Mobile Health Applications of Breath Analysis: Challenges and Solutions

by

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ABSTRACT

The world of healthcare can be seen as dynamic, often an area where technology and science meet to consummate a greater good for humanity. This relationship has been working well for the last century as evident by the average life expectancy change. For the greater of the last five decades the average life expectancy at birth increased globally by almost 20 years. In the United States specifically, life expectancy has grown from 50 years in 1900 to 78 years in 2009. That is a 76% increase in just over a century. As great as this increase sounds for humanity it means there are soon to be real issues in the healthcare world. A larger older population will need more healthcare services but have fewer young professionals to provide those services. Technology and science will need to continue to push the boundaries in order to develop and provide the solutions needed to continue providing the aging world population sufficient healthcare. One solution sure to help provide a brighter future for healthcare is mobile health (m-health). M-health can help provide a means for healthcare professionals to treat more patients with less work expenditure and do so with more personalized healthcare advice which will lead to better treatments. This paper discusses one area of m-health devices specifically; human breath analysis devices. The current laboratory methods of breath analysis and why these methods are not adequate for common healthcare practices will be discussed in more detail. Then more specifically, mobile breath analysis devices are discussed. The topic will encompass the challenges that need to be met in developing such devices,

possible solutions to these challenges, two real examples of mobile breath analysis devices and finally possible future directions for m-health technologies.

DEDICATION

I would like to dedicate this paper to all the great supporters I had throughout my school career. I would like to dedicate it to my family for always supporting me and pushing me to strive for better in my educational career. I would also like to dedicate this paper to my wonderful friends and colleagues who have helped me to become the person I am today.

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INTRODUCTION

Background

Healthcare is one of the world's largest and fastest growing industries. Many of the world's developed countries spend upwards of 10% of their GDP on healthcare. The United States is the largest spender, spending for healthcare is expected to grow to 17% for the 2012 fiscal year [2]. *Figure 1* below shows the total spending as percent GDP is broken down into categories for the United States' fiscal year 2012. Healthcare spending is clearly one of the largest pieces of the pie.

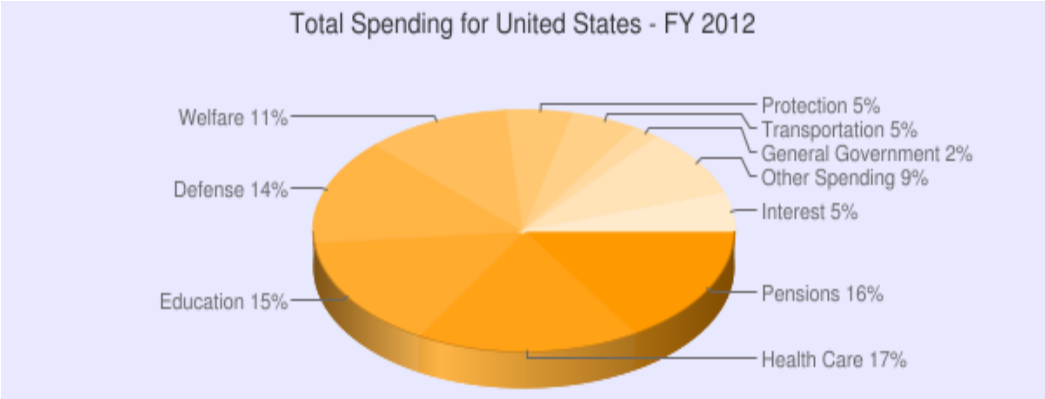


Figure 1. Total Spending for U.S. % GDP. [2]

It is projected that the industry will generate more jobs between the years 2008 and 2018 than any other industry, around 3.2 million new wage and salary positions [3]. This increase is affiliated with today's aging population. As life expectancies grow and fertility rates decrease the world's population is increasingly growing older. This means healthcare will grow ever more important to help the world's aging population to live healthy lives. But with less younger

individuals to care for the elderly, this becomes an increasingly difficult task. *Figure 2* below displays current as well as projected numbers for the world's total fertility rate and life expectancy at birth, notice how the gap between life expectancy and fertility rate continues to increase [1].

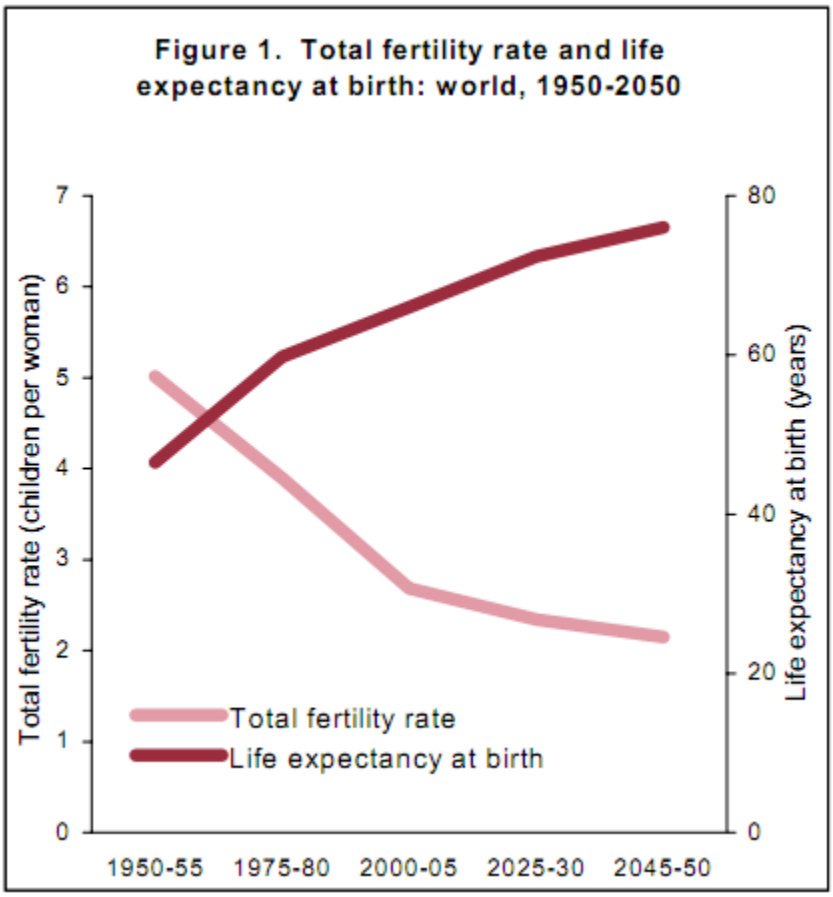


Figure 2. Fertility rate vs. life expectancy at birth for the world. [1]

The growing issue of an aging population with increasing demands for healthcare is one that mobile health (m-health) technologies can help to solve. While defining m-health can be a daunting task in its own right, it is generally accepted that the m-health field encompasses the use of mobile telecommunication and multimedia technologies in health care delivery [4].

These “mobile health” technologies will help to improve future healthcare in a number of ways. For one, today’s healthcare system is useful, but one issue with the general approach is that individuals only see the doctor when they feel sick. This leads to a single point in time measurement. The doctor must evaluate a patient’s health status off of data only acquired perhaps once a year. Via the use of m-health, physicians can acquire data for that point in time when the patient feels sick and comes in for treatment as well as acquire data that has been tracked for months previous. This health tracking data allows the physician to be provided with a better overall picture of the individual patient’s condition leading to a more focused and successful treatment plan. Not only will m-health help to improve the diagnosis and treatment of individual patients but it will also help to alleviate the growing issue of an aging population in need of more healthcare services. As the world’s population ages there will be more and more elderly in need of healthcare services but there will be less and less young healthcare professionals to provide these services. M-health can help healthcare professionals treat more individual patients and treat them more efficiently. Patients who would not normally have complete or any access to proper healthcare services can also benefit from mobile health technologies. Health information can be monitored remotely and sent to the proper physician over a network for diagnosis. The physician can then suggest further action or a possible treatment solution all without ever needing to see the patient face to face. With all the benefits mobile health technologies can bring to the healthcare field via

simply increasing access and improving diagnosis and treatment it is needed to know what applications are currently available.

One application growing in the m-health field is that of breath analysis. Breath analysis is a non-invasive tool that can help to diagnosis a variety of illnesses/symptoms. Breath analysis is not only now being considered as a tool to help diagnose human health conditions. Since the time of Hippocrates physicians have known that the human breath could provide sound health information [5]. Since Hippocrates's days breath analysis has come a long way. More recently a major milestone for human breath analysis was completed. In the 1970s Dr. Linus Pauling used gas-liquid chromatography analysis on the human breath and then reported some 250 substances found in exhaled breath [6]. The major compounds found in the human breath can be seen below in *Figure 3*.

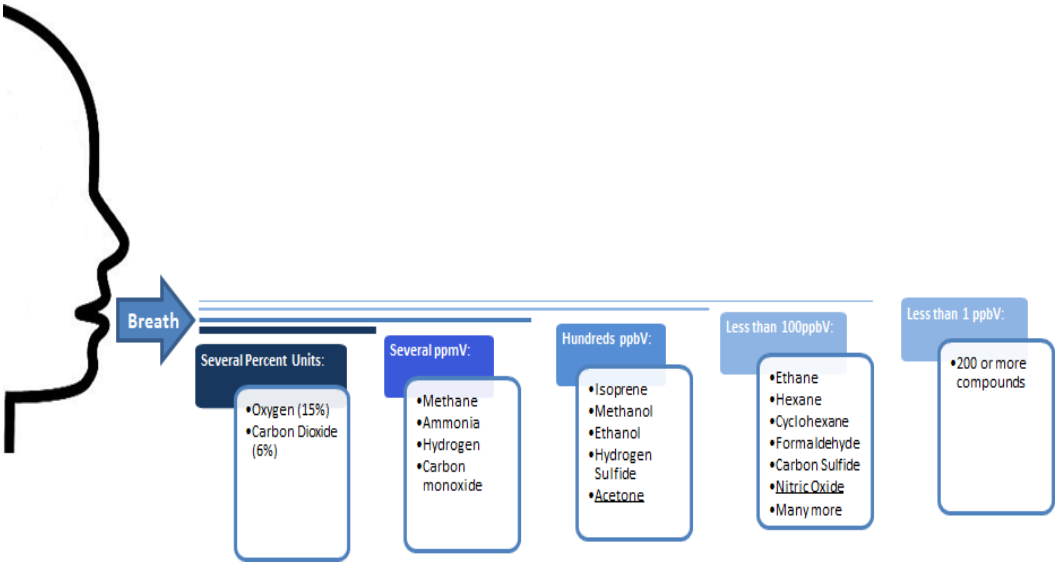


Figure 3. Some major components of exhaled breath.

A large number of the compounds found in the human breath can be linked to a variety of health issues. Studies have shown promise for the detection of lung cancer via measuring certain VOCs in the human breath samples.

"Every year, about 180,000 people develop lung cancer in the U.S.A., with a 5-year survival rate of only 14%. This increases up to 50% if lung cancer is localized at the time of diagnosis and treated promptly." [6]

With earlier treatment due to earlier detection via breath analysis many more lives could be saved from lung cancer. It has also been shown that many inflammatory lung diseases could be monitored using breath analysis [6]. These diseases range from bronchiectasis to cystic fibrosis to asthma. There are a number of biomarkers that have been identified for inflammatory diseases. Nitric oxide for example has been shown to be a promising biomarker for monitoring asthma attacks and lung inflammation [6]. With around one in twelve adults and one in nine children affected by asthma and the costs growing to $56 billion in 2007 in the United States, advanced treatment via breath analysis could prove to be invaluable [7]. Another large market where breath analysis and its non-invasive measurements could play a crucial role is that of ketone detection, more specifically acetone. Acetone is known to be a marker for Diabetes [6]. Diabetes is the seventh leading cause of deaths in the United States currently affecting more than eight percent of the U.S. population. Diabetes costs in the U.S. were $174 billion in 2007 and have continued to grow since [8]. It is estimated that associated healthcare costs due to Diabetes could be as high as $500 billion in 2011 and that by year 2030 as many as 1 out of 3 persons in the United States will

be Diabetic [9]. Acetone is useful in more than just determining if a person is pre-diabetic; it can also help in tracking one's diet.

"Acetone is an indicator for metabolizing fat accumulated in the abdominal cavity into the energy due to its β-oxidation, and thus acetone levels in the breath may be higher due to the progress of body weight loss by fasting or calories-limited diet. Therefore, repeated measurements of acetone in the breath are useful for accurately monitoring effective loss of body weight or body fat mass, and thus can also be used as a motive for continuing dietary therapy of obesity." [10]

With more than one-third of the United States' adults being obese better diet tracking could prove to be very useful tool [11]. Described above are some of the major applications for breath analysis, though the list does not end there. New applications are being discovered every year.

Current Methods

Today typical methods to perform breath analysis are gas chromatography, mass spectrometry and laser spectroscopy. Gas chromatography measures the substances within a known volume of gas sample via utilizing a carrier gas (usually an inert gas such as helium) to move the sample through a long narrow tube called the column. The constituents of the sample gas pass through and exit the column at different rates due to their differing chemical and physical properties. A detector monitoring the outlet of the column is used to detect the different constituents of the sample and their respective amounts. Factors such as

the carrier gas flow rate, column length and temperature can be altered to help insure the constituents of the sample gas exit the column at different times. Packing materials filled within the column called the stationary phase can also be utilized in order to help insure the constituents of the sample gas exit the column at different times [12]. A simple schematic displaying the main components of a gas chromatograph can be seen below in *Figure 4*.

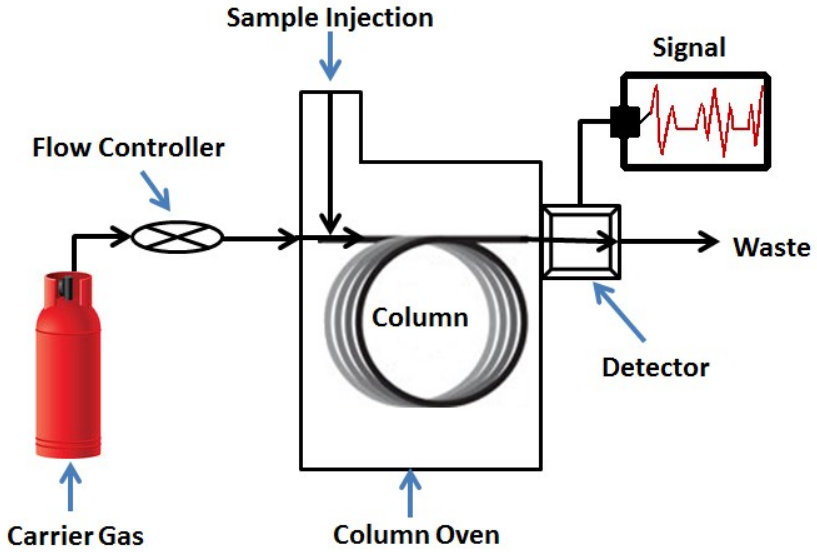


Figure 4. Gas Chromatograph Schematic.

Mass spectrometry is a technique that measures the differing mass-to-charge ratios of the sample gas constituents. The mass spectrometry completes this task by following this typical procedure [13]:

1) *A sample is loaded onto the MS instrument and undergoes vaporization.*
2) *The components of the sample are ionized by one of a variety of methods (e.g., by impacting them with an electron beam), which results in the formation of charged particles (ions).*

3) *The ions are separated according to their mass-to-charge ratio in an analyzer by electromagnetic fields.*
4) *The ions are detected, usually by a quantitative method.*
5) *The ion signal is processed into mass spectra.*

The three main modules of a mass spectrometer device are the ion source, the mass analyzer and the detector. These components come in many different types; the ionization method could be electron impact, chemical ionization, electrospray or another type. There are many different types of analyzers as well including a quadrupole, time-of-flight ion cyclotron resonance and more. There are many different types of detectors though most work by producing an electronic signal when struck by an ion [14]. The different types of ionization method, analyzer and detector all have their pros and cons ranging from resolution, speed, relative ease of use and cost. Gas chromatography is often coupled with mass spectrometry to produce a more powerful measuring system. First the gas chromatograph separates the sample gas constituents and completes its measurements these separated constituents then enter the mass spectrometer where they are ionized and their mass-to-charge ratio is measured.

The SIFT-MS is a more specific variation of a mass spectrometry device which can be used for real time measurement of concentrations of trace gases and vapors of volatile compounds in humid air including exhaled breath [15]. The BioSensors & BioElectronics laboratory utilizes the SIFT-MS device to measure compounds in exhaled breath including acetone. A picture of the SIFT-MS

device in the BioSensors & BioElectronics lab being used to perform a breath analysis for acetone can be seen below in *Figure 5*.

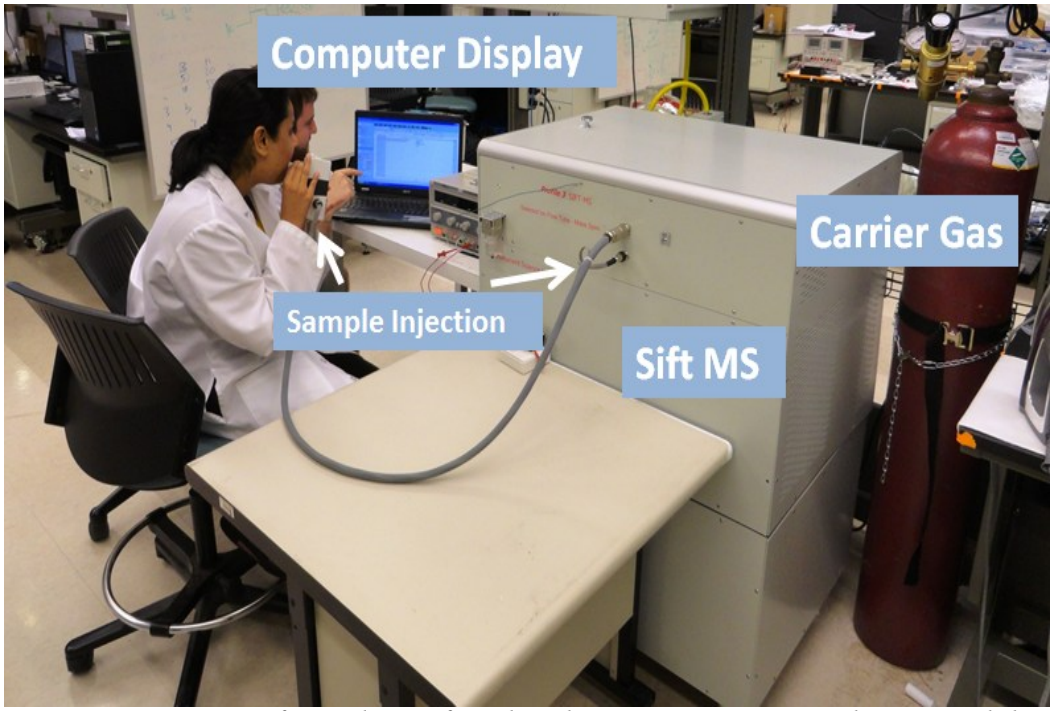


Figure 5. Sift MS device found in the BioSensors & BioElectronics lab.

Laser spectroscopy is another method which can be used to measure gas samples. In a general sense to perform laser spectroscopy a scientist trains a laser beam on the sample which yields a characteristic light source that can then be analyzed by a spectrometer. There are many different types of laser spectroscopy from laser-induced florescence (LIF) to laser-induced breakdown spectroscopy (LIBS). A simple diagram showing the typical setup of a LIBS setup can be seen below in *Figure 6* [16].

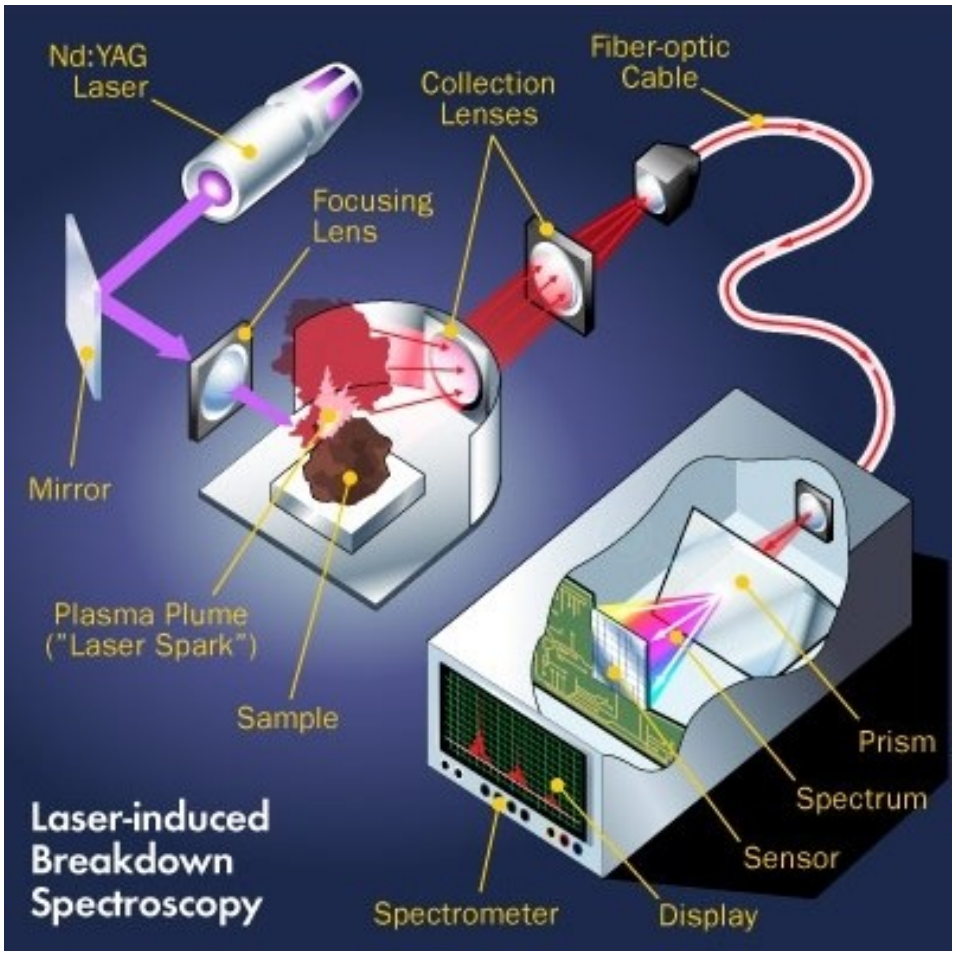


Figure 6. Laser-induced breakdown spectroscopy. [16]

Other than the more general detection devices discussed above there are also a number of devices which focus solely on one or a few compounds to detect. These more specialized devices are generally cheaper and smaller in size than the previously discussed devices though still far from being considered a mobile health device. One device in particular worth mentioning is the nitric oxide analyzer NOA280i from GE Analytical Instruments. The NOA280i device utilizes ozone-chemiluminescence technology to detect liquid and exhaled breath nitric oxide samples. A picture of the NOA280i device in the BioSensors &

BioElectronics lab being used to perform a breath analysis for nitric oxide can be seen below in *Figure 7*.

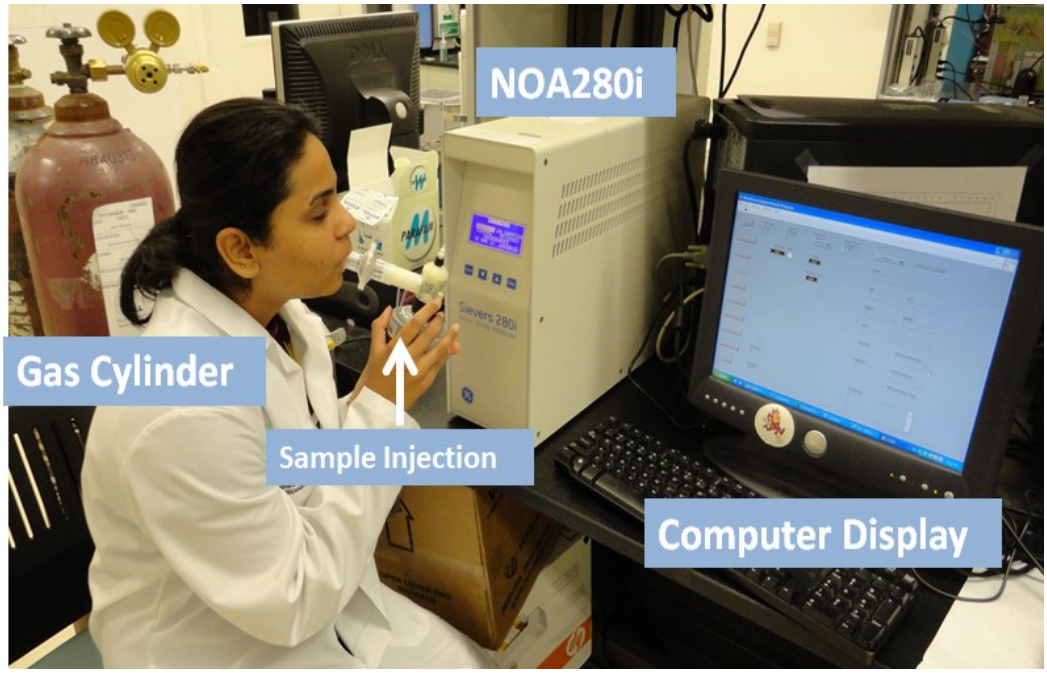


Figure 7. NOA280i device found in the BioSensors & BioElectronics lab.

Challenges

With all the positives described and the great impacts breath analysis could have on helping to treat some of the world's more damaging and prevalent health concerns, why is it not being utilized more? There are a number of factors making it hard for breath analysis to really catch on in the healthcare field. Cost is one of the largest limiting factors. With gas chromatographs costs typically ranging from $2,000 to more than $30,000, mass spectrometers ranging from $5,000 to more than $70,000, GC/MS devices ranging from $25,000 to more than $100,000 and laser spectroscopy devices ranging from $25,000 to more than $150,000 it is obvious that not everyone can afford these devices. More than just cost all of the above mentioned devices are also large in size and not easily moved

around or “bulky”. This bulky nature makes the devices not conducive to mobile use. As well as cost and size another factor limiting the widespread usage of the above mentioned devices is user friendliness. Gas chromatographs, mass spectrometers and laser spectroscopy devices all require training to use effectively. They are not devices just any one can bring home and with a little practice be proficient with. Many of these devices also need lab grade supporting equipment to operate correctly, such as carrier gas cylinders for the gas chromatography machine. The supporting lab equipment needed to operate the devices can themselves be very costly and not user friendly outside the lab area. These challenges can all be address by developing a simpler mobile device designed more specifically for certain types of breath analysis rather than lab grade equipment designed for a multitude of measurements.

Even though designing a mobile health device specifically for certain types of breath analysis could alleviate issues like cost and bulkiness that lab grade equipment has, a new set of challenges will still need to be addressed. One of the largest challenges a breath analysis device will have to overcome is that of interference. As described above in *Figure 3*, the human breath contains a plethora of different chemicals and compounds. When trying to measure just a few or a single compound found within the human breath, a breath analysis device needs to be capable of extracting the desired compound without the reading being affected by the other multitude of compounds in the sample. For example breath condensate or the relative humidity of a breath sample is one key factor that can really interfere with a sample measurement of many compounds. Another

challenge which needs to be addressed when collecting a breath sample is that of correct sample collection. For instance when measuring nitric oxide levels in a human breath sample the flow rate is critical. Flow rate that is too low or too high can result in a significantly different reading of nitric oxide levels in a human breath sample [17]. For this reason, a standard of 50ml/s for nitric oxide breath analysis has been set by the American Thoracic and European respiratory societies (ATS/ERS) [17]. Another challenging area for mobile breath analysis devices is testing condition variations. The conditions of one testing area can differ greatly from the conditions of another testing area. For instance a test done in an air controlled lab space will have relatively low levels of compounds such as volatile organic compounds (VOCs) compared to a test done in a location near congested motorways. The breath analysis device will need to be able to compensate for differences in locations and not allow the readings to be affected adversely via the outside environment, within reason. Finally the mobile breath analysis device will need proper integration of the components to insure a cost effective, reliable and user friendly solution.

Chapter 2

ADDRESSING THE CHALLENGES

M-health breath analysis devices need to overcome many challenges in order to provide an accurate and reproducible measurement. There are many different ways to address these challenges depending on factors such as cost, simplicity and the type of device or measurement the device is making. The major challenges that need to be addressed and solutions to these challenges are discussed in the sections below.

Interference

Quite possibly one of the most difficult challenges for any breath analysis device is that of interference. Because a human breath sample contains so many different compounds, now confirmed to be more than a thousand [6], measuring a select compound or compounds can be quite a daunting task. For instance humidity tends to wreak havoc on many sensors including those later discussed for acetone and nitric oxide detection. Considering a human breath sample typically has a relative humidity of 100% it is easy to see how humidity could be an issue. A human breath exhalation also typically contains 5% water vapor which can condense on device components causing more trouble. In order to remove humidity the breath sample needs to pass through a dehydrator. This dehydrator can be tuned depending on its application; for instance some devices may need less than 5% humidity where others may be able to tolerate much larger percentages of humidity. For the mobile breath acetone device developed in the

ASU BioDesign Institute BioSensors & BioElectronics lab the dehydrator used is a desiccant called Calcium Chloride or $CaCl_2$. The amount of desiccant need for the dehydrator is based off of testing done using the acetone detection device. Similarly the mobile nitric oxide breath analysis device developed in the ASU BioDesign Institute BioSensors & BioElectronics lab uses a dehydrator which uses the desiccant Calcium Sulfate or $CaSO_4$. Relative humidity does not affect the performance of the nitric oxide device as significantly as it does the acetone device. Therefore the nitric oxide device requires less work from the desiccant to remove humidity from the breath. The amount of desiccant used in the nitric oxide mouthpiece is an order of magnitude less than that used in the acetone mouthpiece. Although the nitric oxide device utilizes more than one technique to remove humidity from the breath sample the acetone device only uses one. The nitric oxide sensor also utilizes nafion tubing to remove humidity from the breath sample. Nafion tubing is commonly used to remove humidity because of its hygroscopic nature and selective permeability to water, although it cannot be used in a device such as the acetone device because of its ability to also remove ketones from the sample.

Selective Detection

Humidity is only one source of interference. There are still a thousand or more different elements in the human breath that could contribute to undesired performance of a breath analysis device. Due to the plethora of possible interference compounds in a human breath sample selective detection is important

to properly collect data on the desired compound. Selective detection can be accomplished in multiple fashions. The methods discussed will be the chemical methods of selective detection utilized by the acetone device and nitric oxide device developed in the BioSensors & BioElectroncis lab. Both these devices utilize optical detection based on selective colorimetric chemical reactions. The acetone device utilizes a sensory probe which is a chromophore. The chromophore is a specific chemical species that can change color upon interaction with the analyte. This color change will be quantified as an electrical signal by measuring the amount of light intensity able to pass through the substrate. The light intensity which passes through the substrate is measured via a pair of photodiodes. There are two photo diodes present because one acts as a reference measurement while the other acts as a sensing measurement. *Figure 8* below shows a simple schematic layout of the discussed acetone device sensing components [19].

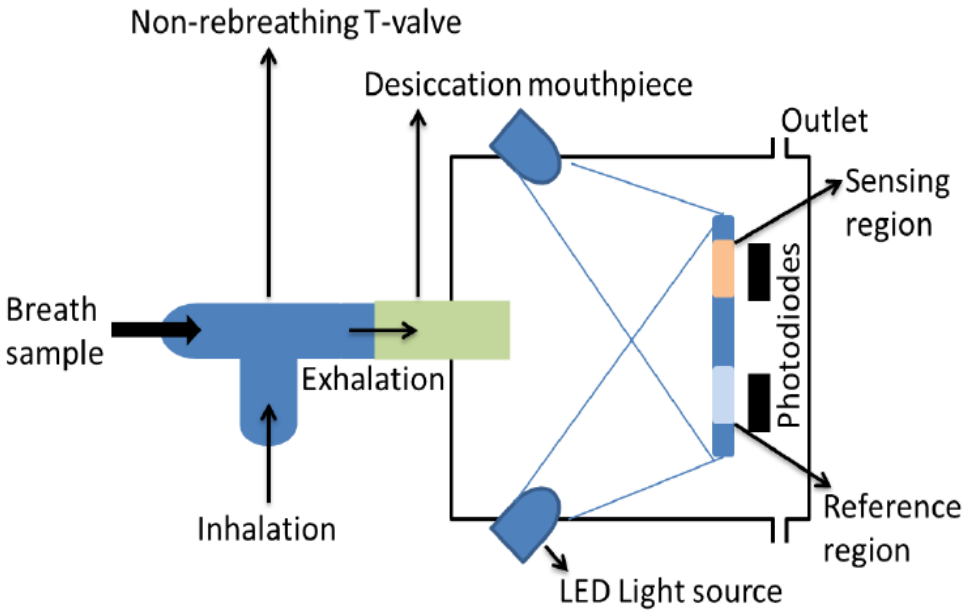


Figure 8. Simple schematic layout of acetone device sensing components. [19]

The nitric oxide sensor utilizes a very similar operation principle to nitric oxide in a human breath. The nitric oxide sensor also utilizes two photodiodes, one for reference and one for sensing. The nitric oxide sensing element is based on redox chemistry of phenylenediaine derivatives. Similar to the acetone device the nitric oxide device quantifies a color change in the sensing element via measuring the light intensity passed through the sensor cartridge. *Figure 9* below displays a simple schematic of the discussed nitric oxide sensing components.

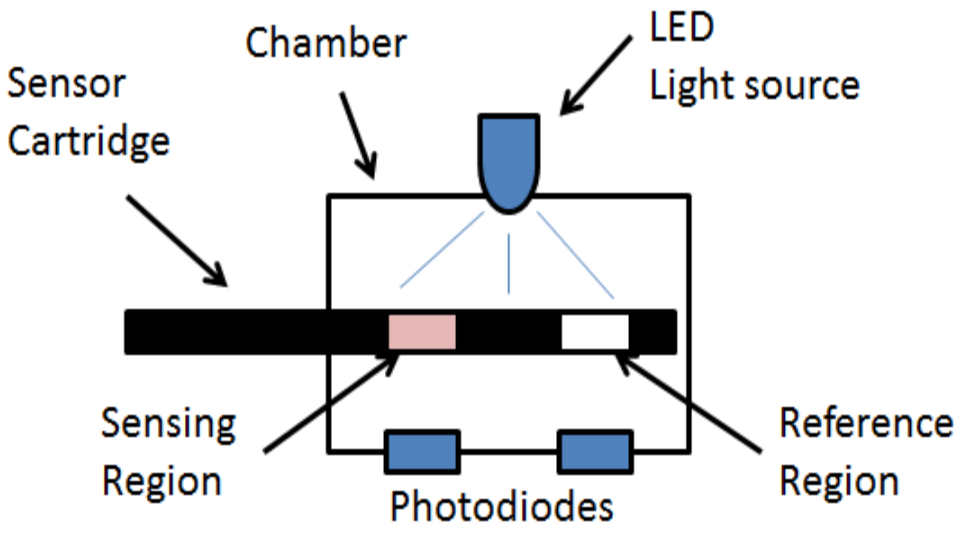


Figure 9. Simple schematic layout of nitric oxide sensing components.

Correct Sample Collection

Apart from interference another sometimes equally challenging task for many breath analysis devices is acquiring the correct sample. One key task to acquiring the correct sample is controlling flow rate. Controlling flow rate will provide a more consistent measurement of the desired compound in the breath sample and allow for more accurate comparisons between previous subject tests as well as different subject populations. Many compounds found in a human breath sample correlate directly with the exhaled flow rate. While studies for the relationship between exhaled flow rate and acetone detection are currently lacking, there are a few studies that have shown acetone detection response may be partially dependent on flow rate. Though recent tests performed in our lab have shown that flow rate has little effect on the quality and reproducibility of an acetone tests utilizing our breath acetone analysis device. Various quantities of

acetone all near 0.5ppm were tested with various flow rates. The results show that even flow rates differing by more than 400% only have a change in response of 20%. The relative standard deviation between the response values of all the different flow rates was below 15%. *Table 1* below shows the results from the flow rate vs. acetone response test.

Acetone level	Time to collect 3L or Flow rate	response	Response/acetone level
0.538 ppm	87 s -> 34.5ml/s	0.08045	0.14954
0.531 ppm	120 s -> 25ml/s	0.07963	0.14996
0.520 ppm	170 s -> 17.6ml/s	0.10061	0.19348
0.597 ppm	270 s -> 11.1ml/s	0.09955	0.16675
0.604 ppm	360 s -> 8.3ml/s	0.113	0.18709
Relative standard deviation			12.5%

Table 1. Results of flow rate vs. acetone response.

The relationship between exhaled flow rate and the detection of nitric oxide on the other hand has been studied extensively and is well known. As mentioned earlier a standard has been set for the exhaled flow rate when detecting nitric oxide in a human breath sample by the American Thoracic and European respiratory societies of 50ml/s. As far as nitric oxide detection in the human lungs is concerned, backpressure is also a critical parameter to control. The ATS/ERS requirements for backpressure when measuring nitric oxide are set as

an upper and lower limit. The upper pressure limit is 20 cm H_2O and is set in order for patients to comfortably provide a sample. The lower pressure limit is 5 cm H_2O which is necessary for velum closure to avoid contamination of the sample with nasal NO which has been shown to measure in concentration an order of magnitude larger than that of alveolar NO [19]. *Figure 10* below displays the relationship between exhaled NO levels and flow rate in ml/s. From this plot we can see that a low flow rate and resulting low back pressure does not allow the velum to close properly and hence the values of FE_{NOppb} are very high due to the contamination of NO from the nasal cavity [20].

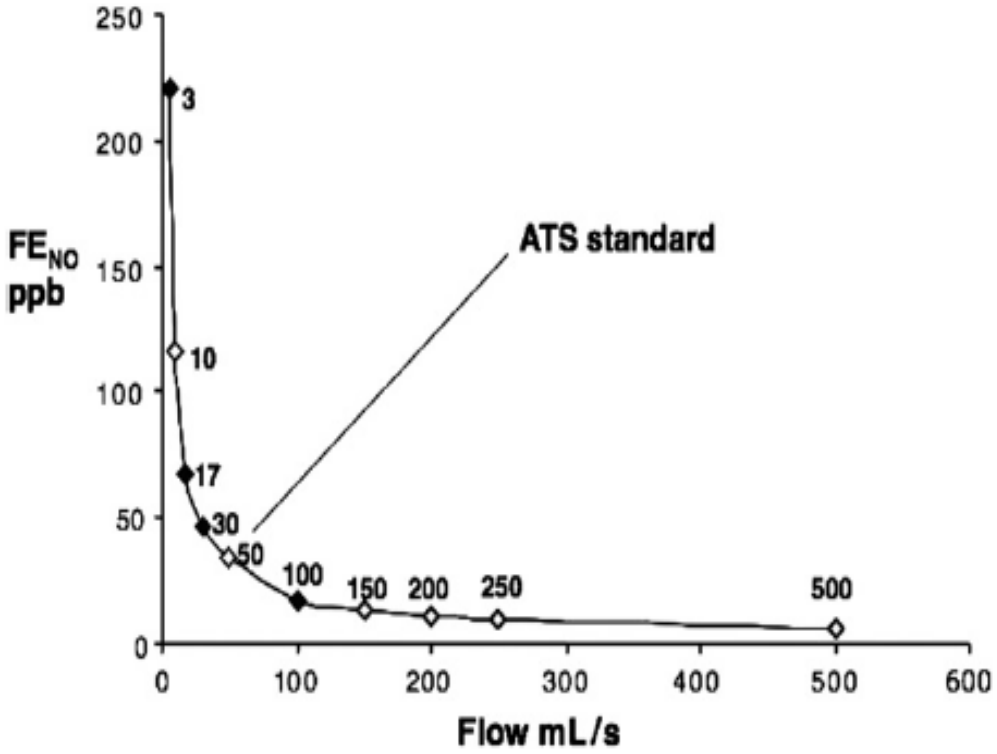


Figure 10. Plot displaying multiple subjects measured breath NO (ppb) vs. flow (ml/s). [20]

Controlling flow rate can be accomplished using a variety of methods. Different parameters can be measured to attain the same effect, which is measuring and controlling flow rate. One method for measuring flow rate often used as an early laboratory test method is to measure the amount of time it takes for a known volume to be filled with the breath sample. This method was used in the prototype stages of the acetone detection device discussed earlier. A bag of known volume was fixed to the exhaust of the device. When a subject began to supply a breath sample the test administrator would start a timer and once the bag of known volume was full the test administrator would stop the timer. Dividing the bag's known total volume value by the time in which it took the subject to fill the bag will provide the flow rate value. *Figure 11* below helps to depict the method of flow rate measurement discussed.

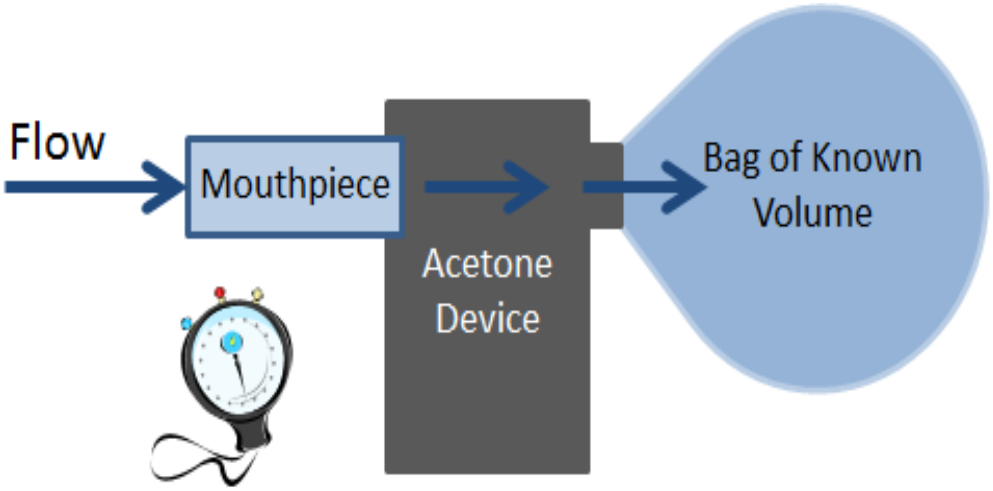


Figure 11. Flow rate measurement via known volume and time recording.

Another method utilized to measure flow rate is by measuring pressure and from pressure calculating the flow rate value. Utilizing Bernoulli's equation a relationship between pressure and flow rate can be constructed, one of the

simplest forms of Bernoulli's equation can be seen below in *Figure 12* [21]. From this relationship pressure values can be paired with their corresponding flow rate values, therefore when pressure is measured the flow rate can be determined. This method of measuring flow rate will require preliminary data analysis and simulation. These simulations can be quite complex based on device structure and operation. To aide in simulation there are a number of finite element analysis software packages capable of performing fluid dynamic simulations like COMSOL. It is advised to run these simulations on a relatively powerful computer to avoid crashes, freezing and significantly long analysis times.

$$static \quad pressure + dynamic \quad pressure = total \quad pressure$$

$$P_s + \frac{\rho V^2}{2} = P_t$$

$$For \quad flow \quad through \quad a \quad changing \quad cross-sectional \quad area:$$

$$\left(P_s + \frac{\rho V^2}{2} \right)_1 = \left(P_s + \frac{\rho V^2}{2} \right)_2 = Constant = P_t$$

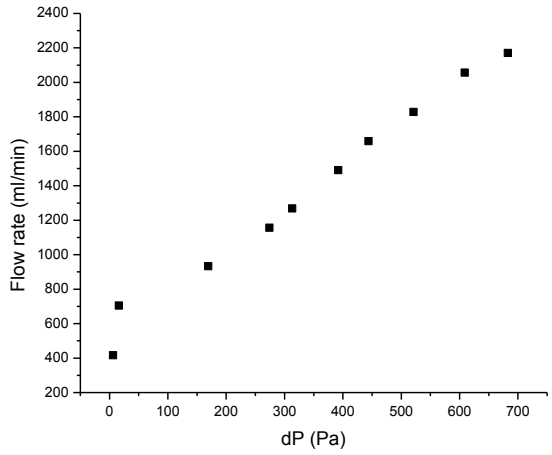
$$Where: P_s = static \ pressure, \rho = density \quad of \quad fluid,$$
$$V = velocity \quad of \quad fluid, \quad and \ P_t = total \quad pressure$$
$$(\ )_1, (\ )_2 = represent \quad differing \quad cross-sectional \quad areas$$

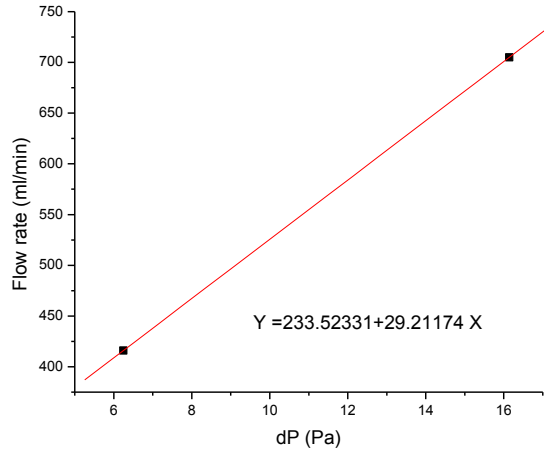
Figure 12. Simple form of Bernoulli's Equation. [21]

When the resources to run a proper simulation are not available, software or hardware, a pressure and flow rate relationship can still be built experimentally. Via measuring a number of pressure and corresponding flow rate values through the desired sections of a device a calibration plot for pressure vs. flow rate can be constructed. From this calibration plot a calibration curve can be determined.

Using the calibration curve with a measured pressure value as an input the flow rate can be calculated. This experimental method to find a pressure vs. flow rate relationship is often used in place of the simulation method due to simplicity. While simulating a flow often seemingly unimportant or just overlooked input parameters can lead to an inaccurate pressure vs. flow relationship. For more complex flows these parameters are not simply overlooked but at times very complicated and hard to model correctly using software packages. Using the experimental method there should be no exclusion of any parameters and all should be modeled correctly assuming a proper test setup.

The experimental method described above is the method currently used in both the acetone and nitric oxide devices used in the BioSensors & BioElectronics lab. Data for such a pressure versus flow rate calibration for the acetone device can be seen below in *Figure 13*. The first plot displays the data attained from the test. The flow rate values were measured using a laboratory flow rate meter and the pressure values were measured using the devices on board pressure sensor. Once the data was plotted it could be fitted, the following two plots show the linear fitting completed for the data set. Once the equation for the fitting is attained it is applied and loaded to the micro-controller code. From then on every time a pressure reading within the devices range is recorded this value can be converted to a flow rate value. This method of flow rate measurement is extremely advantages for two reasons. First the pressure sensors are very cheap, often $10 or less. Second the pressure sensors can be quite small and quite robust thus easily integrated into a variety of systems with great results.





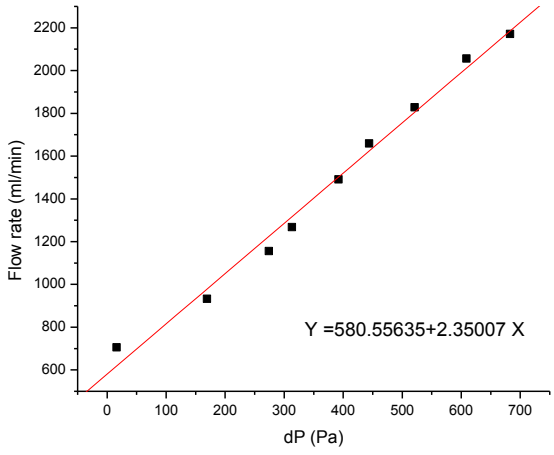


Figure 13. Pressure vs. flow rate results from the acetone device.

Another method to measure flow rate is to utilize a turbine flow rate sensor. Turbine flow meters have an internal (axial) turbine that translates the rotational motion of the turbine blades to a readable flow rate value. These sensors can be bought off the shelf ranging from small sizes less than two inches across to much larger industrial sizes more than a foot across. Though there are two parameters which can be a real downside to turbine flow meters; the flow needs to often be cleaned before reaching the sensors to insure long lifetime and the costs are often high compared to sensors such as the pressure sensors ($100+ compared to $10+ respectively).

One alternate method to measuring flow rate is via the utilization of a thermal mass flow meter. The typical thermal mass flow meters utilize two temperature sensors, one upstream and one more slightly down stream in terms of the fluid flow. Mass flow is measured as a function of the difference in temperature between the two temperature sensors. The advantages to this type of flow measurement are that the device has no moving parts, provides very little obstruction to the flow and can accurately detect a wide range of flow rates. The large disadvantage is that today's off the shelf thermal mass flow meters are quite costly easily costing hundreds of dollars.

Testing Conditions

Testing conditions can vary greatly due to a number of factors including location, time of day, local weather and more. These changes in testing

conditions can greatly impact the performance and reliability of a breath analysis device. Most human breath analysis tests are performed in a lab setting with the lab grade equipment discussed in the current method sections of this paper. Lab settings have very stable and controlled conditions. Though depending on the laboratory setting many labs control the temperature to 25ºC and pressure to 100kPa or 0.986 atm. Laboratory air is generally "clean" and free of any excess concentrations of VOCs or other compounds. The humidity is often well controlled in laboratory settings as well, typically relative humidity levels are controlled to between 35-60% depending on the laboratory. These controlled settings allow for consistency while performing tests allowing the equipment to account for fewer variables while testing. Though this is not the case for mobile health applications, it is impractical to expect every subject utilizing a mobile health device to perform testing in a laboratory setting. Therefore a mobile health device needs to account for variables for which lab grade equipment may not. One solution to aide in accounting for changing testing conditions is to set device operations limits. Nearly all consumer products in today's market have operating conditions. These conditions provide the consumer with information including a minimum and maximum temperature, humidity levels, pressure levels and more depending on the device. The same operating conditions will need to be established for a mobile breath analysis device in order to help insure quality performance and reliability of the device. These operating conditions cannot be too stringent as to require every test be taken in a laboratory grade setting and as

such supporting measures may need to be taken to insure satisfactory performance of the device.

Supporting methods to normalizing test conditions other than setting strict testing conditions include various built in components to help insure more consistent testing. These built in components are ones that provide functions such as air scrubbing to remove possible interferences from the ambient air. The nitric oxide breath analysis device discussed utilizes such components. This sensor is continuously running, sucking ambient air from a separate port and passing it through the system. Then when a human subject provides a breath sample a valve is switched and the breath sampling begins. Therefore when the ambient air is being passed through the system it needs to be "cleaned" of any harmful interference particles and chemicals. In order to clean the air the nitric oxide sensor utilizes a zeroing filter. This filter can scrub the air and remove harmful interferences which could be present in the ambient air such as excess VOC's, ozone and nitrogen dioxide. Then design of the zeroing filter may need to be specific for the device though many commercial devices make use of off the shelf zeroing filters for different applications. A common material used in many zeroing filters is activated carbon also known as activated charcoal as it is derived from charcoal. Activated carbon has an extremely porous surface and thus very large surface area. The surface area can exceed 500 meters squared for just one gram of activated carbon. This porous surface and large surface area make activated carbon great for adsorbing many chemicals [22]. In addition to activated carbon the zeroing filter also contained Purafil SP, sodium

permanganate and alumina based compound. This compound effectively removes nitric oxide, nitric dioxide as well as other reactive gases and unsaturated hydrocarbons. The removal of nitric oxide and nitrogen dioxide was critical for the nitric oxide device's reference channel to record a clean baseline. *Figure 14* below shows a picture of a typical zeroing filter filled with the chemical components described above.

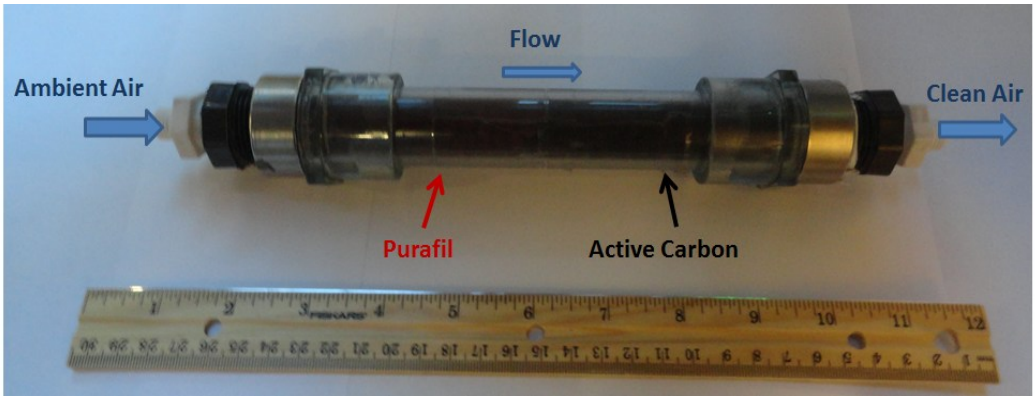


Figure 14. Zeroing filter from the BioSensors & BioElectronics lab.

Once the challenges discussed are met by specifically designed solutions, the next major step for any mobile breath analysis device is integration. The device needs to be integrated properly to insure low cost, high performance, reliable operation and user friendliness.

Chapter 3

DEVICE SOLUTIONS

System Integration

The proper integration of all the components within a system is essential for any device to be successful. Each subsystem in a device needs to properly perform its function and then properly connect with its partner subsystems within the device. If even one subsystem is to be disassociated with its complimentary subsystems the device could perform improperly. Therefore it is important to design accordingly insuring all subsystems communicate and operate with one another correctly. Whether designing from the top down or bottom up it is important to remember to have a plan of action outlining the different subsystems needed, subsystem functions and communication/cooperation between the subsystems. *Figure 15* below shows a basic system flowchart which can be the simplified design for many mobile breath analysis devices. The acetone and nitric oxide detection devices discussed earlier both follow this same system flowchart.

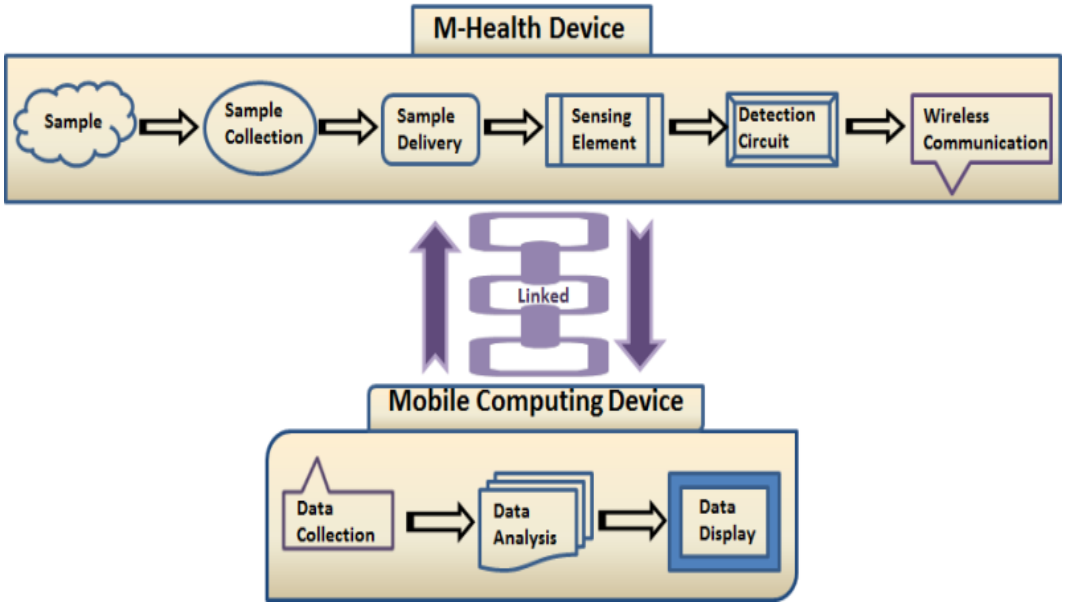


Figure 15. M-health device system flowchart.

In the flowchart above the sample is the substance to be collected and later analyzed, whether it be acetone or nitric oxide for the devices discussed in this paper. Sample collection is the first process in attaining the sample from the subject. In the case of the acetone and nitric oxide devices this could be identified as the mouthpiece as well as the flow rate mechanisms in place insuring the correct sample collection. Sample delivery is insuring the correct sample is delivered to the site where the sample will be analyzed. The acetone device utilizes simply tubing and delivery components to complete the sample delivery. Whereas the nitric oxide device has a slightly more complicated delivery system, this system includes a pump, valve and multiple tubing pieces. Once delivered properly the breath sample must be analyzed. For the acetone and nitric oxide device examples both are chemical based sensors and so the sensing element is a substrate where a specific chemical reaction can take place. Once the chemical

reaction has taken place there needs to be a subsystem in place which can quantify the reaction and deliver a more readable signal. In the case for both the acetone and nitric oxide device the sensor is a detection circuit together with photodiodes which quantifies the chemical reaction as an electrical signal that can be read. In both the acetone and nitric oxide device case an electrical signal is read as a voltage value. Once the signal is measured it needs to be analyzed and return a reading which can be easily interpreted by the user, in most cases the concentration of the analyte. In the case of the acetone and nitric oxide device example an outside source is used to analyze and display the data, a mobile computing device. This saves cost on the side of development and production for the device and also allows for a device that is simpler and smaller. For both the acetone and nitric oxide device the mobile computing device used to analyze and display the data is a smartphone. The smartphone is a great mobile computing device in which to design a mobile health device around. Their ever growing computing power and ubiquitous nature in the cell phone market make the smartphone a promising technology. *Figure 16* below helps drive the point home that the smart phone is a great tool to build a mobile health device around as smartphone penetration in the United States market has grown 26% from 2009 to 2011 [23].

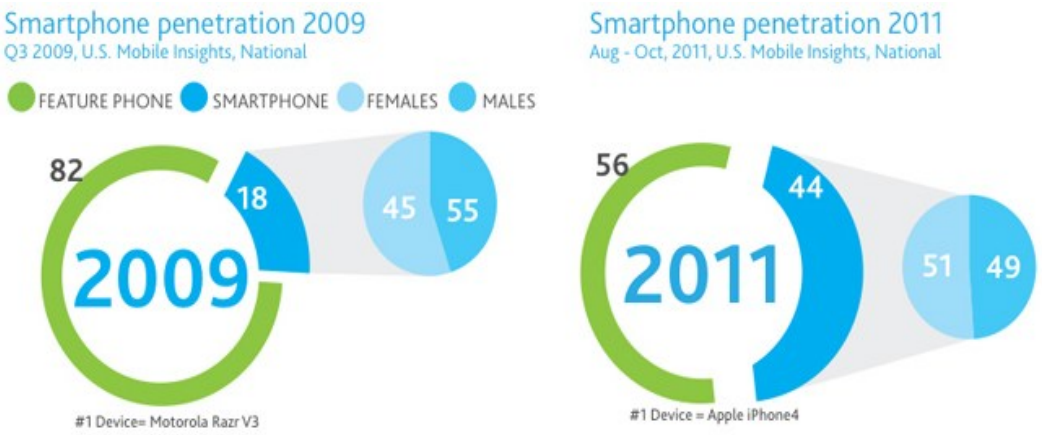


Figure 16. U.S. smartphone market penetration, 2009 compared to 2011. [23]

Because a smartphone is used to analyze and display the data, there needs to be a mean of communication between the mobile health device and the smartphone. In the case of the acetone and nitric oxide device this communication is wireless utilizing a Bluetooth module. Though the connection does not need to be wireless it does make utilization of the device and smartphone very convenient. Once the data is received by the mobile computing device, smartphone, it needs to be analyzed. In the case of the acetone and nitric oxide devices discussed in house software was developed to analyze the data, as this will often be the case. Application based smartphones make developing and delivering software packages a relatively easy task. Once analyzed the data needs to be displayed in a fashion which can be easily interpreted by the user. The same software application that analyzed the data will then also need to intuitively display the data, often in the form of an easy to read plot, bar graph and/or number representing an important quantity.

The Mobile Breath Acetone Detection Device

The acetone breath analysis device discussed throughout this paper is still in development at the ASU BioDesign Institute BioSensors & BioElectronics lab. Though many promising developments have been made in regard to this device, for instance the response of the device is quite linear as tests of a prepared sample composed to simulate human breath have shown great results. Four artificial breath samples were tested for acetone; 80, 702, 950 and 1938ppb. All four samples had a clear response and when acetone concentration was plotted versus absorbance and the plot was very linear with an R value exceeding 0.99. *Figure 17* below displays the initial artificial breath acetone test results discussed.

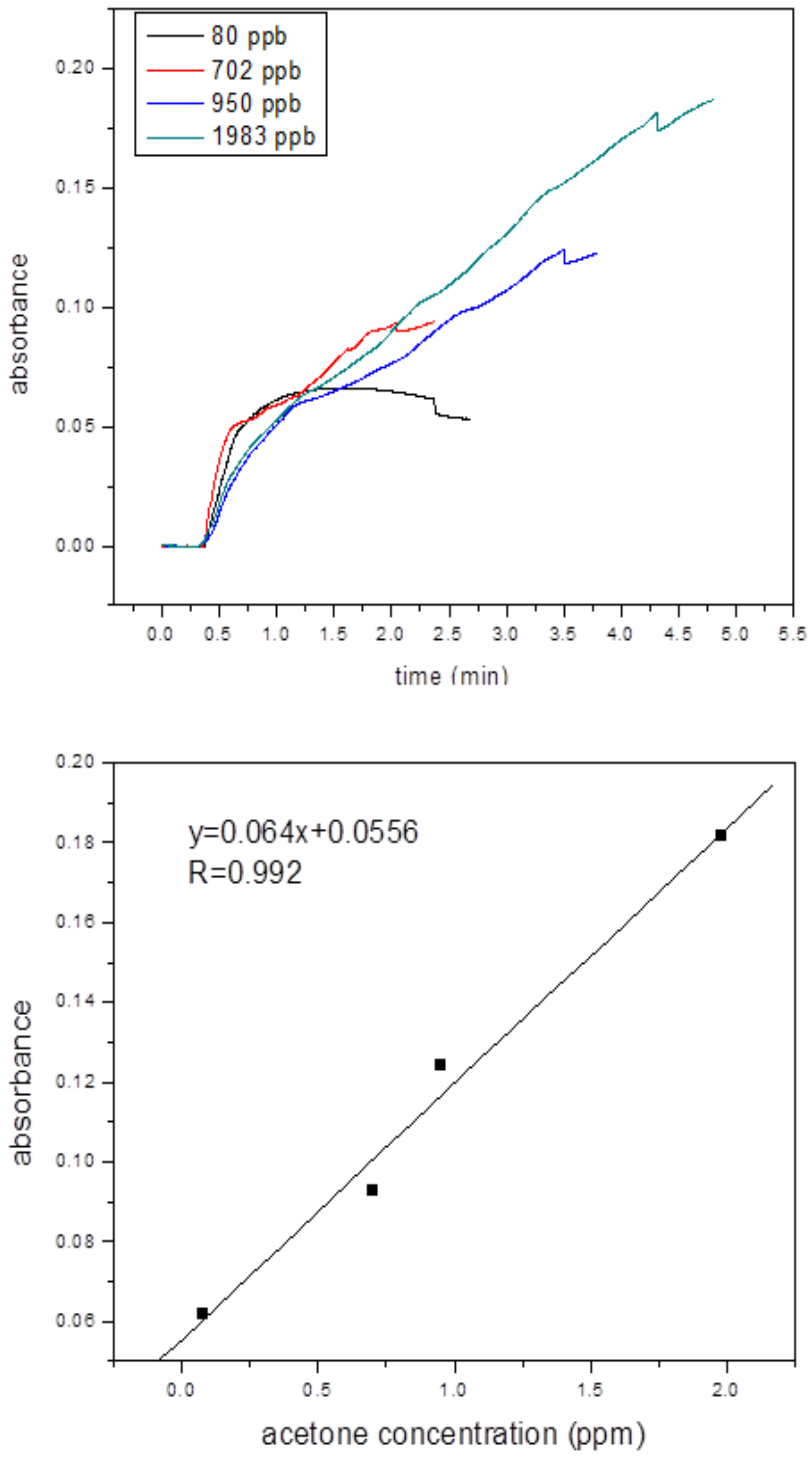


Figure 17. Artificial breath sample results from the acetone device.

Figure 18 directly below displays a picture of the actual lab tested acetone device discussed throughout the paper.

Figure 18. The acetone device as developed/tested in the BioSensors & BioElectronics lab.

The Mobile Breath Nitric Oxide Detection Device

The nitric oxide device discussed throughout this paper is also still in development at the ASU BioDesign Institute BioSensors & BioElectronics lab, though this project is nearing its completion. A great number of tests have been completed using the developed nitric oxide sensor, including inference, precision, calibration and correlation. One of the more recent tests completed was a correlation test between the mobile nitric oxide device and the industry's gold standard bench top device GE Analytical Instrument's Nitric Oxide Analyzer. To complete the test individuals were tested with the mobile nitric oxide device and the GE Nitric Oxide Analyzer nearly simultaneously. During the test a number of

individuals were tested multiple times. Totally more than sixty data points were collected for the correlation test. The results were very positive. The slope of the linear fitment between the two devices was almost exactly one and the R value of the data was greater than 0.9 indicating strong correlation between the two device readings. The mobile nitric oxide device can be seen pictured below in *Figure 19*, and the correlation test results discussed can be seen below in *Figure 20*.

Figure 19. The NO device as developed/tested in the BioSensors & BioElectronics lab.

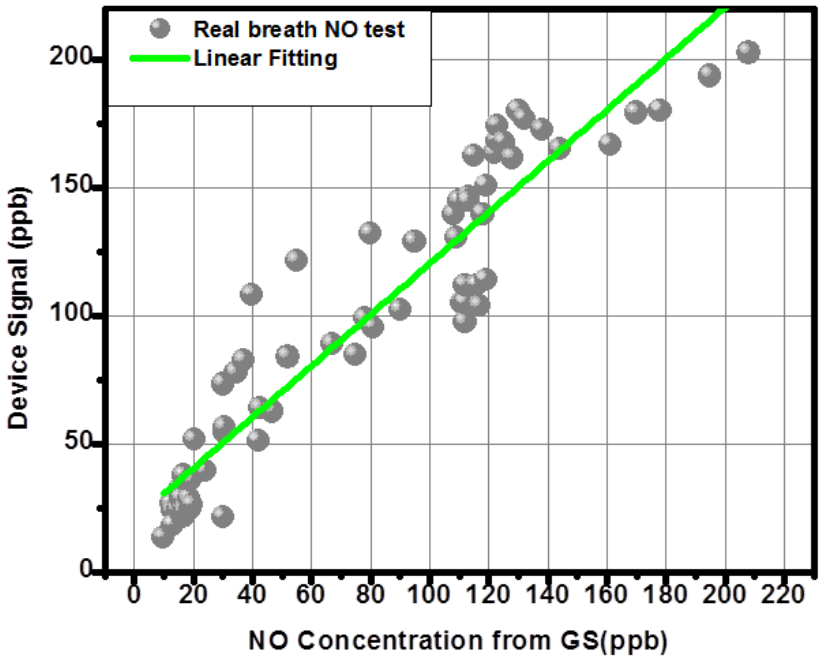


Figure 20. NO device correlation plot.

Chapter 4

CONCLUSIONS

The healthcare world is changing. As the world's population is growing larger and older more and more are in need of healthcare services every day. But there continues to be a void as the supply of healthcare professionals lags behind demand and the cost of healthcare continues to increase. M-health technologies are poised to make a real impact on the healthcare world helping more professionals reach more patients easily and reducing the cost of healthcare significantly.

Mobile breath analysis devices are one form of m-health devices sure to make an impact on the future healthcare system. With the large number of detection capabilities and a non-invasive sampling method it is just a matter of time before more breath analysis devices are developed and accepted in the healthcare world. The mobile breath analysis devices discussed in this paper are just two examples demonstrating the possibility of worthwhile technologies. The acetone detection device is currently midway in development but has shown excellent promise with accurate measures of breath acetone concentration. With further development and study this device could help diet tracking and even more importantly a possible alternative non-invasive method to tracking Diabetes. The mobile nitric oxide device has also shown real promise in its ability to accurately and reliably measure breath nitric oxide levels. This project is nearing its final stages at the BioSensors & BioElectrnics lab and could make its way into the industry in the future. Both mobile breath analysis devices successfully surpassed

many challenges associated with the breath analysis instruments: correct sample collection, interference and testing conditions. Also of major importance, both devices developed are relatively simple and very cost effective as compared to current industry methods of detection. Finally the devices are very user friendly able to run utilizing the computing power of a near ubiquitous technology in today's society, a smartphone.

In conclusion this paper suggests that mobile breath analysis devices as well as other m-health technologies have a unique possibility to provide real solutions in helping solve many of today's growing healthcare issues. This advancement in health devices is more than just a possibility through example this paper shows it is possible to develop cost effective, reliable and user friendly m-health devices that will help propel the world's healthcare system in a more positive direction.

Chapter 5

FUTURE WORK

What the future holds in store for breath analysis devices as well as other mobile health technologies is hard to predict with the constantly improving modern technology and the very difficult challenge of understanding the human body and its complicated physiology. As the smartphone technologies continue to improve and become more powerful it is not hard to believe that these devices may soon be a real "Swiss-army knife" capable of performing more than just common computing tasks but might also perform the mobile health device functions of the future. As more and more health sensors are developed and improved to be smaller and more cost effective they could be integrated into the future's smartphones. These smartphones could then become the devices that not only update our Facebook statuses, answer our calls and play our music but also inform of possible health concerns. Technologies like nano-sensors could help to make this possible. There are also many other promising technologies which are sure to play a hand in improving the impact mobile health technologies have on the ever changing healthcare system.

Improved Integrated Flow Rate Measurement

With further improved flow rate measurement devices that are more easily integrated into mobile devices the mobile health devices of tomorrow could be smaller and more accurate. It has been discussed how flow rate can be an extremely important parameter to attaining an accurate breath analysis thus

improved flow rate measurement techniques can help improve the accuracy of a breath analysis device. The device which is used to measure flow rate whether it is a pressure sensor or turbine sensor or other device is often one of the larger components compared to the other single components of a breath analysis device, thus a smaller flow rate device could help to shrink the size of future mobile breath analysis devices. Finally more accurate detection and the smaller size of future flow rate measurement devices could simplify their ability to be integrated into future mobile breath analysis devices leaving the engineers more freedom in the design layout of mobile breath analysis devices.

One such flow rate technique that could be improved upon for a reduction in size and ease of integration is that of thermal mass flow rate detection. This method is briefly described previously in this paper though not in great detail. This flow rate technique has already proved to be very accurate, current off the shelf models often have an error within 1%. As stated before this technique can also accurately measure a large range of flow rates and does not negatively obstruct flow. The real down side to this technique is that off the shelf thermal mass flow rate devices are not relatively small and that they can be quite costly. But more research in this area could provide future thermal mass flow rate devices that are smaller and less costly. Today thermistors are produced that are extremely small and cost competitive. Integrating two micro thermistors together with a temperature/flow rate calibration could prove to be a cost effective flow rate solution that is extremely small and thus easily integrated into the mobile

breath analysis devices of the future. It would be exciting to see more research on this flow rate technique in the future.

Cloud Computing and M-Health

One promising technology sure to bring about positive changes towards better connected and provided healthcare solutions is cloud computing. Cloud computing is about as easily defined as m-health as of today there still is not a completely universal definition. Though as a generally accepted definition, cloud computing is a model for enabling convenient, on-demand network access to a shared pool of configurable computing resources that can be rapidly provisioned and released with minimal management effort or service provider interaction [24]. An illustration helping to describe cloud computing can be seen below in *Figure 21* [25]. With the use of cloud computing individuals carrying a mobile computing device, tomorrow's smartphone or other device, could collect large sets of data without putting the computing burden on their device but rather the cloud. These large sets of data can then be transmitted to the cloud where they are stored and analyzed. Once analyzed the key results of the data can be re-transmitted to the mobile computing device which can display the information in a user friendly manner. Moreover should proper privacy and data security measures be put in place a cloud network working with mobile health devices could do so much more than just provide feedback to an individual from their single device or single test. If the cloud were servicing a large number of individuals with multiple sensor technologies over a broad region, this

information could be displayed to all individuals whom want or need the information. In other words a regional health map could be constructed. Though for this structure to be properly put in place each individual's subject readings may need to be kept anonymous. The concepts of integrating mobile health devices and cloud computing are certainly interesting and the possibilities and capabilities will continue to be explored and grow with time.

Figure 21. Cloud computing illustration. [25]

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