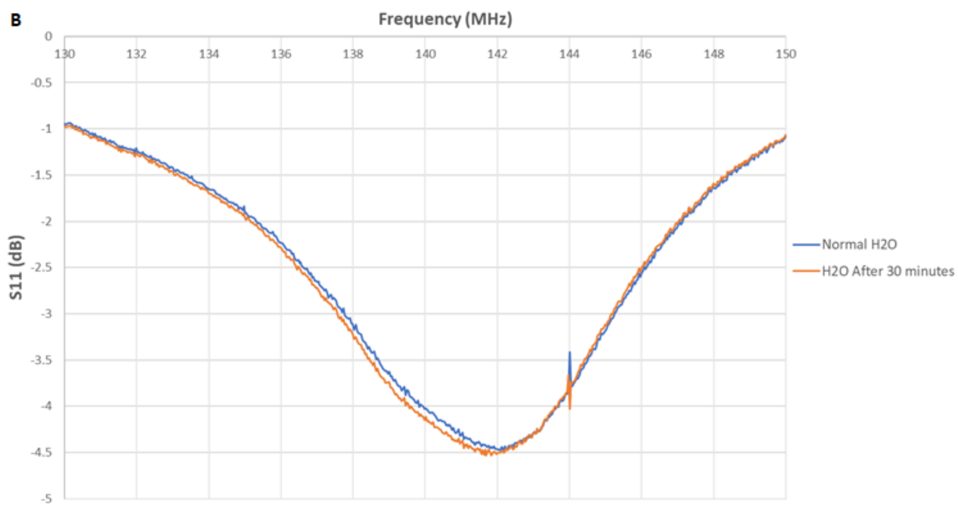


Figure 3.5: Raw baseline waveform of the sensor recorded by the VNA across the area of interest for 400 mL of DI water with no added CO_2, with the x-axis showing frequency and the y-axis showing the S_{11} amplitude

The resulting data showed a consistent shift in resonant frequency response as a result of the dissolved CO_2 added to the water. Figure 3.6 A gives an example of one recorded shift in response to the addition of 1g of $NaHCO_3$. The waveform difference shown there was fairly typical for the recorded results in that there was both a negative shift in resonant frequency and a decrease in the amplitude of the S_{11} as well. Figure 3.6 B and C show how the shift in overall waveform was less for lower amounts of added $NaHCO_3$, and negligible overall for the control with no CO_2 added, respectively- though there was some variability within groups.





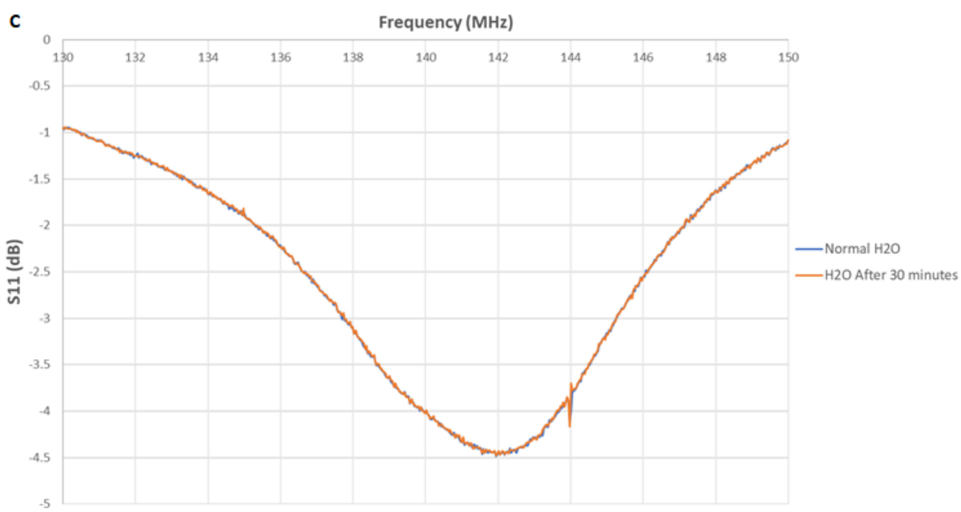


Figure 3.6: A) Comparison of VNA-measured responses of the sensor for H2O before (blue) and 30 minutes after (orange) the initial introduction of dissolved CO_2 gas produced from 1g of $NaHCO_3$ B) The same comparison in response to the dissolved CO_2 gas produced from 0.5g of $NaHCO_3$ C) Comparison of VNA frequency sweep for part of the control group with no added CO_2 after 30 minutes

Average values of resonant frequency shift were determined- with most of them being negative so they were represented as positive values of shift in the negative direction. One significant outlier was found for the 0.75g group which was excluded. There was an average negative shift of –0.0561 MHz for the control group, 0.120 MHz for 0.25g of added $NaHCO_3$, 0.168 MHz for 0.5g, 0.219 MHz for 0.75g, and 0.448 MHz for 1g. A linear regression performed with these results found a correlation between the negative resonant frequency shift and the CO_2 amounts, with an R^2 value of 0.923 indicating a strong relationship as shown in Figure 3.7 A one-way analysis of variance (ANOVA) was performed as well to verify the significance of the results. The ANOVA indicated a statistically significant effect on the resonant frequency shifts with a p-value of 0.0041.

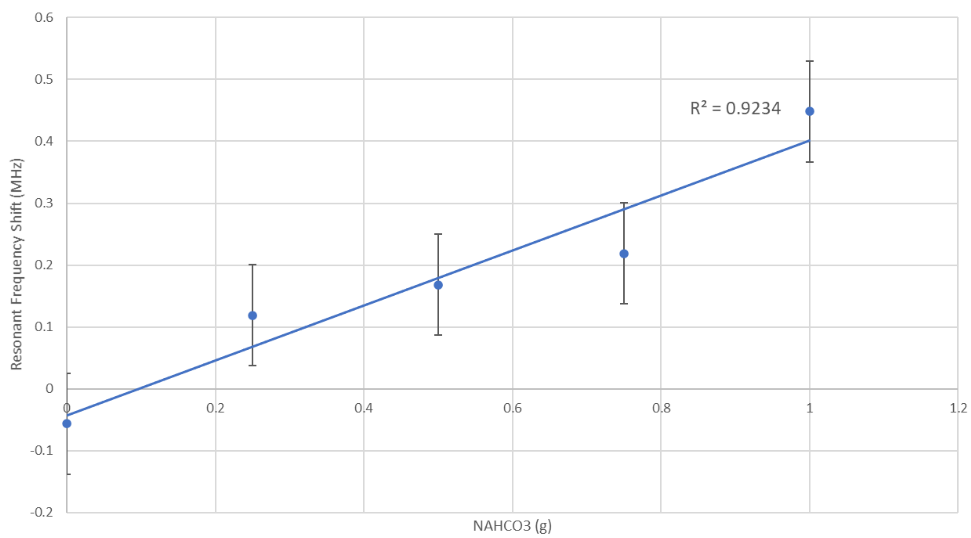


Figure 3.7: Change in average negative resonant frequency shift in relation to the amount of NaHCO3 which reacted to create the dissolved CO_2 gas and the trendline from the linear regression, with bars showing standard error

3.5 Discussion

3.5.1 Significance

The results of this study demonstrate the potential of an RF resonant sensor to measure changes in dissolved CO_2 gas content. The spiral resonator sensor used in this study showed a clear negative shift in resonant frequency in measured water when CO_2 gas was dissolved into it. Additionally, the results of this study demonstrated that the degree of the recorded resonant frequency shift was correlated with the amount of increase in CO_2- with an R^2 value of 0.9234 showing the relationship. The experimental data matches the theoretically expected result that the addition of dissolved CO_2 gas would decrease the resonant frequency. The additional CO_2 molecules interspersed between the H2O molecules increases the overall permittivity of the water being measured as a whole- affecting how strongly the molecules are polarized by an electromagnetic field like that generated by the sensor. This permittivity increase effectively increases its capacitance as a lumped circuit element, which has an inverse relationship with resonant frequency- explaining the shifts that were observed. Overall, this recorded resonant frequency shift gives a strong indication that the spiral resonator used in this study could be used to reliably detect and measure dissolved CO_2 gas in water (and most likely other dissolved gases as well, as CO_2 has a relatively small dielectric constant compared to denser gases).

Based on the linear regression model from the results of this study, it's possible to develop a calibration method for the sensor to measure CO_2 concentration by calculating the change in resonant frequency with respect to CO_2 concentration change. The exact CO_2 concentration change must be estimated based off of the dimensions of the overall system being used and the amount of $NaHCO_3$ dissolved. For this estimation, the volume of the acetic acid and the resulting products from the reaction with $NaHCO_3$ are assumed to be negligible due to their small size compared with the overall volume (less than 5 mL). Given that $NaHCO_3$ has a molar mass of roughly 84 g/mol [National Center for Biotechnology Information, 2021], the 0.25g used in each step of the study equates to 2.976*10^-3 moles of $NaHCO_3$ and, therefore, 0.002976 moles of CO_2 produced. The partial pressure of CO_2 in the air can be estimated using the ideal gas law given in equation (3.3):

$$PV = nRT \tag{3.3}$$

where P is the pressure of the gas, V is the volume of the total system (estimated at 1200 mL after excluding the space occupied by water), n is the number of moles of gas, R is the ideal gas constant, and T is the temperature [Kautz et al., 2005]. For this experiment, then, the partial pressure increase of CO_2 for each 0.25g of $NaHCO_3$ would be about 5.946 kPa.

With the partial pressure of the CO_2 above the water being measured determined, it's possible to calculate the concentration of dissolved gas in that water at equilibrium as well. This can be found using the previously discussed Henry's law, one formulaic version of which is equation (3.4):

$$C = kP \tag{3.4}$$

In this case, C is the concentration of the dissolved gas in moles per liter, k is the Henry's law constant (which is specific to the gas, solvent, and the temperature of the system), and P is the partial pressure of the gas above the solvent [Conover, 2009]. Based on equation (3.4), and with the Henry's law constant of CO_2 in water at room temperature being roughly 0.035 M/atm [NIST, 2021] the concentration increase generated from 0.25g of $NaHCO_3$ can be estimated at 2.053 millimoles per liter. Therefore, the sensor has a sensitivity of 105.1 kHz in negative resonant frequency shift per 2.053mM (or 44.56 mmHg as it's often represented using typical ABG systems) of dissolved CO_2 gas.

This correlation between recorded resonant frequency shift and dissolved CO_2 gas concentration could potentially make it suitable for usage in a lightweight skin patch sensor which would allow for the convenient and accurate monitoring of blood CO_2 levels without requiring exceptional operator training or any sort of invasive procedure. However, there are a number of limitations to this experiment and challenges with future testing of this methodology for blood CO_2 concentrations which could make the process of developing such a sensor for practical use a difficult challenge.

3.5.2 Limitations

In the case of this study, one of the main limitations was the equipment used. In particular, the DG8SAQ VNWA 3 which was used to power the sensor and make measurements. While it covered the desired frequency range, it limited in the number of measurements that could be made along that sweep, effectively limiting the resolution of the sensor across the swept range to about 50 kHz. It was still sufficient to draw conclusions about the concentrations for the levels of CO_2 explored in this study, but the levels of CO_2 which were calculated for this study were also relatively high compared to those found in the blood. The smallest difference in dissolved gas CO_2 partial pressure that was measured in this experiment was 44.56 mmHg, while the normal level of CO_2 gas dissolved in the blood in that range would only change enough to be detected under extreme circumstances. Therefore, a VNA with a better resolution (and potentially a different sensor design which is also more sensitive) will likely be required to effectively detect and measure CO_2 changes at the levels at which they would be found in vivo. The other main limitation of the DG8SAQ VNWA 3 in moving forward in this testing is its sampling frequency- which, at best, was found to be about 1.2 Hz- or 8.3 sweeps per second. This was not a concern in the test presented in this study where the system was found to be relatively stable after 30 minutes- but again, will pose some challenges for in vivo applications.

3.5.3 Future Studies

Advancing this sensing methodology to the point of developing a functional sensor which could evaluate human blood CO_2 levels would require a number of intermediate challenges to first be overcome through future tests. Due to the pulsatile flow of blood, the change in volume of blood in the artery being measured will have to be accounted for and filtered out in order to make any claims about the blood's content. The volume shifts will affect the relative permittivity measured by the sensor at a likely much greater degree than the CO_2 changes would. To measure and properly filter out these changes due to blood flow, a sampling frequency of at least twice the rate of the characteristic being measured is required so that the signal being measured (in this case, whatever permittivity changes are caused by the pulsatile flow of blood) is fully accounted for without major loss, according to the Nyquist theorem [Colarusso et al., 1999]. And as the human heart rate ranges from 60 to 100 beats per minute under normal conditions, and can go higher under stress or strenuous circumstances, a sampling frequency of at least 3-4 Hz (or 180-240 measurements per minute) would be needed- though the sampling rate could be higher to measure more accurately. Previous studies using these spiral resonators have utilized the Rohde & Schwarz ZNC3 Vector Network Analyzer 9 kHz – 3 GHz VNA, which is capable of better addressing both the issue of sensitivity and sampling frequency as it has a greater resolution and has been used with a sampling rate of at least 200 Hz [Becker et al., 2018]. This Rohde & Schwarz VNA model has sufficient specifications to test spiral resonators capability to detect blood CO_2 levels and could enable tests which would help to further characterize pulsatile flow and blood permittivity properties. This could include tests on arm phantoms which model arterial blood flow and potentially tests using blood analogues to better represent the actual dielectric properties of blood. Different experimental methods will have to be developed to properly modify the CO_2 levels of the measurand under these circumstances.

Another step would be to work towards limiting the area measured by the sensor to a smaller size so that it could focus primarily on the blood vessel being evaluated. In the case of current arterial blood gas tests, and many other procedures requiring access to an artery, the radial artery is most often used because as it's relatively close to the skin and easy to access. While some testing methods have explored using veins, arteries give a more accurate representation of CO_2 levels in the blood. These properties would make the radial artery an ideal candidate for this type of noninvasive sensing as well. Previous studies using this sensor design have utilized smaller sized spiral resonators- which will need to be explored in more detail for this potential application to get the area of the sensor's focus down to 3-4mm to fit these blood vessels. The sensor itself could be be miniaturized a great deal further and the design of the sensor could be changed to focus the resonator's electromagnetic field to a smaller area to prevent any interference from surrounding tissues. This could include changes in the spiral shape (which was square in this study but has been investigated in other shapes as well in previous studies), characteristics like gap width and number of turns, or the entire RF resonator design. Other studies using RF resonators for sensing applications have used different designs like complementary split ring resonators to measure parameters like blood glucose content in drawn blood [Govind and Akhtar, 2020]. These RF resonators have somewhat similar properties to the sensor used in this study in that they employ the coupling of elements. Further investigation will be required to determine if the spiral resonator is optimal for this application.

The fact that spiral resonators can have multiple resonant frequencies, though, makes them a good option for solving another problem in noninvasively detecting blood CO_2- specificity. Since the CO_2 dissolved in the blood is a relatively small portion of the whole, it will likely be challenging to discern resonant frequency changes from CO_2 concentrations from changes caused by other factors. The pulsatile flow of blood is fairly consistent in amplitude and thus should be able to be filtered out with frequent enough recordings of the resonant frequency shift over time. But some other factors like blood sugar, blood cells, and platelets may be more difficult to address or require calibration. Previous studies attempting to use RF sensors to noninvasively evaluate blood glucose have encountered some of these issues [Yilmaz et al., 2018]. In the case of CO_2, some key factors of concern might include blood glucose levels which will be different before and after a patient has eaten, hormones in the blood that may change over time, and many other confounding factors like platelets, proteins, and waste products in the blood which might not stay constant and would affect its overall permittivity as a result. Measuring more than one resonant frequency at once, however, may allow for the better identification of how a specific factor affects the sensor's response. A 2018 study used this type of methodology to better analyze the results of sensor for microfluidic chemicals and help discern one chemical from another [Zhou et al., 2018]. Another approach for focusing specifically on the CO_2 levels would be continuous monitoring of the patient over time to help filter out nuisance factors. This could be done either over a testing period of several minutes, at least, for more significant changes in CO_2 levels- or as a wearable device which would constantly evaluate CO_2 levels throughout the day and be better able to identify and account for other changes as they occur.

The lightweight and noninvasive nature of the spiral resonator sensor would make it ideal for a wearable device, which could be worn around the wrist to measure the blood in the radial artery. It would also have the added benefit of being able to immediately identify when CO_2 levels are rising- and help to identify acute causes of hypercapnia. In the case of monitoring during spaceflight, a wearable device would be especially helpful in that it would allow for the identification of specific situations in which CO_2 levels are high, alert astronauts to potential leaks in air supply before they begin to notice other symptoms, and identify specific areas of stations and spacecraft in which air circulation is insufficient so that they can be addressed. Other methods to improve the potential CO_2 detection ability of a sensor could include attempting to measure the dissolved bicarbonate rather than the gaseous CO_2, as it's the state in which most of the CO_2 is stored- though it might affect permittivity differently or in lower amounts than the dissolved gas does. All in all, being able to isolate resonant frequency shifts due to CO_2 changes using an RF spiral resonator will likely take considerable time and resources, but still has potential to allow for the development of a lightweight noninvasive sensor to detect changes in the concentration of CO_2 in the blood.

3.6 Conclusion

RF resonant sensors have shown potential to be used in the measurement of key health diagnostics noninvasively. They can be lightweight and convenient devices, which makes them ideal candidates for the monitoring of blood CO_2 levels aboard spacecraft where these factors and potential CO_2 exposure are a concern. This study examined the use of a square spiral resonator to detect CO_2 gas dissolved in water to prove its potential for detecting CO_2 in the blood as well. A strong correlation was identified between the resonant frequency shifts recorded by the sensor and the changes in dissolved CO_2 concentration. While these results are promising, there are still limitations to this study and many other confounding factors which would need to be addressed and differentiated from the shifts caused by CO_2 levels in the blood. Future studies could address these limitations by modifying the sensor design, using equipment with a higher sampling rate, and examining multiple resonant frequencies to help account for and filter out undesired signals. If these challenges can be overcome, this type of spiral resonator could be developed into a wearable blood gas CO_2 sensor that could alert astronauts or anyone else at risk of hypercapnia to the presence of excessive CO_2 in their blood before they notice more severe and potentially detrimental effects.

REFERENCES

REFERENCES

Z. Ahmadi, A. Bornefalk-Hermansson, K. A. Franklin, B. Midgren, and M. P. Ekström, "Hypo- and hypercapnia predict mortality in oxygen-dependent chronic obstructive pulmonary disease: a population-based prospective study," Respiratory Research, vol. 15, no. 1, p. 30, 2014-12-01 2014, doi: 10.1186/1465-9921-15-30.

J. G. Allen, P. Macnaughton, U. Satish, S. Santanam, J. Vallarino, and J. D. Spengler, "Associations of Cognitive Function Scores with Carbon Dioxide, Ventilation, and Volatile Organic Compound Exposures in Office Workers: A Controlled Exposure Study of Green and Conventional Office Environments," Environmental Health Perspectives, vol. 124, no. 6, pp. 805-812, 2016-06-01 2016, doi: 10.1289/ehp.1510037.

F. Alruwaili, K. Cluff, J. Griffith, and H. Farhoud, "Passive Self Resonant Skin Patch Sensor to Monitor Cardiac Intraventricular Stroke Volume Using Electromagnetic Properties of Blood," IEEE Journal of Translational Engineering in Health and Medicine, vol. 6, pp. 1-9, 2018-01-01 2018, doi: 10.1109/jtehm.2018.2870589.

G. S. Anderson, R. C. Miller, and A. R. H. Goodwin, "Static Dielectric Constants for Liquid Water from 300 K to 350 K at Pressures to 13 MPa Using a New Radio-Frequency Resonator," Journal of Chemical & Engineering Data, vol. 45, no. 4, pp. 549-554, 2000-07-01 2000, doi: 10.1021/je9903092.

D. Castro, S. M. Patil, and M. Keenaghan, "Arterial blood gas," in StatPearls [Internet]: StatPearls Publishing, 2021.

K. Chapman and K. E. Dragan, "Hypercarbia," in StatPearls [Internet]: StatPearls Publishing, 2020.

K. Cluff et al., "Passive Wearable Skin Patch Sensor Measures Limb Hemodynamics Based on Electromagnetic Resonance," IEEE Transactions on Biomedical Engineering, vol. 65, no. 4, pp. 847-856, 2018-04-01 2018, doi: 10.1109/tbme.2017.2723001.

P. Colarusso, L. H. Kidder, I. W. Levin, and E. Neil Lewis, "Raman and Infrared Microspectroscopy," in Encyclopedia of Spectroscopy and Spectrometry, J. C. Lindon Ed. Oxford: Elsevier, 1999, pp. 1945-1954.

W. Conover, "Chemistry, (by Stephen S. Zumdahl and Susan A. Zumdahl)," ed: ACS Publications, 2009.

A. Conway et al., "Accuracy and precision of transcutaneous carbon dioxide monitoring: a systematic review and meta-analysis," Thorax, vol. 74, no. 2, pp. 157-163, 2019-02-01 2019, doi: 10.1136/thoraxjnl-2017-211466.

L. Da Silva Araujo and A. J. Belfort De Oliveira, "The square spiral resonator: Investigating its electromagnetic performance for filter design," in 2015 SBMO/IEEE MTT-S International Microwave and Optoelectronics Conference (IMOC), 2015-11-01 2015: IEEE, doi: 10.1109/imoc.2015.7369227.

DDBST GmbH. Dielectric Constant of Carbon Dioxide, DDBST GmbH, 2021 [cited March 12, 2022]

R. Dezube, "Exchanging Oxygen and Carbon Dioxide," Merck Manuals, 2019.

F. H. Alruwaili, J. Griffith, K. Cluff, and J. Patterson, "Non-invasive point-of-care method for measuring left-ventricular stroke-volume using a passive electromagnetic skin patch sensor," Journal of the American College of Cardiology, vol. 69, no. 11_Supplement, pp. 1068-1068, 2017, doi: doi:10.1016/S0735-1097(17)34457-1.

M. Ganter and A. Zollinger, "Continuous intravascular blood gas monitoring: development, current techniques, and clinical use of a commercial device," British Journal of Anaesthesia, vol. 91, no. 3, pp. 397-407, 2003-09-01 2003, doi: 10.1093/bja/aeg176.

M. R. Georgescu, A. Meslem, and I. Nastase, "Accumulation and spatial distribution of CO_2 in the astronaut's crew quarters on the International Space Station," Building and Environment, vol. 185, p. 107278, 2020-11-01 2020, doi: 10.1016/j.buildenv.2020.107278.

G. Govind and M. J. Akhtar, "Design of an ELC resonator-based reusable RF microfluidic sensor for blood glucose estimation," Scientific Reports, vol. 10, no. 1, 2020-12-01 2020, doi: 10.1038/s41598-020-75716-z.

J. Griffith et al., "Non-invasive electromagnetic skin patch sensor to measure intracranial fluid–volume shifts," Sensors, vol. 18, no. 4, p. 1022, 2018.

U. Guler, I. Costanzo, and D. Sen, "Emerging Blood Gas Monitors: How They Can Help With COVID-19," IEEE Solid-State Circuits Magazine, vol. 12, no. 4, pp. 33-47, 2020, doi: 10.1109/mssc.2020.3021839.

H. Huang, "Flexible Wireless Antenna Sensor: A Review," IEEE Sensors Journal, vol. 13, no. 10, pp. 3865-3872, 2013-10-01 2013, doi: 10.1109/jsen.2013.2242464.

S. E. Huttmann, W. Windisch, and J. H. Storre, "Techniques for the Measurement and Monitoring of Carbon Dioxide in the Blood," Annals of the American Thoracic Society, vol. 11, no. 4, pp. 645-652, 2014-05-01 2014, doi: 10.1513/annalsats.201311-387fr.

N. M. Ismaiel and D. Henzler, "Effects of hypercapnia and hypercapnic acidosis on attenuation of ventilator-associated lung injury," (in eng), Minerva Anestesiol, vol. 77, no. 7, pp. 723-33, Jul 2011.

J. T. James, "Surprising effects of CO_2 exposure on decision making," in 43rd international conference on environmental systems, 2013, p. 3463.

C. H. Kautz, P. R. Heron, M. E. Loverude, and L. C. McDermott, "Student understanding of the ideal gas law, Part I: A macroscopic perspective," American Journal of Physics, vol. 73, no. 11, pp. 1055-1063, 2005.

S. W. Kim, S. B. Choi, Y.-J. An, B.-H. Kim, D. W. Kim, and J.-G. Yook, "Heart Rate Detection During Sleep Using a Flexible RF Resonator and Injection-Locked PLL Sensor," IEEE Transactions on Biomedical Engineering, vol. 62, no. 11, pp. 2568-2575, 2015-11-01 2015, doi: 10.1109/tbme.2015.2439681.

S. Kodali, Bhavani, "Capnography Outside the Operating Rooms," Anesthesiology, vol. 118, no. 1, pp. 192-201, 2013-01-01 2013, doi: 10.1097/aln.0b013e318278c8b6.

J. Law et al., "Relationship Between Carbon Dioxide Levels and Reported Headaches on the International Space Station," Journal of Occupational and Environmental Medicine, vol. 56, no. 5, pp. 477-483, 2014, doi: 10.1097/jom.0000000000000158.

J. Law et al., "Carbon Dioxide Physiological Training at NASA," Aerospace Medicine and Human Performance, vol. 88, no. 10, pp. 897-902, 2017-10-01 2017, doi: 10.3357/amhp.4552.2017.

C. Li et al., "A noncontact wireless passive radio frequency (RF) resonant pressure sensor with optimized design for applications in high-temperature environments," Measurement Science and Technology, vol. 25, no. 7, p. 075101, 2014/05/14 2014, doi: 10.1088/0957-0233/25/7/075101.

B. Loflin, K. Cluff, J. Griffith, and N. Mohammed, "Identification of shoulder joint clearance in space suit using electromagnetic resonant spiral proximity sensor for injury prevention," Acta Astronautica, vol. 170, pp. 46-54, 2020/05/01/ 2020, doi: https://doi.org/10.1016/j.actaastro.2020.01.013.

N. Mohammed et al., "Radial Pulse Detection Using SWR Bridge and RF Spiral Resonator," in IEEE-EMBS International Conference on Wearable and Implantable Body Sensor Networks (BSN'19), Chicago, IL, USA, 2019.

C. Molnar and J. Gair, "Concepts of biology: 1st Canadian edition," BCcampus: Victoria, BC, Canada, 2015.

N. Mohammed, K. Cluff, J. Griffith, and B. Loflin, "A Noninvasive, Electromagnetic, Epidermal Sensing Device for Hemodynamics Monitoring," IEEE Transactions on Biomedical Circuits and Systems, vol. 13, no. 6, pp. 1393-1404, 2019, doi: 10.1109/TBCAS.2019.2945575.

B. S. Nassar and G. A. Schmidt, "Estimating Arterial Partial Pressure of Carbon Dioxide in Ventilated Patients: How Valid Are Surrogate Measures?," Annals of the American Thoracic Society, vol. 14, no. 6, pp. 1005-1014, 2017-06-01 2017, doi: 10.1513/annalsats.201701-034fr.

N. C. f. B. Information. "PubChem Compound Summary for CID 516892, Sodium bicarbonate." https://pubchem.ncbi.nlm.nih.gov/compound/Sodium-bicarbonate (accessed March 20th, 2022.)

NIST, "Carbon Dioxide," ed. NIST Chemistry WebBook SRD 69: National Institute of Standards and Technology, 2021.

D. P. O'Neill and P. A. Robbins, "A mechanistic physicochemical model of carbon dioxide transport in blood," Journal of Applied Physiology, vol. 122, no. 2, pp. 283-295, 2017-02-01 2017, doi: 10.1152/japplphysiol.00318.2016.

N. Pandit, R. K. Jaiswal, and N. P. Pathak, "Real-time non-intrusive RF biochemical sensor," Electronics Letters, vol. 56, no. 19, pp. 985-988, 2020-09-01 2020, doi: 10.1049/el.2020.1661.

J. Petersson and R. W. Glenny, "Gas exchange and ventilation–perfusion relationships in the lung," European Respiratory Journal, vol. 44, no. 4, pp. 1023-1041, 2014-10-01 2014, doi: 10.1183/09031936.00037014.

J. Rogers, B. Jayakumar, J. Patterson, and K. Cluff, "Electromagnetic properties of blood-flow for screening of peripheral artery disease," Arteriosclerosis, Thrombosis, and Vascular Biology, vol. 36, no. suppl_1, pp. A516-A516, 2016.

C. Roussos and A. Koutsoukou, "Respiratory failure," European Respiratory Journal, vol. 22, no. Supplement 47, pp. 3s-14s, 2003-11-16 2003, doi: 10.1183/09031936.03.00038503.

G. Schmalisch, "Current methodological and technical limitations of time and volumetric capnography in newborns," BioMedical Engineering OnLine, vol. 15, no. 1, 2016-12-01 2016, doi: 10.1186/s12938-016-0228-4.

J. W. Severinghaus, P. Astrup, and J. F. Murray, "Blood Gas Analysis and Critical Care Medicine," American Journal of Respiratory and Critical Care Medicine, vol. 157, no. 4, pp. S114-S122, 1998-04-01 1998, doi: 10.1164/ajrccm.157.4.nhlb1-9.

A. Shrivastava, G. K. Mani, and K. Tsuchiya, "Real Time, Flexible RF Sputtered ZnO Nano-film CO_2 Sensor for Capnographic Applications," in 2019 International Symposium on Micro-NanoMechatronics and Human Science (MHS), 2019-12-01 2019: IEEE, doi: 10.1109/mhs48134.2019.9249267.

Z. A. Siefker et al., "Manipulating polymer composition to create low-cost, high-fidelity sensors for indoor CO_2 monitoring," Scientific Reports, vol. 11, no. 1, 2021-12-01 2021, doi: 10.1038/s41598-021-92181-4.

F. Suarez-Sipmann, S. H. Bohm, and G. Tusman, "Volumetric capnography: the time has come," Current Opinion in Critical Care, vol. 20, no. 3, pp. 333-339, 2014, doi: 10.1097/mcc.0000000000000095.

V. Turgul and I. Kale, "RF/Microwave Non-invasive Blood Glucose Monitoring: An Overview of the Limitations, Challenges & State-of-the-Art," in 2019 E-Health and Bioengineering Conference (EHB), 2019-11-01 2019: IEEE, doi: 10.1109/ehb47216.2019.8970032.

W. Van Weteringen et al., "Novel transcutaneous sensor combining optical tcPO2 and electrochemical $tcPCO_2$ monitoring with reflectance pulse oximetry," Medical & Biological Engineering & Computing, vol. 58, no. 2, pp. 239-247, 2020-02-01 2020, doi: 10.1007/s11517-019-02067-x.

J. J. van Wijk, F. Weber, R. J. Stolker, and L. M. Staals, "Current state of noninvasive, continuous monitoring modalities in pediatric anesthesiology," Current Opinion in Anaesthesiology, vol. 33, no. 6, p. 781, 2020.

R. V. Walley, "Assessment of Respiratory Failure in Poliomyelitis," BMJ, vol. 2, no. 5142, pp. 82-85, 1959-07-25 1959, doi: 10.1136/bmj.2.5142.82.

S. R. Wilcox, "Management of respiratory failure due to covid-19," BMJ, p. m1786, 2020-05-04 2020, doi: 10.1136/bmj.m1786.

S. R. Wylie, A. Shaw, and A. I. Al-Shamma'a, "RF sensor for multiphase flow measurement through an oil pipeline," Measurement Science and Technology, vol. 17, no. 8, pp. 2141-2149, 2006/07/13 2006, doi: 10.1088/0957-0233/17/8/013.

T. Yilmaz, R. Foster, and Y. Hao, "Radio-Frequency and Microwave Techniques for Non-Invasive Measurement of Blood Glucose Levels," Diagnostics, vol. 9, no. 1, p. 6, 2019-01-08 2019, doi: 10.3390/diagnostics9010006.

H. Zhou et al., "Multi-Band Sensing for Dielectric Property of Chemicals Using Metamaterial Integrated Microfluidic Sensor," Scientific Reports, vol. 8, no. 1, 2018-12-01 2018, doi: 10.1038/s41598-018-32827-y.