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Foreword

This year I am happy to present the seventh volume of the UIC Bioengineering Student Journal. Over the five years that I have been involved with the journal as a reviewer, editor, and during this second time that I am serving as Editor-In-Chief, I have had the pleasure of meeting and working with many talented bioengineering students. It is my hope that in the course of writing and reviewing articles, and by serving on the editorial board, students experience academic and personal enrichment in the bioengineering department here at UIC. Undergraduate students that strive to succeed not only in their coursework, but also in extracurricular activities such as the UBSJ and research, graduate with not only a superior resume, but with a more finely honed set of personal and academic skills.

Although I am finally reaching the end of a ten year period of study at UIC (B.S. 2011, Ph.D. 2016), my experiences will be fondly remembered, along with the UIC students and faculty that I worked with, through UBSJ and otherwise. The students that will continue to facilitate our journal will have many wonderful journal issues to look back on for reference and inspiration, and I am sure that each new issue will continue to be better than the last.

I would like to thank our Faculty Advisor, Dr. Magin, for giving us all the freedom and opportunity to create a truly student-led project and for allowing us to bring our visions to life. I would also like to thank Department Head Dr. Royston for continually supporting the journal’s financial and logistical needs and allowing us to host release parties every year. Lastly, I would like to thank and congratulate the authors, reviewers, and editors who worked tirelessly to make this year's issue of the journal such a great success.

Cierra Hall
Editor-In-Chief
Carbon Nanotubes as a Medical Imaging Tool
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Abstract
Early detection and non-invasive disease monitoring are crucial parts of disease treatment. The difficulties with these aspects are largely due to the limitations of current imaging techniques. A potential solution to these constraints could lie within one of the most common elements in biological systems, carbon. The valency of carbon allows it to form many different allotropes. These include a variety of shapes and commonly known forms such as diamond and graphite as well as more unusual forms like fullerenes. One of these atypical forms, carbon nanotubes, has recently become a common topic of research. The popularity of research into carbon nanotubes (CNTs) is due to their superior physical properties which confer many potential applications in medicine and industry. The extraordinary strength, elasticity, conductivity, and optical properties of CNTs have been well documented. They are of particular interest to the field of medical imaging because their application could provide low-risk and high resolution imaging of live cells. Some interesting applications include CNTs based detectors that can detect terahertz frequency waves, injection of fluorescent CNTs with subsequent imaging, and CNTs based magnetic resonance imaging (MRI) contrast agents. These and many other applications are limited by factors such as the degree of toxicity of CNTs in biological systems and manufacturing complications. Current research is based on navigating challenges involved with CNT applications, and could potentially lead to highly efficient and effective methods for widespread utilization of CNTs.

Keywords: Carbon Nanotubes, allotropes, Medical imaging

1. Introduction

The existence of carbon nanotubes was proposed theoretically in 1990 by Rick Smalley based on his research with buckminsterfullerene. He found the mysterious compound when he was testing abnormalities in the mass spectrometry of graphene. [9]. Although CNTs were probably observed experimentally many years before this, the importance of fullerenes was just coming to light, thus providing the motivation to delve deeper. Shortly after Smalley's proposal, transmission electron micrographs provided physical evidence of existence of CNTs. Ever since that time CNTs have become widely popular among researchers. An example of CNT imaged by transmission electron micrograph is shown in figure 1.

The study of carbon nanotubes is an important venture. CNT application opens enormous possibilities in a wide variety of industrial and medical applications. It is particularly significant for medical imaging because of the scope and variety of potential applications. Previous impractical and inefficient methods could be brought within the realm of routine practices. With careful analysis and development, these tiny molecules can be used as detectors, emitters, and contrast agents. All of these instruments already exist in imaging. Therefore, intensive study of CNTs begs the question of their superiority over current agents. CNTs must have some advantage and enough so that companies and government grants will fund their research.

This indeed turns out to be the case. CNTs display unique physical properties which yield many advantages over current instruments. In this article the focus is on application of CNTs in medical imaging. Pending applications and challenges are discussed.

2. Carbon Nanotube Structure and Properties

![Figure 1. Electron Micrograph of a SWNT [3]](image-url)
2.1 Carbon Bonding and Structure

Carbon nanotubes are made of a crystalline network of sp² hybridized carbon atoms. This network forms a tubular scaffold which can exist in single or multiple walled forms [8]. The physical strength of CNTs are due to the strength of Carbon bonding. The sp² bond is 33% stronger than the sp³ bond of diamond, the hardest known mineral [13].

Furthermore, carbon nanotubes have extremely high surface area due to the fact that all their atoms are on the surface (see figure 2). This property make them very useful for biomedical applications. Many different molecules can be conjugated to CNTs so they can be conjugated in ways that target particular cells and biomolecules. For example, they can be attached to antibodies or cell recognition proteins. This property is a major value of CNTs in medical imaging. Surface conjugation makes CNTs particularly useful tool which can provide functional physiological information and can be beneficial in structural imaging [8].

2.2 Single and Multiple-Walled Carbon Nanotubes

The more studied and more currently useful form of CNTs are single-walled carbon nanotubes (SWNT). They are made up of a single sheet of graphene rolled into a tubular shape (Figure 2). These are essentially one atom thick and usually do not necessarily have a constant radius. They can exist as different sizes in diameter and length, ranging from 0.4 – 4 nm in diameter and from 50 nm up to 1cm in length [16].

![Figure 2. Structure of a single-walled carbon nanotube (SWNT) [3](image)](image)

Multiple-walled carbon nanotubes (MWNTs) are simply concentrically stacked SWNTs. They can consist of many different layers of graphene. While they don't exhibit the same optical properties of SWNTs, their larger size may provide an adequate platform for conjugation with larger biomolecules [6].

2.3 Properties

2.3.1 Electrical and Thermal Conductivity

Depending upon the strength of a magnetic field applied to CNTs, they can be induced to be either semi-conducting or metallic [8]. A very small magnetic field applied parallel to the tube axis make them semiconductors. Conversely, when a high magnetic field is applied, they become metallic. This unique phenomenon is due to a gap in energy band. This property is particularly of interest to scientists who are working on terahertz frequency detectors [4].

In addition to electrical conductivity, CNTs have very high thermal conductivity. They remain stable up until temperatures nearing 4000K [13]. This varies however with the size of the nanotubes. Like most of their properties, their thermal and electrical conductivity are only as reliable as the preciseness of their synthesis.

2.3.2 Strength and Elasticity

CNTs also exhibit strength and elasticity which far outcompete other materials. Their strength is due to the carbon bonding and elasticity is a function of their size. There are different possibilities for the interlayer spacing, which in turn are responsible for the degree of elasticity. It is easy to imagine that a SWNT with a large radius would be more elastic than one with a smaller radius as the angle of carbon bonding in a tighter circle is more strained.

Perhaps the illustration of a Chinese finger trap demonstrates this. As the diameter decreases (trapping fingers in the process), the rigidity of the trap noticeably increases [13]. Nevertheless, even CNTs with relatively small radii exhibit elasticity that far surpasses other materials. Nanotubes of varying diameters have shown the highest ever measured Young's modulus (standard measure of elasticity) [13]. This elasticity could facilitate bending of the CNTs to allow multiple binding sites of functional groups which would lead to enhanced binding affinity of nanotubes [6].

2.3.3 Optical Properties

SWNTs have sharp densities of electronic states which imparts distinct optical properties. Semiconducting SWNTs have small energy band gaps, thus exhibit photoluminescence in the near-infrared (NIR) range [6]. They also have distinctive resonance-enhanced Raman signatures for Raman detection and imaging.
3. Imaging Application

The properties of CNTs make them useful in many different imaging modalities. A few examples of applications still in process are highlighted in Table 1. As these areas of CNT use are explored, more potential applications could surely be pictured.

<table>
<thead>
<tr>
<th>Properties</th>
<th>Application</th>
<th>Advantage</th>
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<tr>
<td>Semiconductance</td>
<td>Terahertz Detectors</td>
<td>Development of Terahertz technology</td>
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<td>High Surface Area</td>
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<td>Photoluminescence</td>
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3.1 CNT Detectors

Studies of CNTs have shown extensive detection of electromagnetic radiation at many different frequencies. This property has led to the investigation of the extent of their limitations in this area. Unlike other imaging detectors, those made from CNTs could detect frequencies up to the terahertz wavelength [15].

The benefit of terahertz detection is that it is safe, non-invasive, and painless. These extremely high frequency waves are non-ionizing and their low photonic energies do not damage tissues and DNA. They can also penetrate a wide variety of materials, including the human body. The difficulty with terahertz waves is that there are limited number of materials that can absorb that frequency of photonic wavelength and convert it into an electrical signal. This problem could be solved by use of carbon nanotubes [17]. In fact, SWNTs have been used to create a thin film of nanotubes which detect the high frequency waves. Development of viable terahertz detectors have been in progress for years, and CNTs just may be the highly sought-after answer [15].

3.2 CNT Fluorescence

We have discussed that SWNT surfaces can be modified to target certain cells. This becomes particularly useful for near-infrared spectroscopy (NIR) and photoacoustic imaging (figure 3). When excited by shorter wavelengths (550-850nm), CNTs emit frequencies in the NIR range (900-1600nm). This is a phenomenon known as Raman scattering. The large difference between incident and scattered wavelengths reduces background from Raman scattering of tissues and is the basis of fluorescence in the NIR range [8].

NIR light is normally harmless to the body and can penetrate tissues which are intrinsically non-fluorescent. This would allow contrast between normal tissues and those targeted by CNTs. This has already been used as a way to image endocytosis and exocytosis of SWNTs in biological cells in real time [16]. SWNT targeting of cancer cells can also enhance tumor recognition. For example, SWNTs have been functionalized with folate which has many receptors on cancer cells. The cancer cells then allow functionalized SWNTs to enter while normal tissues without folate receptors remain free of SWNTs. Thus, SWNTs are localized to cancer cells and can be detected with NIR or even destroyed by NIR laser radiation [8].

The photoluminescent properties of SWNTs can also be used in photoacoustic imaging. Photoacoustic images are superior to ultrasound because they have high resolution and allow deeper penetration than NIR imaging. This is yet another way in which CNTs could enhance development of an imaging modality that is new and superior to commonly used methods. The cellular recognition tripeptide RGD can be attached to SWNTs and used to target certain tissues and create contrast in photoacoustic images (Figure 3) [6].

![Figure 3. Surface conjugation and photoluminescent tumor targeting][1]

[1]: https://example.com/figure3.png
SWNTs can also be used in Raman microscopy to image cells. They have distinctively strong resonance Raman scattering because of their quasi 1-D nature. Their electron density states cause strong isotopic peaks which can be easily distinguished from other tissues. To fully realize their potential in Raman imaging, isotopically unique SWNTs can be conjugated with various targeting ligands. This effectively color codes images because different isotopes produce different Raman shifts [6]. These methods for innovative manipulation of CNT optical properties are intriguing and further exploration of these ideas could produce completely new imaging styles.

3.3 MRI Contrast Agents

Since magnetic resonance imaging (MRI) is a safe and highly effective method of medical imaging, much effort is put into advances in its utilization. The ability to image soft tissue with high resolution and without use of ionizing radiation is unique to MRI. It can also provide functional information, much like positron emission tomography (PET) imaging, but with sub-millimeter resolution. This information requires the use of a contrast agent which can not only be targeted to specific biomolecules but also produce a signal strong enough to be detected.

CNTs could hold potential value as a contrast agent, and research to develop this technology is under way. Nuclear magnetic resonance (NMR) produces images in MRI by detecting variations in proton density via magnetic spins, and for this reason a pure carbon compound like a CNT cannot be detected. Since CNTs do not have any protons available for detection they must be altered to produce a form that is useful to MRI [11]. Researchers have found that the hollow tube structure can be used to trap magnetic particles which produce a signal that can be detected by NMR. Surface functionalization or conjugation of CNTs can also alter their chemical makeup to render them useful in NMR.

Contrast arises from differences in signal arising from water content of tissue. The differences in water content are indicated by different tissue relaxation times of hydrogen nuclei termed \( T_1 \) and \( T_2 \) [14]. The proton density of the tissue, \( \rho(x,y) \), in addition to these relaxation times are proportional to (denoted by \( \propto \)) the intensity of the signal, \( I(x,y) \). The relationship between the intensity of signal and \( T_1 \) and \( T_2 \) times is given by:

\[
I(x,y) \propto \rho(x,y) (1 - e^{-\frac{TR}{T_1}}) e^{-\frac{TE}{T_2}}
\]

Strong signals can be detected from separate tissues but unless their relaxation times differ they cannot be distinguished. This is where contrast agents come into play. These agents shorten relaxation times in target tissues by exerting a magnetic force upon the surrounding water protons. Paramagnetic complexes such as Gadolinium and Manganese chelates accelerate \( T_1 \) relaxation and Superparamagnetic nanoparticles like iron oxide accelerate \( T_2 \) relaxation. The resulting signal with addition of contrast is given by the equation:

\[
[T_i]^{-1} = [T_i^0]^{-1} + r_i[CA] \quad i = 1,2 [11]
\]

Where \( r_i \) is the relaxivity of the agent (a measure of the change in relaxation implemented by the contrast). \([CA]\) is the concentration of the contrast agent and \( T_i^0 \) is the relaxation time without contrast. This equation illustrates that the signal intensity for MRI depends not only the concentration of the agent but also its relaxivity. Currently used contrast agents require relatively high concentrations in order to produce desired effect [12]. This must be monitored carefully since those agents can be toxic in high concentrations.

A contrast agent with higher relaxivity than existing agents would require a lower concentration to achieve the same effectiveness. This scenario is clearly desirable because minimizing injection of potentially toxic materials reduces risk to the patient. It turns out that SWNTs conjugated with magnetic particles can yield enhanced relaxivity. For example, Gadolinium-loaded CNTs exhibit an effectiveness that is 40-90 times larger than any present contrast agents [11]. Other CNT-linked substrates such as NMR active isotopes like \(^{19}\)F are under scrutiny for use as contrast agents. These are still in developmental phases since they are still insoluble and toxic [11].

4. Current Research

In order for Carbon Nanotube use to have a significant impact, development of standardization and quality control must be achieved. Many potential applications are limited by the unpredictability inherent of the manufacturing process. It is difficult to control the purity of a CNT sample (such as creating only SWNT instead of a mixture with MWNT) and much of current research is based on quality control [8].

Further investigation of their properties could yield many exciting discoveries, but perhaps the focus right now should be on the manufacturing process. Owing
to their extremely small size (figure 1), it can be difficult to control the exact length and radius of each tube and any defects could potentially render them toxic in a biological environment. There are many different methods of CNT synthesis and this should be the focus of research [13].

All forms of manufacturing involve very high temperatures which presents a physical challenge. Different methods produce varying results, and there are costs and benefits to all of these processes. A close analysis of the tradeoffs involved could reveal the superiority of some methods over others [13]. Whatever the chosen process, synthesis and use of CNTs is sure to be an exciting field of discovery with the next few decades.

5. References


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10. Material Scientist Talk. CC-BY-SA-3.0; Released under the GNU Free Documentation License. June 4 2009


THE DISCOVERY OF RADIOACTIVE ELEMENTS THAT LED TO
BIOMEDICAL ADVANCEMENTS
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Abstract
Wilhelm Roentgen was the first to discover the existence of X-rays. He discovered that rays could travel through solid objects, and not knowing much about the science behind this new phenomenon, he labeled them X-rays, X standing for unknown. Shortly after this discovery, Henri Becquerel witnessed a similar occurrence with uranium, which peaked Marie Curie’s interest, and eventually led to her finding of radium and polonium. From studying Becquerel and Roentgen’s findings further, yet another discovery was made, this time by Paul Villard and Ernest Rutherford. Together they uncovered another type of ray that Rutherford labeled as a “gamma ray.” The science behind these discoveries was indeed groundbreaking and soon after, radioactive spas started emerging around the globe and cures to many ailments were believed to be from these newfound radioactive elements. While we know now that radioactive elements must be handled with extreme care, a great deal of good has come from these discoveries. X-ray and nuclear imaging techniques are still used today and are based off of the science from these experiments. Delving into these discoveries further, we can see how these scientists have helped the world of biomedical imaging, and society as a whole.

Keywords: Biomedical Imaging, X-ray, PET, SPECT, CT, radioactivity

1. Introduction
A series of events led to the discovery of radioactive material. In December of 1895, a man by the name of Wilhelm Roentgen discovered that rays could travel through solid objects, not knowing much about these rays, he labeled them as X-rays, X standing for unknown. His research began at the University of Wurzburg, where he focused on light phenomena by discharging electrical current in Crookes tubes. In 1901 he was awarded the first Nobel Prize in physics for his finding of a “different type of ray” [1]. Shortly after his discovery, Henri Becquerel discovered a similar phenomenon with uranium. Becquerel’s discovery happened by accident, when he put his uranium salts and photographic plates in a drawer on a cloudy day. He found that the images of the crystals were outlined on the plates, even though they had not been in direct sunlight. The results were astounding to Becquerel; however most ignored this finding because it seemed too similar to Roentgen’s discovery. The mystery associated with Becquerel’s work lured Marie Curie into learning more about uranium. Since there was very little literature on this subject at the time, she went straight away to the lab to run experiments. It was while Marie was working with pitchblende, which is a form of the mineral uraninite occurring in brown or black viscous masses, that she noticed a highly radioactive substance that was greater than uranium [2]. Her husband, Pierre Curie, helped her and eventually they discovered two new elements: radium and polonium. Industrial firms saw this as a promising field of work and offered to help the Curies by providing additional lab space. As they gained more and more attention, they were able to get the tools they needed to make further discoveries in this realm of work, which eventually led to some of the tools we have today in biomedical imaging.

Figure 1. Image of pitchblende [3]

Five years after the discovery of X-rays came the discovery of gamma-rays. In 1900, Paul Villard made this discovery while investigating radiation from radium [4]. Villard was running experiments on radium and noted rays differing in penetrating depths, but did not label this type of ray as separate from alpha and beta rays, which had already been discovered and labeled as a form of radioactive decay. It wasn’t until a year later in 1901 that Ernest
Rutherford discovered in a separate experiment that these types of rays that were emitting from uranium were indeed different than alpha and beta rays; hence he named them gamma rays [5].

2. X-rays Versus Gamma Rays

The difference between X-rays and gamma rays stems from their origin and energy levels.

X-rays are produced by their change in energy states of orbital electrons or by the deceleration of an electron beam [7]. Gamma rays come from nuclear decay and have much higher energies ranging from 80 to 200 keV, however gamma radiation within the energies of 90 to 200 keV are better suited for camera imaging and provide a source of activity that is short lived, which lowers a patient’s radiation dose. It should be noted that there are other types of nuclear decay, such as alpha and beta rays, however gamma rays have higher energies and are thus able to penetrate sources better, making it a more suitable option for imaging. X-rays have energy levels ranging from a maximum energy of 150 keV and a minimum energy of 20 keV [7]. The energy of an X-ray or gamma ray can be calculated by the following equation:

\[ E = \frac{hc}{\lambda} \]  

(1)

Where \( h \) is Planck’s constant and \( c \) is referencing the speed of light. The wavelengths for X-rays vary between 0.062 and 0.0082 nanometers. To better illustrate where these wavelengths stand in a spectrum as noted in Figure 2, visible light has a range of wavelengths from 400 to 700 nanometers. Gamma rays have wavelengths shorter than .001 nanometers. In general, a decreasing wavelength will produce an increase in energy, based on the inverse relationship seen in equation (1). Since gamma rays characteristically have shorter wavelengths and higher energies, they are assumed to be more damaging based on this principle. Both ray types pose a health risk due to ionizing radiation. This is an undesirable property because it can lead to mutation of cells in vivo, causing unwanted DNA, cells or tissue damage. Alternatively, scientists were able to find a use for this property by targeting unwanted cells. X-rays and gamma rays can be used in sterilization procedures to kill unwanted bacteria, or in treatments to kill cancerous cells. Ironically, for the very reason that they are dangerous, they can also be used productively. X-rays and gamma rays differ vastly in the ways in which they are produced, and vary slightly in terms of their physical properties, but ultimately the reasons that they are used in biomedical imaging are for the same purpose.

3. X-rays and Computerized Tomography Imaging

As Roentgen later figured out, in order for X-ray production to occur, there must first be a source of negatively charged electrons, or a cathode, which is generally composed of tungsten. Energy is involved when heat is present. Once the wire reaches around 2200 degrees Celsius the amount of energy in the system will be sufficient to allow the electrons to leave the cathode. Cooling systems are often present to allow for proper heat removal. On the other end, there is an anode, which is created by a large positive voltage on a metal target. Once a voltage is applied, electrons will leave the cathode and strike the anode. A high-energy electron from the cathode ejects an electron in the inner shell of the anode, causing an outer electron to fill the hole. The resulting difference in binding energies creates X-rays that are emitted. Often a negatively charged focusing cup surrounds the cathode to concentrate the electrons.

\[ E = \frac{hc}{\lambda} \]  

(1)

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the detector to be picked up [9]. Two types of detectors exist: computed radiography and digital radiography. Computed radiography is composed of phosphor crystals. When X-rays hit the phosphor layer, electrons are released, eventually creating light. This light leads to a latent image, which is ultimately processed in a computed radiography reader. Photodiodes convert light into voltage, which is then filtered and digitized. The whole process can happen in a matter of seconds. In the case of digital radiography, there are two main types: indirect and direct. Indirect digital radiography X-rays are first converted into light by a scintillator before being converted into a voltage. Direct digital radiography eliminates the middle step.

Figure 4. Image of X-ray [10]

As you can see in Figure 4, bone appears brighter on the X-ray image due to an increase in intensity. Intensity can be modeled by the following equation:

\[ I = I_0 \exp(-\mu x) \] (2)

Where \( \mu \) is the attenuation coefficient and \( x \) is a distance [9]. Areas in the body that absorb X-rays will prevent the X-ray from reaching the detector. Tissues appear gray and air will appear black on an X-ray image. Contrast agents such as iodine or barium sulphate are used to better detect soft tissues since these agents provide a higher image intensity. The higher the image intensity, the easier it is to detect deformities in the body.

In 1979 a Nobel Prize was given to Sir Godfrey Hounsfield and Allan Cormack for their invention of the computed tomography scanner, or CT scanner [9]. This invention uses the principles of X-ray imaging, but goes a step further by allowing the medical personnel to acquire a 360 degree picture of internal organs. This two dimensional image is created by combining multiple one dimensional X-ray images at different angles. Only looking at a single slice of an organ serves us limited information, so to negate this issue, generally a patient is moved along the head/foot direction to accumulate multiple slices of an organ for better data analysis. This is known as a “spiral” or “helical” scanning mode [9].

Before this could be fully implemented in hospitals, considerations of overheating and reconstructive image algorithms had to be taken into account. It wasn’t until the 1990’s that the first CT scanner was used by clinicians to assess organs in the body such as the brain, lymph nodes, lung, pelvis, liver, gastrointestinal tract, etc [9].

![Image of helical CT scan along z-direction](image)

Figure 5. Image of helical CT scan along z-direction [11]

4. Nuclear Imaging

After the discovery of radioactive materials making X-ray imaging and CT scans possible, a new field of imaging emerged known as nuclear medicine. The first notable mention is SPECT, also known as single photon emission computed tomography. In SPECT imaging, a series of adjoining two-dimensional images are created using a radiotracer. Often \(^{99m}\text{Tc}\), or metastable technetium, is used as a radiotracer. Metastable technetium works by producing gamma rays upon its decay. The half-life of any radiotracer can be computed by:

\[ \tau_{1/2} = \ln 2 / \lambda \] (3)

As noted in Figure 6, technetium has a half-life of 6.0 hours. The half-life is important because radiotracers with too short of a half-life make imaging difficult by reducing the time clinicians are able to allot for set up and imaging procedures. Too long of a half-life requires a long waiting period for the patient before results can be shown, as well as a higher time of exposure to radioactive substance for the patient.

In order to create images using SPECT, a large scintillation crystal is used to convert the gamma rays into light after striking the gamma camera. The light is then converted into an electrical signal by a photomultiplier tube (PMT), and eventually into an image. To prevent noise from interfering with the signal, a pulse height analyzer is present to reject signals from gamma rays that have been Compton scattered [9]. While SPECT scans can provide useful information due to their high sensitivity and
specificity, they are noted for having poor signal to noise ratio (SNR), low spatial resolution and slow image acquisition.

<table>
<thead>
<tr>
<th>Radiotracer</th>
<th>Half-life (hours)</th>
<th>$\gamma$-ray energy (keV)</th>
<th>Clinical application</th>
</tr>
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<td>$^{99m}$Tc</td>
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<td>140</td>
<td>Various</td>
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<td>$^{67}$Ga</td>
<td>76.8</td>
<td>93-394</td>
<td>Tumor detection</td>
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<td>$^{133}$Xe</td>
<td>127.2</td>
<td>81</td>
<td>Lung ventilation</td>
</tr>
<tr>
<td>$^{201}$Tl</td>
<td>72</td>
<td>82-167</td>
<td>Myocardial viability</td>
</tr>
<tr>
<td>$^{111}$In</td>
<td>67.2</td>
<td>171, 245</td>
<td>Inflammation</td>
</tr>
</tbody>
</table>

Figure 6. Properties of common radiotracers used in SPECT [9]

Another nuclear imaging technique that has advantages over SPECT is PET, or positron emission tomography. PET has between 100 and 1000 times higher SNR and significantly higher spatial resolution over SPECT [9]. When radiotracers are used in PET, they emit positrons. When positrons annihilate each other in a tissue a certain amount of energy is released, which can be detected by solid-state detectors. The detectors are arranged in a circle around the gamma rays, so when gamma rays collide, their origin can be traced back since they have trajectories 180 degrees apart.

Similar to SPECT, PET has a detector made of crystals, which are coupled to PMTs. The image is created by digitizing the voltages. Unlike SPECT, PET imaging uses isotopes such as $^{11}$C, $^{15}$O, $^{18}$F and $^{13}$N to create radiotracers. The most commonly used radiotracer is $^{18}$FDG, or $^{18}$F-fluorodeoxyglucose. When $^{18}$FDG enters the body, it becomes phosphorylated by a kinase, creating FDG-6-phosphate, which halts the glycolytic cycle. A high glucose metabolic rate is prevalent in many tumors, thus making it easy to pin point their origin with this tool. The radiotracers used in PET have half-lives on the order of a few seconds, compared to the hour long half-lives used in SPECT. SPECT tracers are much cheaper than PET tracers, and in addition to this, PET-CT scanners can cost around $2 million, while a SPECT gamma camera costs between $400,000 and $600,000 [12]. With a cheaper price comes a lower quality image. SPECT scans are long-taking up to two hours or more to complete, and produce low-resolution images, which can lead to misidentification of perfusion defects. Regardless of the setbacks of SPECT, it is still widely used since the images produced are not significantly different enough to cause PET scans to completely replace SPECT.

5. Safety of Nuclear vs. X-ray Imaging

Shortly after being discovered, radium was manufactured synthetically in the U.S. in 1910 [13]. Radium started popping up in foods, cosmetics, and even toys.

Radium water crocks became very popular, with claims that this radium-laced bucket could cure anything ranging from arthritis to wrinkles. Alfred Curie created a line of dental care products, along with cosmetic creams and powders that were promised to rejuvenate and brighten skin [13]. Radioactive spas took off in the 20s and 30s. Patrons could soak in radium mud or water, or even sit in radium mines and caves that were deemed “healing rooms.” Some spas still exist today in parts of Europe and Japan.

Scientists have come a long way since the discovery of radioactivity and the beliefs in its medicinal cures for everyday use. While scientists were able to channel some good from this discovery by creating imaging modalities and treatments for cancers, some negative consequences should be noted. Both ray types are in the ionizing zone of radiation, as shown in Figure 2. Both X-rays and gamma rays can cause ionization in the body, which can lead to radicals that can latch on to proteins or DNA molecules and cause
denaturization or mutations, which can lead to tumors or cancers. In certain cases, the p53 tumor suppressor protein becomes activated and phosphorylated when DNA damaging agents are present, such as ionizing radiation [15]. When the p53 protein becomes activated, it attracts DNA repair proteins where prolonged damage is present, otherwise programmed cell death, also known as apoptosis, occurs where damage is irreparable.

![Figure 9. Image shows direct and indirect damage caused from ionizing radiation [16]](image)

In cases where too much ionizing radiation is present, it is easy to see how tumors can form, leading to life-threatening problems.

So how much ionizing is acceptable, given the negative consequences? Let’s take a look at the typical effective doses that are actually used today, and what this could mean for our bodies.

![Figure 10. Image shows the typical effective dose received in different diagnostic procedures [9]](image)

<table>
<thead>
<tr>
<th>Diagnostic Procedure</th>
<th>Typical Effective Dose (mSv)</th>
<th>Number of Chest X-rays (PA films) for Equivalent Effective Dose</th>
<th>Time Period for Equivalent Effective Dose from Natural Background Radiation?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest x-ray (PA films)</td>
<td>0.02</td>
<td>1</td>
<td>2.4 days</td>
</tr>
<tr>
<td>Skull x-ray</td>
<td>0.1</td>
<td>5</td>
<td>12 days</td>
</tr>
<tr>
<td>Lumbar spine</td>
<td>1.5</td>
<td>75</td>
<td>182 days</td>
</tr>
<tr>
<td>I.V.ogram</td>
<td>3</td>
<td>180</td>
<td>1.9 year</td>
</tr>
<tr>
<td>Upper GI exam</td>
<td>6</td>
<td>300</td>
<td>2.0 years</td>
</tr>
<tr>
<td>Barium enema</td>
<td>6</td>
<td>400</td>
<td>2.7 years</td>
</tr>
<tr>
<td>CT head</td>
<td>2</td>
<td>100</td>
<td>243 days</td>
</tr>
<tr>
<td>CT abdomen</td>
<td>8</td>
<td>400</td>
<td>2.7 years</td>
</tr>
</tbody>
</table>

One sievert (Sv) is considered to be a large dose; the recommended threshold limit value is an average annual dose of 0.05 Sv, or 50 mSv. The repercussions on your body for encountering 10 Sv is the risk of death within days or weeks. At a 1 Sv dose, you have a 0.05 % chance of facing the risk of cancer later in life. At 100 mSv the risk lessens to 0.005% chance of contracting cancer. 50 mSv is the threshold limit value for a worker in any one year, or 20 mSv for an annual dose averaged over five years [17]. PET and SPECT emit slightly higher effective doses than X-ray or CT imaging, as seen in figure 10. For a whole body PET, a dose of 15 mSv is delivered. When combined with a CT scan, the dose increases to 25 mSv [18]. For a SPECT scan, an average effective dose of 10.7 mSv is noted [19]. For imaging purposes, the effective doses seen with X-ray and CT imaging, along with PET and SPECT scans, are low enough to be considered relatively safe, since imaging modalities are used more often for prevention and diagnostic procedures and not on a routine basis.

For treatment of certain cancer patients, much higher doses are seen. Those who have developed thyroid cancer receive a dose of 20 Gy, or 20,000 mSv [20] as a means of treatment. This is double the dose assumed for causing death. This is the price some people pay when battling cancer, and in certain cases, the benefits will outweigh the consequences. A study shows that ionizing radiation can also be used to treat tumors by taking advantage of properties of VEGF proteins, or vascular endothelial growth factor proteins. These proteins are prominent leaders in angiogenesis of tumors. Evidence proves that the inhibition of these proteins blocks the growth of metastatic experimental tumors [16]. In the study, they proved ionizing radiation in combination with anti-VEGF therapy produced the best results. When anti-VEGF therapy is used alone, no detectable tumor growth inhibition is seen after 18 days. When ionizing radiation is solely used, the tumor growth is inhibited by 68.8%, relative to untreated controls. However, when both treatments are used in combination, 83.4% inhibition is achieved [16]. So while a high dose of radiation is received in cancer patients, this amount is necessary to kill off the unwanted pre-cancerous or cancerous cells. One should be advised that this high amount of exposure is not recommended unless necessary.

### 6. Discussion

By now, it is apparent that without these initial discoveries of radioactivity, none of these imaging modalities would have been invented. X-ray imaging was among the first to be created, but was later modified with CT scanning technology to create a 360 degree picture that was of better use for clinicians trying to locate abnormalities inside of internal organs. CT scans allow for cross-sectional views of the body. After the discovery of gamma rays, SPECT and PET imaging became possible. As shown in Figure 11, PET produces images with a
higher resolution, but both PET and SPECT can be used to locate tumors using radiotracers. PET scans take less time to complete, with a timeframe of around 30 to 40 minutes, while SPECT can take 2 or more hours to complete. PET uses computerized images of chemical changes occurring in the body, such as sugar metabolism, to locate tumors, while SPECT imaging uses the decay of technetium to detect signals and generate images. To improve nuclear imaging, clinicians found that combining PET/SPECT with CT scanners provides even better results when trying to pinpoint locations of body abnormalities.

![PET vs SPECT Imaging](https://upload.wikimedia.org/wikipedia/commons/a/a7/Uraninite-usa32abg.jpg)

Figure 11. Picture showing differences in PET vs. SPECT imaging. PET provides an image with a higher resolution [21]

It is clear that the newer methods in imaging still rely on the primitive principles upon which all of this was built. Overtime, we have seen some major improvements in biomedical imaging, and as we gain more knowledge and creativity, surely there will be more to come, but we must not forget about the historic people that made all of this possible. Thanks to the discoveries of radioactivity, clinicians have the power to diagnose and treat patients in need, with the ultimate hopes of prolonging patient’s lives.

### 7. References


3. Image of uraninite at <https://upload.wikimedia.org/wikipedia/commons/a/a7/Uraninite-usa32abg.jpg>


6. Spectrum of x-ray vs. gamma ray at <http://3.bp.blogspot.com/-64aVd3zFPo8/VH4aqQWRRm8I/AAAAAAAAC2Y/63FTsQCUbY/s1600/EM-spectrum-701135.png>


8. Image of X-ray emission at <http://www2.rgu.ac.uk/life_semweb/xrayfig1.gif>


11. Image of helical CT scan along z-direction at <https://dta2gzjs97bag.cloudfront.net/content/ehsupp/7/suppl_G/G4/F3.large.jpg>


21. Image showing PET vs. SPECT differences at <http://www.auntminnie.com/user/images/content_images/sup_mol/2014_11_13_17_25_44_197_JNM_PET_SPECT_Alz_DLB_images_450.jpg>
EEG Arm Wrestling
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Abstract
Electroencephalography (EEG) is a method of measuring brain activity from electrodes placed on the scalp. Electrodes placed over the occipital region of the brain measure information in the primary visual cortex. When an awake and alert subject closes their eyes, the primary visual cortex begins to produce “Alpha waves” which are typically around 10 Hz. These waves are some of the most robust brainwaves that can be detected with EEG and can be used to control an external device. It’s been demonstrated that multiple individuals can collaborate and combine their alpha waves to give multiple degrees of control to a neurally-controlled robot. Here, it is shown that alpha waves can also be used in a competitive setting.

Keywords: EEG, Alpha waves, OpenBCI, LabVIEW, Arduino

1. Introduction
Brain-Computer Interfaces (BCIs) have been a method of using non-invasive EEG signals to interface with robotics for decades. However, only recently has the price of BCI hardware and software dropped significantly enough for researchers that are not directly tied to a neuroscience lab to be able to access these brain signals.

OpenBCI is one of the first companies to develop and produce low-cost, open-source BCI boards. Previous groups have demonstrated the efficacy of using alpha waves as the control method for robotic systems [1, 2]. However, these multi-user BCI applications had the users working together instead of in competition with one another.

The goal behind this project was to use the new BCI technology to acquire, process and compare alpha waves between two participants in real time. EEG data was first collected using the OpenBCI and then was sent to two separate PCs via Bluetooth. Data was then transferred to a LabVIEW VI designed to acquire data from the USB ports and filter the signal according to the alpha frequency band for use in spectral analysis. Spectral data was then analyzed and calibrated manually to determine whether or not a strong alpha wave was present.

While the initial objective of the project was completed following spectral analysis, it was determined that the real time data comparison between two individuals could be elegantly visualized in the form of a competitive game. This competition was based on the ultimate one-on-one test of strength: arm wrestling. If either participant’s alpha power exceeds a predetermined threshold, a voltage is output via data acquisition module to an Arduino Uno microcontroller. The microcontroller simultaneously collects data from both participants. If both or neither participant reaches threshold, nothing happens. However, if only one participant reaches threshold the microcontroller sends a voltage to a servo motor attached to an arm wrestling apparatus, turning 3 degrees in that participant’s favor [Figure 3]. The goal of the competition is to maintain a strong alpha wave and turn the servo motor 90 degrees.

2. Methods
The 10-20 system is a standardized map of electrode placement for recording EEG signals. Each position is denoted by a letter and number combination. The letters represent the lobe of the brain that the electrode is positioned over. The letters F, T, P, and O represent the frontal, temporal, parietal, and occipital lobe, respectively. The occipital lobe is where the primary visual cortex is located. This makes the O1 and O2 positions the best locations for recording primary visual cortex activity and alpha waves [4].
While previous work has demonstrated the feasibility of each step in the process, they had never been combined sequentially in this way.

2.1 OpenBCI

To measure the brain waves from each subject, the OpenBCI 8-bit board was connected to the individual using standard gold cup electrodes and conductive paste. The brain signals are then sent from the OpenBCI board to the computer through a Bluetooth enabled USB dongle.

Measuring alpha waves from an individual requires three electrodes connected to an EEG-processing board (e.g. an OpenBCI). Two of the electrodes attach the subject’s earlobes to the SRB and BIAS pins on the OpenBCI board.

The SRB pin is the “default ‘reference pin’” which compares the signal from the brain waves to the biological noise from the rest of the body. The BIAS pin “uses destructive interference waveform techniques to eliminate the ‘common mode noise’ of all of the active channels” [5]. These are critical steps to eliminate as much noise as possible and measuring EEG frequencies would not be possible without these filters.

The final electrode is placed over the occipital region of the brain at the O1 position.

2.2 LabVIEW

After acquiring the brain signals from the USB dongle, these raw signals are then imported into LabVIEW. Within LabVIEW, the signals are processed and filtered to isolate the alpha waves.

To begin, a bandpass filter with cutoff frequencies at 5 and 15 Hz was applied to the raw EEG data. This was done to minimize noise outside of the range of typical alpha frequencies.

Next, the Fourier spectrum of the signal was measured. A peak around 10 Hz meant that the system was detecting an alpha wave from the subject. Through training and observation, it is possible to determine the change in the amplitude of the frequency spectrum when the subject closes their eyes and begins to produce alpha waves. After determining the typical amplitude change, a threshold is set to determine whether or not an alpha wave is present.

If the threshold is met and/or exceeded, the program will trigger the DAQ (Data Acquisition System) to output a 2 volt DC signal.

2.3 Arduino and Arms

An Arduino is connected to the DAQ modules for each subject. Inputs from the DAQ modules are constantly assessed and binned in one second intervals. Every second, the voltages coming from the DAQ modules were measured and a winner was determined according to whomever was able to produce an alpha wave for a longer period of time within that window.

The Arduino is also connected to a 3.5kg servo motor (Tower Pro MG92B) which drives the rotation of the arms to indicate who is winning. The servo rotates from a neutral (90°) position in increments of 3 degrees in the direction of the victor for each second-
long time bin. This continues until it either indicates a subject 1 victory (0°) or a subject 2 victory (180°). Once the motor reaches its limit in either direction, it ceases movement and triggers an LED alert.

Figure 4. The arms that visually identify which team is winning. While there are two servo motors mounted to the arms, only one is used during competition.

If the inputs are absent or equal, the Arduino will not change the angle of the servo motor from the previous result.

The arm angle and voltages from each DAQ are displayed every second on the monitor of the computer that is running the Arduino. Once a winner is determined, the monitor will also display a text alert announcing the winner.

When each subject closed their eyes began generating alpha waves, the LabVIEW VI would detect an amplitude and trigger an output to the Arduino. If the Arduino only receives inputs from a single side, it powers the servo and the arms move toward the winning side.

Figure 5. Two competitors attached to the EEG Arm Wrestling system.

3. Discussion

Previous work has shown the ability for multiple users to control multi-directional robotics [1, 2]. However, these systems had the users working toward a common goal. This system requires the users to work against one another in competition. In the future, brain-to-brain competition could lead to sporting alternatives with extremely low risks of physical injury.

Work is currently underway to filter out the remaining noise and drift that can lead to confounding variables during the competition. Furthermore, research is being done to determine better methods to quantify alpha wave quality which will be applied in a more sophisticated algorithm to determine the winner of the competition.

4. Acknowledgements

This project was undertaken as part of the course Neural Engineering II – Neural Coding, taught by Dr. Hananeh Esmailbeigi. Students that contributed to the project but are not authors on this paper include Narasimhan Narasimhan, Robert Pacie, Sebastian Parnel, and Martin Strama.

5. References


EXTRACORPEAL SHOCK WAVE THERAPY
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Abstract
To build off the utility of acoustic pressure waves to generate images, researchers have adjusted certain parameters and engineered a new field of treatment options that target localized pain caused by built up calcification deposits. Extracorporeal shock wave therapy (ESWT) aims to fragmentize unwanted and often times extremely painful calcifications. The method provides a completely non-invasive and low risk procedure with high success rates from randomized clinical trials (RCT). Originally introduced to combat kidney stones, it has since expanded its reach to treat patients suffering from musculoskeletal calcification of the bones and joints, such as heels spurs in the case of plantar fasciopathy and stress fractures. ESWT exerts higher amplitude pressure waves into tissue than diagnostic ultrasound imaging. This results in increased vascular circulation to the focus area which provides nutrients and ultimately healing.

Keywords: Lithotripsy, Plantar Fasciopathy, Acoustics, Cavitation

1. Introduction
1980 was the advent of lithotripsy, a newly refined option for patients suffering from kidney, gallbladder, and pancreatic stones that relies on ESWT [1]. Recently these therapies have shown tremendous promise in relieving pain caused by common conditions such as tennis elbow, knee tendonitis, and plantar fasciopathy [2]. Mostly caused by overuse, a decrease in the body’s healing capacity with age, and improper or excessively used footwear, plantar fasciopathy (FS) commonly demonstrates itself as a pain while walking. Initial treatment is non-operative and consists of relative rest, physical therapy, stretching, exercises, shoe inserts/orthotics, night splints, non-steroidal anti-inflammatory drugs, and local corticosteroid injections [2]. To avoid surgery, ESWT can be implemented. The causes of stone formation in other joints are often poor diet, lack of hydration, or sedentary lifestyle. Another cause of localized calcification buildup stems from overuse by athletes who routinely place extra stress on joints, muscles, and bones as they try to heal from repetitive exercise [2].

ESWT exerts two mechanical forces on tissue: direct stress associated with high amplitude shock waves and stresses caused by microjets which are associated with the growth and violent collapse of gas-filled cavitation bubbles [1]. The maximum pressure wave range generated during ESWT is between 40 and 100 MPa. These waves have much higher amplitude than those used in diagnostic ultrasound which hover around 2 MPa [3].

2. Acoustics and Mechanisms of ESWT
As an object moves through fluid, the molecules surrounding it at a given time compress, increase in pressure, and eventually return to resting state after the object passes. In the case of ESWT, the “shock” is due to rapid increase in pressure occurring over a time span less than 5 ns [1]. As seen in figure 1, the instantaneous increase in positive pressure yields an almost infinite slope and reaches around 40 MPa. The peak is followed shortly by a decrease in pressure to around 0 MPa after 1 µs. The wave reaches its most negative pressure of P_− gradually after initial rise to P_+. The energies of waves used in ESWT range between 100 kHz and 1 MHz. The pulse waveform is shown in figure 1.

![Figure 1. Standard pressure waveform in SWT](image)

When a sound wave propagates, it affects the density, pressure, and particle velocity of the fluid surrounding it [2]. All acoustic waves lose a small portion of their energy as they propagate through space. The higher the increase in pressure, the higher the attenuation of energy. So an infinite pressure over time slope (as shown during the shock phase in figure 1) correlates to infinite
attenuation which greatly weakens structural formations of hard tissues. The density of the fluid surrounding the wave increases or decreases depending on the object’s position. The total density is the sum of the ambient density of the medium (\( \rho_o \)) and the density caused by the sound wave (\( \rho_a \)), as shown in equation 1 below:

\[
\rho = \rho_o + \rho_a
\]

(1)

Similarly, this equation can be written in terms of pressures:

\[
P = P_o + P_a
\]

(2)

This pressure is also found through the product of density and speed of sound for a given medium. This is the same as the product of particle velocity (\( u_a \)) and acoustic impedance (\( Z_o \)):

\[
P_a = \rho_a c_o^2
\]

(3)

\[
P_a = u_a Z_o^2
\]

(4)

where \( Z_o \) is the impedance of a material. Particle velocity is the net velocity of molecules in a region of space, and can be defined as:

\[
u_a = \frac{P_a}{\rho_a c_o}
\]

(5)

As seen from the above equations (3-5), density and sound speed in a material influence impedance.

The maximum pressure of diagnostic ultrasound approaches 2MHz, whereas SWT pressures can approach 100 MHz. The ratio between acoustic density and ambient density for ultrasound is roughly \( \rho_a/\rho_o = .0009 \). The ratio for lithotripsy is around .04 which indicates that even for strong acoustic waves, compression of fluid is less than 5% [3].

The transfer of wave intensity between mediums can be described by the intensity transmission coefficient (\( T_i \)). It determines the energy transmitted into and reflected from a material. Between water and air \( T_i \) is very low (around .1%), between water and soft tissue quite high (around 99%), and between water and bone or water and kidney stones between 60-75% and 75-95%, respectively [5]. These percentages are shown in figure 2, below:

For ESWT to be effective and to avoid healthy tissue damage, the acoustic wave must be focused. Typical focal zones for ESWT devices range between a couple millimeters to tens of millimeters in diameter [3]. ESWT repeatedly exerts pulses of high pressure waves onto a calcified surface. This causes stress to the material and ultimately fracture. Fractures combine and amplify to break material into small pieces. The target material is referenced by many names including calcifications solutes, and stones.

2.1. Cavitation

Cavitation refers to the small bubbles (or cavities) of gas that grow in fluids surrounding a calcification or kidney stone in response to the large negative pressure tail of the acoustic pulse [2]. Repeated pulses break down their target eventually forcing it to break into smaller pieces. This process is called fragmentation. The growth time of a bubble in the medium is around 300 µs and 600 µs at the surface of a calcification or kidney stone [7]. Recent studies suggest that bubbles generated by one pulse can be manipulated by a second pulse [8]. Just as collapsing bubbles are effective in wearing away built up calcifications, they can affect healthy tissue in much the same way. Bubbles have the ability to rupture vessel walls during the expansion phase of the bubble cycle. Figure 3 shows the formation and destruction of a bubble and its calculated radius.
Figure 3. Formation and destruction of cavitation bubble with radius estimation [6].

The propagation of sound waves in kidney stones and calcifications exhibits much different behavior than through a standard fluid medium. These solutes have built up over long time periods and their outer surface is often jagged and not uniform [8]. Their formation can be thought of as similar to that of sedimentary rocks—where small pieces of (rock) material compress under constant pressure and over time increase in size.

2.2. Spalling, Superfocus, and Squeezing

Although cavitation is the main mechanism behind dissolution of solutes, other factors cannot be ignored. When a shock wave encounters solid material it splits into longitudinal (compression) waves or transverse (shear) waves [2]. A shock wave can break up or weaken solute in 3 ways other than cavitation: namely through spalling, superfocusing, and squeezing.

Spalling occurs toward the back of the material as a result of longitudinal wave propagation. It results from the positive pressure pulse (pressure head) being added to the negative pressure tail. This creates a large tensile stress near the back wall of solute material [9]. And since most solids are weaker under tension than under compression, the material is more likely to sustain micro fractures, become weaker, and ultimately fail.

As stated previously, kidney stones and calcifications have complex geometries. Superfocusing describes the amplification of stress due to solute geometry. Research suggests that stresses are funneled into caustics (regions of high stress) in the interior of the stone and that this can lead to failure in the form of cracks [7].

The last mechanism by which solutes break apart is squeezing. Squeezing occurs due to differences in the speed of sound within the solute and surrounding fluid. The speed of sound is always faster in the solute [2]. Because of this, the head shock wave propagating inside the solute moves faster and increases the distance between it and the wave entering the solute traveling through surrounding fluid. This results in a two high pressure areas in the front and back of the solute, which apply force inward toward the solute center, thus squeezing the solute and causing it to fracture [7]. Figure 4 is a visual representation of these three mechanisms.

Figure 4. Locations on target (kidney stone or calcification) of various fracturing mechanisms [6].

3. Applications

Peak positive and negative pressures vary depending on machine, but typically lie in the ranges of 30 and 110 MPa and -5 and -15 MPa, respectively [8]. There are two main applications of ESWT, lithotripsy and plantar fasciopathy, which are detailed below.

3.1. Lithotripsy

Lithotripsy is a medical procedure involving the physical destruction of hardened masses such as kidney stones or gallstones [7]. Lithotriptors which carry out lithotripsy, are grouped into two main types. The first,
called water-bath lithotripters was developed in 1980 and works by submerging a patient, or certain portion of a patient needing therapy in a water-filled tub. The tub acts to increase coupling between materials (water and tissue) thereby decreasing attenuation. The tub must be continuously degassed to halt any bubbles from wedging themselves between the device and skin [1].

The second and more commonly used method involves a device head filled with water and capped by a thin rubber membrane [3]. This membrane is then coupled with the patient’s skin after applying an oil or gel. Compared to water-bath lithotripters, dry-lithotriptors are more convenient but less effective at reducing air bubbles along the skin-membrane interface [9]. Lithotriptor machines differ in their effective range between transmitter and target and their area of focus. There is a trade off between focal size due to patient movements during the procedure and potential to harm tissues not intended for targeting.

### 3.2. Plantar Fasciopathy

Repeated application of pulses to the heel region increases circulation and the metabolisms of tissues. This has the potential to expedite the healing process [4]. The same techniques are applied to shoulder, elbow, and knee joints where calcification buildup can be rampant. Figure 5 shows an ESWT device being applied to a patient’s right elbow.

![ESWT device targeting elbow region](image)

Figure 5. ESWT device targeting elbow region [8].

### 4. Discussion

Each ESWR model varies, and there is currently no standardization between them to adjust parameters such as power, number of shock waves, and rate of shock wave delivery [9]. Although different models all operate on the same technical principles, there is no standardization for adjustment between machines. The notion that lithotripter shock waves can pass harmlessly through the body is not true [10]. Although cavitation bubbles are well understood there has been no empirical recording of the event in its entirety. The scale is too small and the lifespan of a single bubble is so short that it cannot be measured physically [3, 5]. ESWT could also be used by athletes seeking performance enhancement. Sports such as boxing and mixed martial arts (MMA) require bone strength training to increase durability and decrease chance of injury during a fight. The repeated breaking and healing process of bones to gain an advantage over the competition could be more widespread in future years.

### 5. Conclusion

Extracorporeal shock wave therapy is convenient, non-invasive, and requires no anesthesia (in most cases) [2]. Depending on body region a procedure can take 10 minutes or less [5]. ESWT’s main goal is to break up large stones or calcifications into smaller pieces which can then be more easily processed and disposed of by the body. It is a reliable and cost-effective means of non-surgical treatment for common ailments such as plantar fasciopathy and kidney stones. An ageing populace will increase demand for the treatments ESWT provides.

### 6. References


IMAGING TECHNIQUES IN THYROID SCANNING
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Abstract
Thyroid disorders which are the largest endocrine issues in the USA could be reduced through early detection and regular screening. Early diagnosis of these disorders leads to prevention of complications and in cases of carcinomas may even prevent secondary spread to other organs. In the 1940’s the thyroid gland became one of the first organs imaged in nuclear medicine. The gland secretes hormones T3 (triiodothyronine) and T4 (thyroxine) which influences the metabolism, growth and development of the human body. The thyroid gland is also controlled by the pituitary gland which continuously checks the level of thyroid hormone in the blood. Anomalies in the functions or gland could result in thyroid disorders. The most common thyroid disorders are hypothyroidism, hyperthyroidism, thyroid nodule and thyroid cancer. The common diagnostic methods consists of thyroid scintigraphy and ultrasonography. The thyroid scintigraphy (131Iodine) method reflects only the functional state of the gland. To understand the anatomical structure of the thyroid gland other forms of imaging have to be assessed. This paper discusses the various imaging modalities in the evaluation of thyroid disorders.

Keywords:
Single photon emission commuted tomography (SPECT), Positron emission tomography (PET), Magnetic resonance imaging (MRI), thyroid scintigraphy, Optical coherence tomography (OCT)

1. Introduction

1.1 Thyroid Anatomy and Functions

The thyroid is a bilobed structure located in the lower part of neck and is draped anteriorly along the trachea. It is an important part of the endocrine system. It is composed of two lateral lobes that are connected by the isthmus. The thyroid gland secretes the thyroid hormone that travels through the blood to all parts of the body. One of the function of the thyroid gland is to absorb iodine present in our food and convert it to hormones triiodothyronine (T3) and thyroxine (T4).

![The Thyroid Gland](image)

Figure 1. Anatomy of thyroid gland

Thyroid cells in the body can absorb iodine. The combination of amino acid tyrosine and iodine gives T3 and T4. These control the body’s metabolism in many ways, from the rate at which calories are burned, to how fast the heart beats. In simple terms it controls the growth and development of the body. Hence it is important to control the levels of T3 and T4 in the body. Two glands in the brain, the hypothalamus and the pituitary play a role in the homeostasis of T3 and T4. The Pituitary gland produces the Thyroid secreting hormone (TSH) which plays a role in the regulation of the levels of T3 and T4.

Under the influence of TSH, thyroid will manufacture and secrete the T3 and T4 hormones thereby raising their blood levels. The pituitary then senses this increase and decreases the production of TSH. The pituitary gland is regulated by the hypothalamus gland. This hypothalamus gland produces the TSH releasing hormone or TRH which sends signals to the pituitary gland to stimulate the thyroid gland (release of TSH). This is the basic mechanism through which the balance of the thyroid hormones is maintained.
1.2 Thyroid disorder

According to the American thyroid Association more than 12 percent of U.S population will develop a thyroid disorder during their lifetime. The American Association of clinical endocrinologists (AACE) opines that approximately 27 million Americans will experience a thyroid disorder. Therefore thyroid diseases can be considered as one of the leading endocrine disorder in the United States. Studies have also revealed that thyroid disease is typically hereditary and in 80% of cases women are affected more than men.

![Figure 2. Ratio of Women Vs Men affected by thyroid disorder](image)

According to the American thyroid Association, undiagnosed thyroid disease may put the patient at risk for certain serious conditions such as cardiovascular diseases, osteoporosis and infertility.

The causes of thyroid disorders are largely unknown. The most common thyroid pathologies are the following:

- Hypothyroidism
- Hyperthyroidism
- Goiter
- Thyroid nodule
- Thyroid cancer

Hypothyroidism is a disorder that occurs when the thyroid gland does not make enough thyroid hormones to meet the body’s needs. About 4.6 percent of the U.S population age 12 and older has hypothyroidism. [1] Some of its symptoms include breathlessness, fatigue and weight gain. Common cause of hypothyroidism in the US is the Hashimoto’s disease wherein the immune system mistakenly attacks the thyroid.

Hyperthyroidism or overactive thyroid causes the thyroid gland to secrete more hormones than what is required. This speeds up functions like heart rate and metabolism. Most common cause of hyperthyroidism is the Graves’ disease which is an immune disorder. Symptoms include weight loss, anxiety, rapid beating of heart, increased sweating and trouble in sleeping.

A goiter is an unusually enlarged thyroid gland (a swelling or a lump in the neck). A goiter is noted as a sign/symptom of other thyroid disorders which require treatment. The incidence of women having goiter is more than men. Common conditions that manifest as goiter include thyroid nodules, thyroiditis and thyroid cancer.

A thyroid nodule is a swelling in one part of the thyroid gland. The nodule may be solid or filled with fluid or blood. Majority of thyroid nodules are benign. The nodule when left untreated may become cancerous. A solitary nodule is more likely to be cancerous than multiple nodules. The thyroid nodule can occur at any part of the gland. Some nodules can be felt easily while others can be hidden deep in the thyroid tissue or located very low in the gland. This makes it difficult to find its existence.

Thyroid cancer happens when cancer cells form from the tissues of the thyroid gland. Typically there are no signs or symptoms early in the disease. As thyroid cancer grows, it may cause:

- A lump that can be felt through the skin on your neck
- Changes to your voice, including increasing hoarseness
- Difficulty in swallowing
- Pain in the neck and throat
- Swollen lymph nodes in the neck

The type of thyroid cancer determines the treatment and prognosis. The type of thyroid cancer is based on the type of the pathological tissue present in the cancerous tissues. The types of thyroid cancer include papillary, follicular, medullary, and thyroid lymphoma.

The US Department of Health published an article indicating that the incidence of Thyroid cancers in women are three times more than men. The study also states that the incidence of Thyroid cancer is increasing in women and by 2020 they expect that the incidence of thyroid carcinoma in women would double from 34,000 to 70,000 women.
2. Imaging techniques

A regular thyroid screening can help detect and manage various thyroid disorders. Further determining the condition and starting treatment at an early stage can prevent serious health complications like heart disease and associated health problems. Thyroid scans are easily done and are relatively painless. The management of these thyroid disorders are relatively simple once the diagnosis is established.

Usual thyroid scanning uses too much or too little radioactive iodine to reveal specific regions in the thyroid. From the results of the test, doctors can confirm whether a biopsy has to be performed to determine the diagnosis. Another way to screen the thyroid is by obtaining ultrasound images. These images can show the underlying structures and presence of a tumor or a cyst.

Modern imaging techniques like computerized tomography (CT), Positron emission tomography (PET), Single photon emission commuted tomography (SPECT) and magnetic resonance imaging (MRI) – have revealed more thyroid nodules incidentally. This means that nodules are being found during studies that were done for reasons other than examination of the thyroid. Up to 4% to 8% of adult women and 1% to 2% of adult men have thyroid nodules detectable by physical examination. Closer to 30% of adult women have nodules detectable by ultrasound. [1]

Diagnosis of a thyroid nodule is the most common endocrine problem in the United States. Although the majority of thyroid nodules are benign (not cancerous), about 10% of nodules are malignant. Therefore, the primary purpose for evaluating a thyroid nodule is to determine whether it is malignant or not.

2.1 Traditional thyroid scanning

2.1.1. Thyroid scintigraphy

Thyroid scintigraphy is a nuclear medicine procedure that provides us with a visual display of the thyroid tissue. It also provides with excellent functional information based on the uptake of the radionuclide. The commonly used radioactive agents are isotopes $^{131}$Iodine and $^{99m}$Te. The thyroid gland takes up free iodine actively and hence it does not have to be attached to another protein or molecule. [2]

Through the scintigraphy procedure we get one or more planar images of the thyroid. The images indicate

- Functional status of a thyroid nodule
- Offers a Differential diagnosis
- Suggestion of the Presence of thyroid cancer (the definitive diagnosis of cancer is only by biopsy and histopathological examination)

Certain parameters need to be evaluated during patient preparation before conducting the test. Medicines that interfere with uptake of radio-iodine should be discontinued and the Patient should also be fasting (nil per oral) 4 hours prior to testing. [3]

While administering the dose proper timing has to be maintained. $^{99m}$Tc has to be injected intravenously and the images have to be obtained within 15 to 30 minutes of injection. The isotope $^{131}$I is administered orally and the images should be taken in 3-24 hr. [4]

The patient is made to lie facing upwards. The chin is positioned upwards and the neck is extended. This position of the patient is followed for all thyroid imaging. A pinhole collimator with a 3-6 mm aperture is used for image acquisition. The collimator is positioned in such a way that the thyroid fills two-third of the diameter of field of view. Then the position is noted and the nodules are marked.

Three views of image are obtained: anterior, 45-degree LAO and 45 degree RAO each having 100 to 250k counts.

![Thyroid images from a Scintigraphy test](image)

2.1.2. Ultrasound

Thyroid tissues were one of the first set of tissues to be studied through ultrasound. It is well suited to ultrasound because of its superficial location, vascularity and size. [5] First reports of thyroid ultrasound came between 1965 and 1970. The transition from A-mode to B-mode to gray-scale imaging was associated with dramatic improvements in clarity and interpretability of ultrasound images. Current high-resolution ultrasound images are able to
identify virtually all structural thyroid lesions of clinical significance [6].

Sound waves are used to image the thyroid. The sound waves are emitted from a small hand-held transducer that is passed over the thyroid. A lubricant jelly is placed on the skin so that the sound waves transmit more easily through the skin and into the thyroid and surrounding structures. As sound waves hit structures they bounce back like an echo. The probe detects these reflections to make pictures. The ultrasound is an accessible, inexpensive and noninvasive test. It is also quick and highly sensitive where cysts as small as 2mm, solid lesions as small as 4mm can be identified. High resolution and frequency of 7-13 MHz ultrasounds are used. However the image is obtained is poor in quality and specificity. These can be inferior to cross-sectional imaging that can identify lymphs and extended thyroid diseases.

A normal thyroid gland appears homogeneous with lack of internal architecture and with multiple small vessels within and adjacent to the gland on colour Doppler.[7] Ultrasonography for diffuse thyroid disease is limited by its lack of specificity. Hashimoto thyroiditis can be identified as a diffusely heterogeneous gland filled with millimetre-sized hypo echoic nodules separated by echoic septation and without evidence of normal thyroid parenchyma. Depending on the stage and duration of the disease, the size of the thyroid gland may appear normal, enlarged, or small.[8]

CT and MRI are imaging methods which give structural information about the thyroid gland and show the location and size of thyroid nodules. CT is very useful in identifying distant metastases and MRI can be used to evaluate the possibility of recurrent thyroid cancer. However, because of its relatively high cost, it is used less frequently than other imaging methods.

MRI is done when the size and shape of the thyroid needs to be evaluated. MRI can't tell how the thyroid is functioning (i.e., it can't diagnose hyperthyroidism or hypothyroidism), but it can detect enlargement. It is sometimes preferable to x-rays or CT scans because it doesn't require any injection of contrast dye, and doesn't require radiation.

The scans are done in supine position with the head mildly extended. In MRI the surface coil is centered over the thyroid gland and nodules as small as 4mm will be detected. MR imaging has good sensitivity and positive predictive value for the identification of non-ectopic and ectopic abnormal parathyroid glands. The detailed anatomic information provided by MR imaging is useful in planning a surgical approach and is complementary to other imaging methods used in the investigation of recurrent or persistent hyperparathyroidism.
Usually in a T1 weighted sequence normal thyroid intensity is slightly greater than that of the neck musculature whereas in T2 thyroid gland is hyper intense relative to musculature.

The role of CT imaging in thyroid disease is primarily limited to presurgical evaluation with a goal of assessing the extent of the disease, substernal components, or pathologic relationship with extrathyroidal structures. CT provides thin-section (3–5 mm) images by obtaining a series of radiographic projections in various angles and reconstructing them in a 2-dimensional fashion. Because of its high iodine content, the thyroid gland attenuates more than nearby soft tissues, appearing slightly brighter. If possible, CT should be performed without contrast because the iodine load received may delay treatment with radioiodine and may also lead to thyroid storm.

SPECT/CT is a hybrid modality that combines nuclear medicine and CT technology to identify tissue nature and enhanced characteristics of large neck masses. The CT portion provides the structural map to accurately localize the radiotracer uptake site.

SPECT/CT is a hybrid modality that combines nuclear medicine and CT technology to identify tissue nature and enhanced characteristics of large neck masses. The CT portion provides the structural map to accurately localize the radiotracer uptake site.

In oncology F18-fluorodeoxyglucose-PET (18F-FDG-PET) is a well established imaging modality. Its greatest utility is in the evaluation of thyroid cancers with dedifferentiated tumors which are iodine scintigraphy negative but FDG-PET positive. The combination of PET with CT or MRI (PET/CT or PET/MRI) which allows fusion of functional and anatomic information has a very promising role in the evaluation of thyroid cancers. [9]

SPECT is currently used with increased frequency due to its ability to provide the three-dimensional information which improves the overall sensitivity for detection and localization of a thyroid lesion. 131I SPECT-CT has been found to be more accurate than FDG PET-CT in localizing the regional and distant metastasis and in detecting residual/recurrent disease in the case of well-differentiated thyroid cancer. The most important advantage of fusion FDG PET-CT and 131I SPECT-CT is detection of metastasis in normal sized lymph nodes.

3. Modern and futuristic Imaging

3.1 Optical coherence tomography (OCT) and optical coherence microscopy (OCM)

Optical coherence tomography is a non invasive imaging test that uses light waves to take cross-section pictures of the organ in concern. Using this technique we can capture three dimensional, micron scale images in-situ and in real time. [9] Initially the feasibility of optical coherence tomography for imaging thyroid tissue was explored ex vivo on the human thyroid gland. [10]

OCM is an extension of OCT and provides high magnification resulting in cellular imaging. OCT/OCM system uses infrared light in fiber active device that allows visualization of microstructures of gland (1-15 μm cellular range) and provides high resolution images comparable with those obtained using histopathological methods. OCT and OCM can clearly differentiate between benign and malignant thyroid tissue using intrinsic optical contrast.
Figure 8. OCM/OCT images of thyroid nodule

The arrow marks in the above image shows the abnormal cells that are present in the thyroid. Since the OCT and OCM methods provide higher resolution and more specificity these are currently employed while doing biopsies and other procedures. Further studies are being conducted to know more about this imaging’s potentials. Optical techniques are of particular importance in the medical field, because these techniques promise to be safe and cheap and, in addition, offer a therapeutic potential.

4. Conclusion

A regular thyroid screening catches thyroid disorders at the earlier stages thus preventing worsening of thyroid disorders and associated problems. The advances in the imaging have significantly reduced morbidity and failure rates. Modalities like MRI, CT, PET and SPECT represent alternatives and options for equivocal imaging studies with diagnostic uncertainty in re-operative cases. In general, the thyroid imaging has evolved from early radionuclide thyroid scanning to the development of the advanced technique of SPECT, PET and fusion imaging. The advancement in cross-sectional techniques such as USG, CT and MRI has further improved the evaluation of thyroid pathologies.

5. References


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NUMERICAL ANALYSIS OF THE RELATIONSHIP BETWEEN CROSS-SECTIONAL AREA AND PRESSURE IN OVINE AORTA USING THE KELVIN VISCOELASTIC MODEL
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Abstract
The aortic artery and its tributaries have been among the most studied in circulatory mechanics. The goal of the numerical analysis presented here is to further that line of inquiry into the fluid biomechanics of the aorta by expanding upon the work described by Valdez-Jasso et al. Specifically within the scope of the thoracic descending aorta, we will attempt to determine a comprehensive relation between the intricate mechanisms of the pressure changes observed on the aortic wall and the cross-sectional area changes observed in the aortic artery itself. This analytical relationship, determined by using the Kelvin Viscoelastic Model, will be made more robust with numerical optimization methods using Matlab software. With such a relation, the current gap between contemporary conceptual physiological understanding and the reality of fluid phenomena in the aorta can be narrowed.

Keywords: Aorta, Matlab, Gauss-Newton Method, Elastin, Collagen, Smooth Muscle

1. Introduction

Accurate modeling of the fluid dynamics of arteries and vessels has, in general, seen two major approaches. The first is the analytical approach, by which considerations of fluid mechanics warrant the modification of terms in a set of balance equations until the consideration of new phenomena allow modifications to be made. The second is a numerical approach which attempts to describe experimental data in terms of generic fundamental functions and fit parameters of those functions in order to model the data.

Both approaches are applied here, with numerical optimization of pressure data from ovine, or sheep, aorta obtained by Valdez-Jasso et al. [1]. The variation in cross-sectional area can be described in relation to pressure by using the Kelvin Viscoelastic Model, which provides these necessary analytical relationships.

Beginning with pressure data, a model can be adequately fit using the Gauss-Newton Method. In developing the force balance equations in the Kelvin Viscoelastic Model, this pressure can be related to arterial cross-sectional area. By using the numerical differential equation solver ode45 in Matlab software and optimizing parameters to data using the Gauss-Newton Method, a reasonable model for cross-sectional area is determined.

The physiological reality of the aortic wall involves a multitude of vascular layers to consider in the viscoelastic model. As Valdez-Jasso et al. [1] states, there are three main tissue layers which give rise to the viscoelastic properties of the aortic artery, all of which can be seen in Figure 1. Elastin is the primary arbiter of elastic properties. Collagen comprises the basement membrane and provides dampening characteristics to prevent overextension, acting as a counterbalance to increases in wall pressure. Smooth muscle comprises a significant lining in the arterial wall and is the contributor of biomechanical movement in an artery [1].

Modeling of this movement can provide the necessary insight for medical professionals when considering diseases which result from fluid dynamic failure, such as an aortic aneurism. In an aortic aneurism, pressure from blood flow causes a weakened portion of the artery to give way, causing the artery to bulge and extending to approximately a diameter of 5 cm from the normal aortic diameter of 2 cm. Clots can then easily form in the aneurysm and travel to other smaller vessels, thus obstructing flow. This is why early detection using accurate mathematical models for prediction of vessel dynamics is imperative [2].
The thoracic aorta arteries were harvested by Valdez-Jasso et al. [1] from eleven male Merino sheep who were in good health with similar weight and size characteristics. As an anesthetic, 20 mg/kg of sodium thiopental was used. A ventilator was also utilized in order to maintain the composure of the diaphragm. A solid-state micro-transducer (Model P2.5, Konigsberg Instruments, Inc., Pasadena, CA, USA) was positioned in an incision in the arterial wall. In order to measure arterial diameter, two 5 MHz, 2 mm diameter transducers were sutured on two diametrically opposed sides of the arterial wall [1].

A 6 cm arterial segment, measured with calipers, was marked with suture stitches. The sheep were then sacrificed with an overdose of sodium thiopental and potassium chloride. The 6 cm segment was then surgically extracted and placed in a flow simulator, seen in Figure 3, with equilibration for 10 minutes under cyclic flow conditions. The artery was immersed and perfused in 37 °C oxygenated Tyrode solution of pH 7.4, attempting to simulate similar conditions in the artery’s native environment. A pumping rate of 110 beats/min and a mean pressure of 85 mm Hg was given. Flow was monitored using an ultrasonic flowmeter from Transonic Systems. Sampled at a frequency of 200 Hz, the pressure and diameter signals were recorded after removing the flow sensor [1].

All data used in this paper, along with initial conditions for optimization methods, were obtained from Dr. Daniela Valdez-Jasso of Valdez-Jasso et al. [1].

3. Methods

3.1. Derivation of an Equation for Radial Elongation of an Artery in Relation to Pressure by relation to the Kelvin Viscoelastic Model
well as a dashpot representing dampening phenomena with dampening coefficient $\eta_1$.

The force balance of the Kelvin Viscoelastic Model (Figure 4) is shown in Equation 1.

$$F = F_1^{(s)} + F_2^{(s)}$$  \hspace{1cm} (1)

where the forces $F_1^{(s)}$ and $F_2^{(s)}$ of the springs relating to the spring constants $k_1$ and $k_2$ and displacements $u_1^{(s)}$ and $u$, respectively, are

$$F_1^{(s)} = k_1 u_1^{(s)}$$  \hspace{1cm} (2)

$$F_2^{(s)} = k_2 u$$  \hspace{1cm} (3)

by Hooke’s Law. Therefore:

$$F = k_1 u_1^{(s)} + k_2 u$$  \hspace{1cm} (4)

By rearranging Equation 4 to solve for $u_1^{(s)}$, we obtain Equation 5.

$$u_1^{(s)} = \frac{F}{k_1} - \frac{k_2}{k_1} u$$  \hspace{1cm} (5)

Due to spring relating to $k_1$ and dashpot relating to $\eta_1$ lying on the same branch, the forces exerted on each component must be equal.

$$F_1^{(s)} = F_1^{(d)}$$  \hspace{1cm} (6)

With that in mind, and rearranging Equation 2, the following relation is true:

$$u_1^{(s)} = \frac{F_1^{(s)}}{k_1} - \frac{F_1^{(d)}}{k_1} = \frac{\eta_1}{k_1} \frac{du_1^{(d)}}{dt}$$  \hspace{1cm} (7)

Due to the fact that both branches are displaced the same amount when force $F$ is applied, the following balance equation is valid:

$$u = u_1^{(s)} + u_1^{(d)}$$  \hspace{1cm} (8)

Solving for $\frac{du}{dt}$, in order to receive a differential equation, albeit nonlinear, of $u$ in terms of all other parameters.

$$\frac{du}{dt} = \frac{\left(\frac{F - \frac{k_2 u}{\eta_1}}{k_1}\right) + \frac{\frac{\eta_1}{k_1}}{1 + \frac{k_2}{\eta_1}} \frac{dP}{dt}}{1 + \frac{k_2}{\eta_1}}$$  \hspace{1cm} (9)

Equation 9 then allows us to generalize the parameter for force, $F$, applied at two diametrically opposed points on the arterial wall to pressure, $P$, applied along the entire circumference of the arterial wall. Also, we can generalize the distention, $u$, of the arterial diameter along which $F$ is applied to radial arterial elongation, $\varepsilon$. These generalizations, when applied to Equation 9, give Equation 10.

$$\frac{d\varepsilon}{dt} = \frac{\left(\frac{F - \frac{k_2 u}{\eta_1}}{\eta_1}\right) + \frac{1}{k_1} \frac{dP}{dt}}{1 + \frac{k_2}{\eta_1}}$$  \hspace{1cm} (10)

Solving this differential equation thus allows the determination of $\varepsilon$ of an artery in relation to $P$.

### 3.2. Determination of a Mathematical Model for Pressure

In order to determine $P$ as a function of time, the ovine pressure data obtained from Valdez-Jasso et al. [1] must first be plotted and analyzed. Due to its oscillatory nature, the following model was applied:

$$P = a \sin(\omega t) + b \cos(\omega t) + c$$  \hspace{1cm} (11)

First, the amplitude values of each peak and the time distance between them were found, which gave the period. Then the inverse of the period was taken to find frequency. Then both sides of the resulting linear algebraic equation were multiplied by $A^T$ in order to create a pseudo-square matrix to find the coefficients of sinusoids “a” and “b” as well as amplitude shift “c”.

The final result can be seen in Equation 12.

$$\begin{bmatrix} a \\ b \\ c \end{bmatrix} = \left(A^T A\right)^{-1} A^T b$$  \hspace{1cm} (12)

### 3.3. Fitting of a Pressure Model Parameters Using the Gauss-Newton Method

The Gauss-Newton Algorithm, which attempts to close the gap between an analytical model and observed data by modifying values of the model’s parameters, was then implemented in by defining an initial vector of parameters $a$, $b$, $c$, and $\omega$. Two loops, one inside the other, were run. The outer loop dealt with the iterations of the Gauss-Newton method, updating the parameter vector, $\theta$, each time. The inner loop assembled the matrices of the Jacobian and Residual.
The general formula for the Jacobian matrix can be seen in Equation 13. Each new row has a different P value corresponding to the use of a different time point. Note that there are “n” total number of time points. The columns of the Jacobian matrix contain derivatives of P with respect to a, b, c, and ω, seen in Equation 13.

\[ J = \begin{bmatrix} \frac{\partial \theta_1}{\partial a} & \frac{\partial \theta_1}{\partial b} & \frac{\partial \theta_1}{\partial c} & \frac{\partial \theta_1}{\partial \omega} \\ \frac{\partial \theta_2}{\partial a} & \frac{\partial \theta_2}{\partial b} & \frac{\partial \theta_2}{\partial c} & \frac{\partial \theta_2}{\partial \omega} \\ \vdots & \vdots & \vdots & \vdots \\ \frac{\partial \theta_n}{\partial a} & \frac{\partial \theta_n}{\partial b} & \frac{\partial \theta_n}{\partial c} & \frac{\partial \theta_n}{\partial \omega} \end{bmatrix} \]  

(13)

The residual is the difference between the data and the model at any given time point. The general equation for the residual is shown by Equation 14.

\[ r = \begin{bmatrix} \text{PressureData}_1 - P_1 \\ \text{PressureData}_2 - P_2 \\ \vdots \\ \text{PressureData}_n - P_n \end{bmatrix} \]  

(14)

The resulting equation for the updating of θ values can be seen in Equation 15.

\[ \theta_{i+1} = \theta_i + (J^T J)^{-1} r \]  

(15)

Substituting the parameters within θ into Equation 11 gives a Pressure vector with optimized parameter values. The pressure data, model, and Gauss-Newton optimized model are shown versus time in Figure 5, which is found in the Results Section.

Cross-sectional area of the aorta was found using data of the diameter of ovine aorta, obtained using Valdez-Jasso et al. [1] through Equation 16.

\[ A = \pi \left( \frac{d}{2} \right)^2 \]  

(16)

Where “A” represents cross-sectional area and “d” represents diameter. Cross-sectional area was then plotted as a function of time, and can be seen in Figure 6 in the Results Section.

### 3.4. Optimization of Kelvin Viscoelastic Model Parameters

The initial values of parameters \( \eta_1 \), \( k_1 \), and \( k_2 \) obtained from Dr. Daniela Valdez-Jasso of Valdez-Jasso et al. [1] can be seen in Table 1.

![Table 1. Initial and optimized values of parameters used in the Kelvin Viscoelastic Model](image)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Initial Value</th>
<th>Optimized Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>( k_1 )</td>
<td>40 N/m</td>
<td>-0.1345 N/m</td>
</tr>
<tr>
<td>( k_2 )</td>
<td>60 N/m</td>
<td>327.1812 N/m</td>
</tr>
<tr>
<td>( \eta_1 )</td>
<td>20 ((\text{N} \cdot \text{sec}) / \text{m})</td>
<td>27.5135 ((\text{N} \cdot \text{sec}) / \text{m})</td>
</tr>
</tbody>
</table>

The Matlab function “fminsearch”, which serves the same purpose of optimizing parameters in a similar way as the Gauss-Newton Method. The difference is that it is more convenient for coding purposes to use fminsearch over the Gauss-Newton Method. The function fminsearch is an unconstrained optimization regime, meaning a time range does not need to be specified, in order to optimize Equation 10. The initial values were entered as arguments into the fminsearch function as well as a function which solved Equation 10 using the Matlab function “ode45”. The output of this function was the objective function as seen in Equation 17.

\[ \text{ObjFun} = \sum_{j=1}^{n} (\text{AreaData}_j - A_j)^2 \]  

(17)

Thus the function fminsearch minimizes the objective function which represents the difference between the cross-sectional area calculated using the aorta diameter data and the area calculated by solving Equation 10 and substituting it into Equation 18.

\[ A(t) = \varepsilon A_{\text{min}} + A_{\text{min}} \]  

(18)

where \( A_{\text{min}} \) is the smallest cross-sectional area.

The graph of the model of \( A(t) \) can be seen in Figure 6 in the results section.

The resulting parameter values in the vector \( \theta \) were then substituted again into Equation 10 when solving for \( \varepsilon \) using the Ode45 solver. The value of \( \varepsilon \) with optimized values, shown in Table 1, was then substituted into Equation 18 in order to solve for the cross-sectional area. The results are shown in Figure 6.

### 4. Results

A non-stiff method, meaning a numerically stable method, of numerical integration of differential
equations was used to determine $\varepsilon$ in the form of the Matlab function ode45.

Optimized values of Kelvin Viscoelastic model parameters are shown in Table 1.

![Figure 5](image)

**Figure 5.** Ovine Pressure data (blue) fit using a sinusoidal model (red) whose parameters were optimized using the Gauss-Newton Method (green).

![Figure 6](image)

**Figure 6.** Loading and unloading cycles of the vessel seen in terms of the relationship between the cross-sectional areas of the thoracic descending aortic artery. Both the graphs of the cross-sectional area vs. pressure based on experimentally collected diameter and pressure data (blue) and the model with fminsearch optimized parameters, shown in Table 1.

5. Discussion

In considering the extent to which the Kelvin Viscoelastic model represents the data, it can be seen that the Gauss-Newton Optimization regime did not provide an adequate fit with pressure residuals as large as 100 mm$^2$ in Figure 5. This is most likely due to the sensitivity to the model of the initial values.

Equally, in Figure 6, the loading of pressure onto the arteries, represented by the upper portion of the elliptical curve is significantly larger than that represented by the model. This gives a residual of nearly 50 mm$^2$. This large inconsistency can be explained by the stark differences between the initial values by Dr. Valdez-Jasso in Valdez-Jasso et al. [1] and the optimized parameter values. This indicates an unsatisfactory determination of initial values which can be verified by observing the radical difference between initial conditions seen in Table 1 and the resulting optimized conditions used for the model in Table 1.

However, the model of the area, seen in Figure 6, is an exceptional fit for the data. This fact indicates that the discrepancy in the relation between the data and modeled area and pressure relations in Figure 6 arises from an inaccurate pressure modeling, justified by the inadequate pressure fit in Figure 5.

Throughout this analysis, only the surrounding aortic wall and its properties have been considered. The great obstacle which prevents the creation of a truly comprehensive model, is the variable nature of the fluid itself: blood. Not taking into account the energy or mass transfer considerations limits the extent to which this model can truly bring physiological theory and biomechanical reality. Thus more sophisticated and comprehensive analytical models must be studied in order to better account for significant physiological phenomena.

Another significant consideration would be the need to adequately relate the force term to a pressure term and distension term to the elongation term. The format in which the terms are shown here, being simply substituted, without considering the application of the elongation of the artery force across the entire circumference of the artery, must be addressed. In its current state, the system only considers the application of force and arterial distension at two diametrically opposed points.

A solution for this would be to consider a virtually infinite set of Kelvin Viscoelastic Models, applying varying amounts of force at all points along the artery at a given time. This equally allows for the possibility of applying this model of a given circumference along the entire length of the artery in order to observe the dynamic change. Only then can a truly comprehensive model be created which takes into account the
multitude of phenomena along the entire length of an artery.

6. References


Superiority of Proton CT as an Alternative to X-ray CT for use in Proton Therapy Treatment Planning

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Abstract

Proton computed tomography (pCT) is an in-development imaging technique that offers potential benefits to external beam therapy treatment planning. Like X-ray CT (xCT), pCT utilizes iterative algorithms to facilitate image reconstruction based on energy attenuation. However, pCT functions by sending ~200MeV proton beams through the patient as opposed to x-rays, forming an image based on position, and residual energy of exiting protons. While research has shown better contrast resolution and lower radiation dosage in pCT when compared to standard xCT, multiple coulomb scattering (MCS) of protons in the tissue leads to a steep reduction in spatial resolution. This paper reviews the essential physics, technology and techniques underlying pCT imaging, analyzing its feasibility as an alternative to the current standards of xCT in proton therapy planning.

Keywords: Proton CT, Computed Tomography, Medical Imaging, Proton Therapy, Multiple Coulomb Scattering

1. Introduction

With the rapid advancement of cancer therapy in today’s medicine, demand for the refinement of associated instrumentation and technology is at an all-time high [2]. One of the cutting-edge techniques, proton therapy, utilizes precisely tuned proton beams in order to irradiate tumors while minimizing damage to surrounding tissues. Calibration of radiation dosage during this procedure is essential and relies heavily on imaging techniques to determine the stopping power (SP) through the patient. Currently, SP maps are assembled from 3D images acquired through X-ray computed tomography (xCT) [1]. However, tissue interactions differ significantly between X-rays and protons (Figure 1), requiring transformation using a calibration curve [5]. Measurements consistently return 3-4% error in electron density calculation due to this translation [3]. This source of error can be ameliorated by directly measuring energy attenuation using proton computed tomography (pCT).

pCT was first proposed by Nobel laureate Allan Cormack, one of the pioneers of xCT, in 1976. Efforts to study the potential of pCT continued into the 1980’s but poor proton beam quality and slow data acquisition time halted the interest of the imaging community. Combined with the increasing utilization of proton therapy in cancer treatment, advancements in particle physics, instrumentation and computing in the last decade have brought a resurgence of research on the subject [2].

pCT measures and records energy attenuation of beams projected through the patient over 360 degrees. Stored data is then formed into a matrix and an image is reconstructed using filtered back projections or other iterative algorithms [6]. Though pCT corrects for errors in electron density measurements, image spatial resolution is deteriorated by multiple coulomb scattering (MCS) of charged particles passing through matter. Also, despite advancements in detection and computing technology, data-taking rate is still too slow for use in a clinical setting [6]. The following sections review
the intricacies of pCT imaging and examine its efficacy as an alternative to the standards of xCT treatment planning in proton therapy.

2. Proton Therapy

Proton therapy is a type of external beam radiation therapy (EBRT) that is used in the treatment of a wide variety of cancers [1]. The most common form of EBRT uses a beam of photons that easily pass through biological tissues to damage cancerous cells. Although the system is adjusted to deliver the lowest effective dose, photon beams do not discriminate between tissue types and damage all healthy tissues surrounding the tumor [8].

Unlike photons, protons are particles that have a mass of roughly 1800 times that of an electron [8]. Due to their size, protons passing through a material are slowed and can be eventually stopped inside matter. After a particle has stopped, it has the opportunity to interact with surrounding cells, causing ionization of molecules and damage to DNA. This property offers the potential to calibrate beam energies relative to the SP of the cancerous area, sparing healthy tissues located on the distal side of the tumor [8].

The energy deposit of protons is characterized by an entrance plateau. At the end of this curve, there is a point at which a majority of the particle’s energy is attenuated over a short distance referred to as the Bragg peak [2]. Knowledge of the Bragg peak is essential to proton therapy because it allows physicians to ensure that particles are stopped within the desired area. As modeled in Figure 2, modified beams begin at low energies that gradually increase to cover the entirety of the tumor [8].

Presently, xCT uses attenuation of photons in order to estimate electron density of tumors. Unfortunately, since there is no unique relationship between the physical interaction processes of protons and photons data must be transformed using a calibration curve, posing a major source of potential error [2]. xCT also frequently provides poor contrast between cancerous tumors and surrounding healthy tissue, making radiographs virtually useless in proton therapy. Development of a clinical CT system that uses protons instead of X-rays to determine SP is the next step in advancing proton therapy.

3. Physical Principles of pCT

Proton CT measures both the position and residual energy of protons exiting an object. The overall change in energy, \( dE \), over the path length, \( s \), can be derived using the Bethe-Bloch formula [6]:

\[
\frac{dE}{ds} = \frac{N_{e}Z^{2}e^4}{4m_{e}c^2\beta^2} \left( \ln \left( \frac{2m_{e}c^2}{I(1-\beta^2)} \right) - \beta^2 \right) \tag{1}
\]

This equation can be grouped into two functions: \( n_e(x,y,z) \) is the electron density of the material, which determines the relative SP, and \( f[I,\beta(E)] \) depends on the ionization potential of the material, \( I \), and incident proton velocity, \( \beta \) [6].

\[
\frac{dE}{ds} = n_e(x,y,z) f[I,\beta(E)] \tag{2}
\]

Using separation of variables:

\[
\int_{E_{in}}^{E_{out}} \frac{dE}{f[I,\beta(E)]} = \int n_e(x,y,z) ds \tag{3}
\]

\( E_{in} \) is a constant, determined by the energy of the incident proton beam. Proton beam energies used in therapy typically range from 70-250 MeV, depending on the size, type and location of the tumor [1-7]. Eq. 3 can be approximated by the discrete sum of relative SP times traversing the path of the particle [6].

While superior to xCT in SP measurements, steep reductions in spatial resolution have been attributed to MCS [1]. In fact, 200 MeV protons passing through relatively thick objects (20cm) are subject to MCS angles of up to 40mrad, corresponding to a displacement of \( \sim 3 \)mm [7]. Projected scatter angle is approximated using proton velocity and momentum,
β and p, in relation to the thickness of the material in units of radiation length, x/X₀ [3]:

\[ \theta_{\text{mcs}} = \frac{13.6\text{MeV}}{p \beta \sqrt{x/X₀}} [1 + 0.038 \ln \frac{x}{X₀}] \quad (4) \]

X₀ is determined as the inverse of the sum of the fractions by weight of each material traversed, wᵢ, per unit material radiation length, Xᵢ [3]:

\[ \frac{1}{X₀} = \sum \frac{w_i}{X_i} \quad (5) \]

Table 1 shows the potential of these equations in MCS angle approximation when compared to actual values using a phantom hand model in Plautz et al. Angles were calculated to within ~±1 mrad of observed values [3].

Table 1. Expected vs. observed MCS angles of 5 regions of interest in a phantom hand model [3].

<table>
<thead>
<tr>
<th>Region</th>
<th>Expected (mrad)</th>
<th>Observed (mrad)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>17</td>
<td>17.8 ± 0.9</td>
</tr>
<tr>
<td>2</td>
<td>15</td>
<td>14.1 ± 0.9</td>
</tr>
<tr>
<td>3</td>
<td>11</td>
<td>12.3 ± 0.7</td>
</tr>
<tr>
<td>4</td>
<td>10</td>
<td>10.3 ± 1.3</td>
</tr>
<tr>
<td>5</td>
<td>5</td>
<td>5.2 ± 0.4</td>
</tr>
</tbody>
</table>

4. Apparatus

The pCT apparatus is comprised of a beam generator, a tracking system and a calorimeter coupled with a silicon photomultiplier, shown in detail in Figure 3 [7]. Protons are passed through tracker boards equipped with sensors that record the entrance point of each single event. Downstream, another pair of tracker boards and sensors records the position of the exiting particle. This data is interpreted using Monte Carlo algorithms to compute a most likely path (MLP) trajectory through the object [7]. Protons then continue into a calorimeter composed of scintillating crystals located behind the downstream tracker. Particles are ultimately stopped within the crystals and residual energy is recorded.

4.1 Trackers

The detectors consist of 400 µm thick silicon disc sensors implanted with coordinate strips. Four sensors are cut into squares and mounted in a slightly overlapping square pattern onto tracker boards [2]. Each tracker plane consists of two identical tracker boards mounted back-to-back and rotated 90 degrees so that the impact point can be pinpointed on the x,y plane. Sensors from each plane are wired to application specific integrated circuits (ASIC) and transmitted on low-voltage differential signal (LVDS) lines [4]. With the current setup, error contributed by MCS on MLP has been reduced to below .1 mm (Figure 4) [1].

Figure 3. Proton CT apparatus: (a) crystal calorimeter (b) front-end tracker board (c) silicon sensor (d) digital tracker board (f) phantom object (g) beam generator (p1-p4) identical tracker planes

Figure 4. MLP error contributions using 200 MeV proton energy and 20 cm phantom [1].

The silicon sensors used in the apparatus were originally designed in the development of the Gamma Ray Large Area Space Telescope (GLAST). Therefore, specifications for the pitch resolution (228µm), front-end electronics and readout controllers were already optimized for use in data collection [2]. Digital data from the circuits is readout by field programmable gate arrays (FPGA) to be sent to an event builder and processed by a host PC [4].
4.2 Calorimeter

The pCT calorimeter is comprised of rectangular scintillating crystals, stacked and adhered together in a matrix. Each crystal has a 3cm x 3cm square cross-section and a depth greater than 10cm to ensure no particle is able to pass through undetected [1]. Chemical composition of the calorimeter crystals is chosen based on its emission wavelength maximum to best match the sensitivity spectrum of the photodiode. Both YAG:Ce (Yttrium Aluminum Garnet activated by Cerium) and CsI(Tl) (Thallium activated Cesium iodide) have emission wavelength maximums of 550nm and fast emission decay constants, making them ideal for the silicon photodiodes and a high flux environment [1,2]. Crystals are fabricated with rough surfaces on every side except for where it is coupled with the photodiode. Although cutting a clean edge on this surface degrades light output of the crystal, it results in a more uniform response [2]. Immediately following detection by photodiodes, a preamplifier and pulse shaper prepare signals to be sent to an analog to digital converter (ADC) for data collection [4].

4.3 Data Acquisition

The data acquisition process begins with the digitization of position and energy data. An event builder is interfaced directly with the calorimeter and the FPGAs of the tracking system where it is organized to be processed by the host computer. A block diagram of the data flow is referenced in Figure 5 [4]. While data collection for residual energy is straightforward, position data must be further processed using Monte Carlo algorithms for MLP reconstruction [7]. Monte Carlo programs continuously generate randomized numerical experiments based on mathematical expressions. While proven to be very effective in simulation of physical events, iterations from the order of thousands or even millions can be necessary to return desired precision. Reconstruction of MLP data can take up to 12 hours due the sheer size of simulated data required for each event [7]. In order to be applicable for clinical use, this time needs to become a matter of minutes through reduction of data size or greater processing power [2].

5. Conclusion

Through the direct measurement of residual proton energy, pCT imaging offers superior electron density estimation while also reducing radiation exposure during treatment planning. While MCS initially caused a major reduction in spatial resolution, MLP particle trajectory approximation using Monte Carlo methods has proven to reduce error sufficiently to compare with the quality of xCT. Although data acquisition time is still too slow for use in a clinical setting, its potential to reduce damage to surrounding healthy tissues during proton therapy should drive future research. Studies are currently being done to reduce data size and ultimately allow for faster data acquisition using presently available processing power. Use of plastic scintillators in both the calorimeter and tracking planes may also have the potential to reduce the imaging time to as low as ten minutes [2]. As pCT research progresses, further testing to determine reconstruction accuracy and both spatial and density resolution limitations over a larger field of view is necessary [1].

6. References


MODELING THE EFFECTS OF TEMPERATURE CHANGES ON CARDIAC PURKINJE FIBERS
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Abstract
Purkinje fibers (PFs) rapidly conduct electrical impulses in the cardiac conduction system to initiate the normal excitations of the ventricles. Abnormalities in the PF system caused by temperature changes may result in abnormal excitation of the heart, which can lead to ventricular bradycardia, tachycardia, or fibrillation. The Noble PF (NPF) model is utilized to model the effects of temperature changes on cardiac PFs. As temperature is decreased below body temperature, the number of action potentials (APs) and firing frequency decrease. Conversely, as the temperature is increased, the previous properties increase and the waveforms become distorted. Although the NPF model produces the long plateau duration characteristic of cardiac PFs, the model limits the sodium channel to both the upstroke and plateau phase of the AP. Since the PF system is critical in both normal ventricular excitation and fatal ventricular arrhythmias, accurately modeling PF behavior is essential for future cardiac ventricular models as well as engineering ventricular grafts.

Keywords: Neural Engineering, Purkinje Fibers, Noble Model, Hodgkin-Huxley Model

1. Introduction
The cardiac conduction system (CCS) is a specialized electrical system that regulates the coordinated contraction of the heart by propagating electrical impulses through a network of specialized myocardial cells [1, 2]. The CCS of the adult mammalian heart comprises the sino-atrial (SA) node, the internodal tracts, the atrio-ventricular (AV) node, the His bundle, its right and left branches, and the network of Purkinje fibers (PFs) as shown in Figure 1 [1, 2, 3]. The SA node spontaneously generates electrical pulses within the heart and thus is often described as the principal pacemaker of the heart. The electrical pulses are dispensed as waves of electrical excitation over the atria, through the AV node into the ventricles, to the His bundle, its right and left branches, and into the PFs – the terminal part of the CCS. The PFs are electrically connected to the ventricular muscle, and their main function is to distribute the depolarization signal to the myocardium in order to facilitate ventricular excitation and contraction.

The previously described pattern of excitation within the CCS corresponds to the normal sequence of cardiac activation. Abnormalities in the excitation pattern may lead to potentially fatal cardiac arrhythmias and can occur in any element of the conduction pathway [2]. The PF system is considered to be a critical component in the development and/or maintenance of cardiac arrhythmias such as ventricular bradycardia, tachycardia, and fibrillation [2, 4]. Since the PF system is critical in both normal ventricular excitation and fatal ventricular arrhythmias, modeling PF behavior is essential for future cardiac ventricular models.

Herein, the Dennis Noble PF (NPF) model will be utilized to simulate and characterize the behavior of PFs [5]. Initially, the NPF model will be compared to the classic Hodgkin-Huxley (HH) model by applying various input stimulus currents to each model. Next, the PFs will be subjected to various human physiological temperatures. Lastly, the PFs will receive various input stimulus currents at a constant temperature in order to observe the effects on action potential (AP) firing frequency.
2. Methods

The PF model under investigation is the NPF model, the first cardiac electrophysiological model developed for PFs. The NPF model was based on the HH model of the AP in the squid giant axon, and modified to reproduce the long plateau duration of cardiac PF APs shown in Figure 1.

Briefly, the HH model utilizes the parallel conductance model to describe the major ionic conductances in the squid giant axon as shown in Figure 2A [6]. The model proposed that the nonlinear voltage-gated sodium (Na+) and potassium (K+) conductances were controlled by gating particles — specifically the m-gate and h-gate for Na+, and the n-gate for K+. When combined with the equations of cable theory, the HH model could accurately reproduce the shape and size of the AP, impedance changes, conduction velocity, and the ionic exchanges of the squid giant axon.

Noble modified the HH model to account for the natural excitable membrane behavior of PFs as shown in Figure 2B [5]. As opposed to the squid giant axon, depolarization decreases the K+ permeability of the membrane and thus lowers the membrane conductance to K+. During large depolarizations, part of the decrease in K+ permeability appears to be only transient, and the K+ current slowly increases during the passage of the depolarizing current. Thus, the NPF model assumes that the K+ current flows through two types of channels as seen in Figure 2B. In one of the K+ channels, the K+ conductance gK1 is assumed to be an instantaneous function of the membrane potential and falls when the membrane is depolarized. In the second type of K+ channel, the K+ conductance gK2 slowly rises when the membrane is depolarized. As seen in Figure 2B, the two types of K+ channels are represented by two parallel rectifiers in series with the K+ Nernst potential. The K+ conductance gK1 is represented by a rectifier that easily passes inward current, while gK2 is represented by a rectifier which easily passes outward current. Furthermore, the NPF model incorporates a chloride (Cl-) current instead of a leak current and a background Na+, neither present in the HH model.

2.1 Calculations

The NPF model conforms to the convention usually adopted in experimental work with intracellular electrodes, where the potential Em is the potential of the inside with respect to the outside. As a result, positive currents are therefore outward and not inward, as in the HH model.

The NPF model utilizes four state variables: membrane potential Vm, slow K+ activation gate n, Na+ activation gate m, and Na+ inactivation gate h. All analyses and computations were done using custom MATLAB scripts (MATLAB R2014a, MathWorks). The complete NPF model is listed below. (See ref. [6] for the complete HH model.)

\[
dV_m/dt = \left(I_0 - J_{ion}\right)/C_m
\]  

\[
J_{ion} = J_{Na} + J_{K} + J_{Cl}\cdot b + J_{Na}\cdot b
\]  

\[
J_{Na} = \frac{g_{Na}}{m^3 \cdot h} \left(V_m - E_{Na}\right)
\]  

\[
J_{K} = \left(g_{K1} + g_{K2}\right) \left(V_m - E_{K}\right)
\]  

\[
J_{Cl}\cdot b = g_{Cl}\cdot b \left(V_m - E_{Cl}\right)
\]
\[ J_{Na^+} = g_{Na^+} (V_m - E_{Na^+}) \]  

\[ g_{K^+} = \beta_{K^+} \exp \left[ -(V_m + 90)/50 \right] + 0.15 \exp \left[ (V_m + 90)/60 \right] \]  

\[ g_{K^{+}_{CI^2}} = \alpha_{K^{+}_{CI^2}} \cdot n^4 \]  

\[ \alpha_m = \{0.1(V_m + 48)\}/[1 - \exp[-(V_m + 48)/15]] \]  

\[ \beta_m = \{0.12(V_m + 8)\}/[\exp[(V_m + 8)/5] - 1] \]  

\[ \alpha_h = 0.17 \exp[-(V_m + 90)/20] \]  

\[ \beta_h = 1/[1 + \exp[-(V_m + 42)/10]] \]  

\[ \alpha_n = \{0.0001(V_m + 48)\}/[1 - \exp[-(V_m + 50)/10]] \]  

\[ \beta_n = 0.002 \exp[-(V_m + 90)/80] \]  

\[ \frac{dn}{dt} = [\alpha_n (1 - n) - \beta_n n] \cdot \phi(T_C) \]  

\[ \frac{dh}{dt} = [\alpha_h (1 - h) - \beta_h h] \cdot \phi(T_C) \]  

\[ \frac{dm}{dt} = [\alpha_m (1 - m) - \beta_m m] \cdot \phi(T_C) \]  

\[ \phi(T_C) = 3^\alpha(T_C - 37)/10 \]  

Equation 1 represents the characteristic equation for the NPF circuit shown in Figure 2B. The ion current \( J_{ion} \) (µA/cm²) in Equation 2 is the sum of each individual ion channel current in the NPF model. Equations 3 – 6 describe the fast Na⁺ current, the K⁺ current, the background Cl⁻ current, and the background Na⁺ current (not shown in Figure 2B), respectfully. Equation 7 and Equation 8 characterize the pacemaker K⁺ conductance \( g_{K^+} \) and outward rectifying K⁺ conductance \( g_{K^{+}_{CI^2}} \), respectfully. Equations 9 – 14 define the opening (\( \alpha \)) and closing (\( \beta \)) rates (msec⁻¹) for gates \( m, h, \) and \( n \), respectfully. Equations 15 – 17 detail the time dependence for each respective gate. To model the electrical behavior of PFs when subjected to various human physiological temperatures, the gate rates were scaled by a scaling factor \( \phi(T_C) \) defined in Equation 18 [7]. Table 1 presents the simulation parameters utilized to model the electrical behavior of the PFs. The same values were utilized where applicable in the HH model.

<table>
<thead>
<tr>
<th><strong>Table 1. Simulation parameters for the NPF model.</strong></th>
<th><strong>Unit</strong></th>
<th><strong>Value</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Membrane Potential, ( V_m ), mV</td>
<td>mV</td>
<td>-81.6</td>
</tr>
<tr>
<td>Input Current, ( I_0 ), µA</td>
<td>µA</td>
<td>0.4**</td>
</tr>
<tr>
<td>Na⁺ Nernst Potential, ( E_{Na^+} ), mV</td>
<td>mV</td>
<td>40</td>
</tr>
<tr>
<td>K⁺ Nernst Potential, ( E_{K^+} ), mV</td>
<td>mV</td>
<td>-100</td>
</tr>
<tr>
<td>Cl⁻ Nernst Potential, ( E_{Cl} ), mV</td>
<td>mV</td>
<td>-60</td>
</tr>
<tr>
<td>Na⁺ Conductance, ( g_{Na^+} ), mS</td>
<td>mS</td>
<td>400</td>
</tr>
<tr>
<td>K⁺ Conductance, ( g_{K^+} ), mS</td>
<td>mS</td>
<td>1.2</td>
</tr>
<tr>
<td>Background Cl⁻ Conductance, ( g_{Cl} ), mS</td>
<td>mS</td>
<td>0.075</td>
</tr>
<tr>
<td>Background Na⁺ Conductance, ( g_{Na^+} ), mS</td>
<td>mS</td>
<td>0.14</td>
</tr>
<tr>
<td>Membrane Capacitance, ( C_m ), µF/cm²</td>
<td>µF/cm²</td>
<td>12</td>
</tr>
<tr>
<td>Na⁺ activation gate, ( m_0 ), msec⁻¹</td>
<td>msec⁻¹</td>
<td>0.04338</td>
</tr>
<tr>
<td>Na⁺ inactivation gate, ( h_0 ), msec⁻¹</td>
<td>msec⁻¹</td>
<td>0.85218</td>
</tr>
<tr>
<td>K⁺ activation gate, ( n_0 ), msec⁻¹</td>
<td>msec⁻¹</td>
<td>0.60888</td>
</tr>
<tr>
<td>Temperature, ( T_C ), °C</td>
<td>°C</td>
<td>30, 34, 37, 40, 44</td>
</tr>
</tbody>
</table>

*The following input currents were utilized to compare the NPF model to the HH model and to obtain the action potential firing frequency for each temperature.

**The following input current was utilized and remained constant when subjecting the PFs to various temperatures. Variables with the number zero indicate initial values at time equal to zero.

3. Results

3.1 Comparing the Noble Purkinje Model to the Hodgkin-Huxley Model

Both the NPF model and HH model spontaneously elicit an AP when no input stimulus current is applied as shown in Figure 3. Only the NPF model produces characteristic PF AP waveforms. Conversely, the HH model produces a single spike and fails to refract because the Na⁺ inactivation \( h \)-gate immediately reaches a probability of zero, which indicates that the inactivation gate is closed. When the input stimulus current is increased to 5 µA, the NPF waveform becomes distorted and produces a single PF AP due to the decreased \( h \)-gate probability. The NPF gate probabilities approach the HH gate probabilities for each respective gate as the input stimulus current is increased. As a result, the NPF waveform progressively resembles the HH waveform.
3.2 Analyzing the Effects of Temperature on Purkinje Fibers

Altering temperature has a considerable impact on the PF waveform as seen in Figure 4. As temperature is decreased below body temperature (BT, 37°C), the number of APs decrease in a 2 sec time interval, peak amplitudes increase, and gate probabilities lengthen. Furthermore, transient oscillations in AP firing frequency occur as input stimulus current is increased. Conversely, as temperature is increased above BT, the number of APs increase in a 2 sec time interval, peak amplitudes decrease, and gate probabilities shorten. In addition, the APs become distorted and no sharp peaks occur. Furthermore, the transient oscillatory nature seen in waveforms below BT diminish and a linear-like relationship forms.

4. Discussion

The NPF model utilizes three ionic components similar to the HH model: a nonlinear Na⁺ term, a nonlinear K⁺ term that undergoes rectification, and a nonspecific linear anion term. Thus the resemblance of the NPF model to the HH model at high input stimulating currents is no coincidence.

Ion currents change at different temperatures and produce large differences in the APs. Temperature can accelerate or decelerate gate kinetics by modifying the rate constants governing the channel conductances. When the temperature of the PFs are not at BT, abnormal waveforms of varying AP firing frequencies are produced that modify the QRS complex shown in Figure 1 to produce cardiac arrhythmias. Although temperature can directly affect the gate kinetics, temperature also modifies the current as seen in the Goldman-Hodgkin-Katz (GHK) current equation.
Implementing the GHK current equation may produce more accurate results.

Although the NPF model reproduces the long plateau duration of cardiac PFs, the model functions because the voltage range of the \( \text{Na}^+ \) current was greatly extended by reducing the voltage dependence of the \( \text{Na}^+ \) activation process [2, 8]. As a result, \( \text{Na}^+ \) is responsible for both the upstroke and plateau phase of the PF AP waveform, as seen in the gate probability graphs. Thus, the \( \text{Na}^+ \) current performs the functions of both the \( \text{Na}^+ \) and calcium \( \text{Ca}^{2+} \) channels, and the PF AP is maintained by a balance between inward \( \text{Na}^+ \) and outward \( \text{K}^+ \) currents. Therefore, the original NPF model does not accurately model the cellular physiology of the heart because of the lack of \( \text{Ca}^{2+} \) channels. Nevertheless, the NPF model continues to serve as the foundation for advanced mathematical models of cardiac cells [8, 9]. Furthermore, accurately modeling PF behavior at various physiological relevant temperatures will be essential for future cardiac ventricular models as well as engineered ventricular grafts for \textit{in vivo} surgical replacements.

5. Acknowledgement

The author would like to thank James Patton, Ph.D., and Yazan Abdel Majeed, B.S., for their contributions throughout this research.

6. References


![Figure 4. The effects of temperature on Purkinje fibers (PFs). A. Purkinje fibers (PF) action potential (AP) waveforms at select physiological temperatures. As the temperature is decreased below body temperature (BT, 37 °C), the number of APs decrease in the specified time interval. Conversely, the opposite result occurs as temperature is increased above BT, and the waveforms become distorted. B. PF gate probabilities at select physiological temperatures. As the temperature is decreased below BT, the gate probabilities lengthen. The opposite result occurs as temperature is increased above BT. C. The effects of input stimulus current on PF AP firing frequency for each temperature. At temperatures below BT, increasing the input stimulus current creates a transient oscillation in AP firing frequency. At temperatures above BT, the transient oscillatory nature diminishes and a linear-like relationship forms. Discontinuities occur after 12 \( \mu \text{A} \) due to the NPF model behaving like the HH model, where the AP no longer refracts (see Figure 3). The input stimulus current was made constant at 0.04 \( \mu \text{A} \) for simulations in panels A and B, but was modified for simulations in panel C.](image)


**BIOPSYCHOSOCIAL VARIABLES AND THE EFFECTS ON IMMUNE SYSTEM: AN ANALYSIS OF THE RELATIONSHIP BETWEEN NEGATIVE MOOD STATES AND PRO-INFLAMMATORY CYTOKINES**

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**Abstract**

Biological and psychological indicators of stress are thought to influence overall immune function. For years, scientists have attempted to analyze the responses of the brain to various stressors. What we call “sickness” is essentially the body’s adaptation to certain biological and psychological attacks. Psychoneuroimmunology, a developing field of study that deals with brain-behavior-immune relationships, has been gaining more awareness, but has not been well documented in the context of the African American population. Evidence suggests that negative mood states such as anxiety and depression, have adverse effects on immunity and trigger off disease. However, little research has been done that discusses the strength of the relationship and how negative mood states in African Americans affect immune function. We know that if a person’s immune system is compromised, health overall is negatively affected as well. This research seeks to determine the extent to which personality traits – neuroticism and extra-introversion – exacerbate or buffer biological responses to depression and anxiety. To answer this question we observed the levels of pro-inflammatory cytokines (interleukin-1) circulating in the blood. Our analysis was from a subset of data from Howard University Hospital’s General Clinical Research Center (GCRC), Washington DC.

**Keywords:** Biopsychosocial Variables, Interleukin-1, Multiple Regression Analysis, Brain-Behavior-Immune Relationships

**1. Introduction**

The relationship between biopsychosocial variables is complex and many sequelae of stress factors are often not understood. In our study we selected specific biopsychosocial variables and tested the relationships among them. We hypothesized that there would be a significant positive relationship between negative mood states and immune response, and that personality traits would serve as moderator variables to this relationship. The independent variables we examined for our research were depression, anxiety, neuroticism, and extra-introversion. Our dependent variable was interleukin-1.

In our research we asked the question, “To what extent do personality traits – neuroticism and extra-introversion – exacerbate or buffer biological responses to depression and anxiety?” To answer this question, we observed the levels of proinflammatory cytokines (interleukin-1) circulating in the bloodstream of the participants in the study. Proinflammatory cytokines are molecules released by the immune system that serve the function of intercellular communication. Signals are sent to the brain to respond to biological or psychological attacks and regulate normal body responses. Interleukin-1 (IL-1) is the cytokine being measured in this study. Research shows that there is a link between major depressive disorder (MDD) and proinflammatory cytokines via a pathophysiological mechanism. Some studies show that patients who have MDD have higher levels of interleukin-1β. When there is an infection, the immune system is alerted and sends out different kinds of cells that have their specific functions in responding to the infection. This is also the case when there is physical injury to the body. The cells circulate through the blood and send messages to the brain to respond to the injury or infection. Since we observe that chronic stress can also lead to “sickness”, we seek to find out whether the body uses similar mechanisms to respond to psychological stress through the immune system. Research suggests that there are specific pathways that are used for responding to injury or infection. It has been argued that, “physical and psychological stressors activate the same bidirectional immune-brain circuits”.

There are specific models that explain these biological mechanisms, however this is beyond the scope of this particular research. We are interested in finding out how these interactions take place when
we are dealing with psychological stressors, which are not as tangible.

2. Materials and Methods

Our independent variables – depression and anxiety – are the psychological states being measured. The moderator variables – neuroticism and extra-introversion – are the personality traits that we expect to alter the strength of the relationship seen in the variables. According to the NEO Personality Inventory, the definition of the variables is as follows: neuroticism pertains to individuals prone to psychological stress; anxiety is the level of apprehension, fear or worry a person has; depression is the tendency to experience feelings of guilt, sadness and loneliness; extra-introversion is the intensity of energy a person directs outwards or inwards into the social world. We measured the effects of the independent variables on the inflammation as indicated by the levels of interleukin-1.

Our analysis focused on a sample of 150 relatively healthy African American adults in the Washington, D.C. Metropolitan Area, recruited from health fairs, using fliers, and by word-of-mouth. Data came from a larger study conducted in the National Minority Organ and Tissue Transplant Education Program (National MOTTEP), which examined the profiles of immune functioning in African Americans. MOTTEP is geared towards educating and creating awareness about organ and tissue transplantation in minority communities. With a preventative approach, MOTTEP creates programs to shed light on the behaviors and diseases that ultimately lead to organ transplantation. [6] We performed a secondary analysis of a subset of MOTTEP data collected at Howard University Hospital’s General Clinical Research Center (GCRC) in Washington, DC. This data consisted of paper-pencil assessments of the participants, with scoring levels for the different mood states and personality variables, including the NEO Personality Inventory-Revised (NEO-PI-R) and Beck Depression Inventory. The biological response variable was measured using blood samples from the participants. We used multiple regression analysis to examine the fit of a series of nested sets of predictors with the goals of: (1) testing our hypotheses, and (2) identifying the most efficient model for explaining variation in our dependent variable, IL-1. (Relevant SPSS statistical analysis software output is provided in tables 1 & 2.)

Following Baron and Kenny (1986), we examined the extent to which: (a) the independent variable (IV) (depression) and the hypothesized mediator (neuroticism) were significantly correlated; (b) the hypothesized mediator (neuroticism) and the dependent variable (DV) (IL-1) were significantly correlated; (c) the inclusion of the mediator (neuroticism) as an additional predictor in the regression of the DV (IL-1) on the IV (depression) resulted in a decrease in the significance of the correlation between the IV and DV.

We found that depression and neuroticism were significantly correlated, \( r(175) = 0.41, p<0.03 \); neuroticism and IL-1 were significantly correlated, \( r(172) = 0.25, p<0.002 \). Finally, we regressed IL-1 on depression and neuroticism simultaneously and found the inclusion of neuroticism as an additional predictor resulted in a decrease in the significance of the correlation between depression and IL-1 from \( p<0.05 \) to \( p>0.37 \).

3. Results

Table 1.

<table>
<thead>
<tr>
<th>Model</th>
<th>R</th>
<th>R Square</th>
<th>Adjusted R Square</th>
<th>Std. Error of the Estimate</th>
<th>P Square Change</th>
<th>F Change</th>
<th>df</th>
<th>Sig. F Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>.254</td>
<td>.065</td>
<td>.068</td>
<td>.509</td>
<td>2</td>
<td>1</td>
<td>0.38</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>.304</td>
<td>.092</td>
<td>.091</td>
<td>.263</td>
<td>2</td>
<td>1</td>
<td>0.12</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>.364</td>
<td>.132</td>
<td>.125</td>
<td>.205</td>
<td>2</td>
<td>1</td>
<td>0.06</td>
<td></td>
</tr>
</tbody>
</table>

As expected, depression was significantly positively related to IL-1 (\( p<0.03 \)) when the relationship between the negative mood states (anxiety and depression) and IL-1 were examined to test our prediction (refer to Model 1 in the first SPSS analysis table); however, anxiety and IL-1 were not significantly related (\( p>0.77 \)). We examined whether adding the personality traits improved our prediction of IL-1 (refer to Model 2). As expected, neuroticism was significantly positively related to IL-1 (\( p<0.002 \)); however, extra-introversion and IL-1 were not significantly related (\( p>0.85 \)), anxiety and IL-1 were not significantly related (\( p>0.56 \)), depression and IL-1 were no longer significantly related (\( p>0.24 \)).
further examined whether the personality traits moderated the relationship between the negative mood states and IL-1 (refer to Model 3). We found none of the predictors were significantly related to IL-1 once the interaction terms were included in the regression model (all p-values >0.22).

Table 2.

<table>
<thead>
<tr>
<th>Model</th>
<th>Unstandardized Coefficients</th>
<th>Standardized Coefficients</th>
<th>B</th>
<th>Std Error</th>
<th>Beta</th>
<th>t</th>
<th>Sig</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>(Constant)</td>
<td></td>
<td>1.51</td>
<td>.108</td>
<td>.108</td>
<td>13.844</td>
<td>.000</td>
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<tr>
<td></td>
<td>Total Depression (Bzk)</td>
<td></td>
<td>.239E-01</td>
<td>.004</td>
<td>.213</td>
<td>2.394</td>
<td>.024</td>
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<tr>
<td></td>
<td>Anxiety (State)</td>
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<td>.800E-04</td>
<td>.003</td>
<td>.021</td>
<td>2.044</td>
<td>.022</td>
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<tr>
<td>2</td>
<td>(Constant)</td>
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<td>1.144</td>
<td>.241</td>
<td>.241</td>
<td>4.732</td>
<td>.000</td>
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<td></td>
<td>Total Depression (Bzk)</td>
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<td>.003</td>
<td>.069</td>
<td>2.350</td>
<td>.020</td>
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<tr>
<td></td>
<td>Anxiety (State)</td>
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<td>.003</td>
<td>.059</td>
<td>2.195</td>
<td>.031</td>
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<tr>
<td></td>
<td>Total Neurotism (Neor Scale)</td>
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<td>.300</td>
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<td>.001</td>
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<td></td>
<td>Total Extra-Intervention (Neo Scale)</td>
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<td>.002</td>
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<td>.894</td>
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<td>1.104</td>
<td>1.104</td>
<td>1.355</td>
<td>.178</td>
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<td>.269</td>
<td>.788</td>
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<td>.007</td>
<td>.200</td>
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<td>.238</td>
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<td></td>
<td>Total Extra-Intervention (Neo Scale)</td>
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<td>.109E-03</td>
<td>.009</td>
<td>.195</td>
<td>.527</td>
<td>.599</td>
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<td></td>
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<td>.000</td>
<td>.020</td>
<td>1.383</td>
<td>.170</td>
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<tr>
<td></td>
<td>Depression x Neurotism Interaction</td>
<td></td>
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<td>.000</td>
<td>.270</td>
<td>.510</td>
<td>.611</td>
</tr>
<tr>
<td></td>
<td>Neurotism x Anxiety Interaction</td>
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<td>.000</td>
<td>.271</td>
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<td>.818</td>
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<td></td>
<td>Extra-Intervention x Anxiety Interaction</td>
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<td>.896E-06</td>
<td>.000</td>
<td>.266</td>
<td>.315</td>
<td>.238</td>
</tr>
</tbody>
</table>

*Dependent Variable: Log (IL-1)

4. Discussion

In conclusion, our hypotheses were only partially supported. In particular, as expected, a personality trait (neuroticism) was a significant predictor of a proinflammatory cytokine (IL-1) that plays an important role as the immune system responds to stressors. Interestingly, this personality trait was the most important predictor of IL-1, more important even than the negative mood states that have frequently been linked to immune function in recent studies, as well as in this study. It does appear as predicted, that psychological states do have an effect on proinflammatory cytokines hence the immune system. From studies we see that proinflammatory cytokines that the immune cells release communicate to the brain and adjust neural activity, ultimately producing the changes seen behaviorally, affectively, and cognitively in sickness. [3] Finally, we did not find support for our hypothesis that the personality traits under study would moderate the biological response (IL-1) to our negative mood states. Rather than exacerbating or buffering this biological response to depression and anxiety, neuroticism appears to function as an important mediator of the response. Thus, it does appear that depression is positively related to this immune response because of neuroticism. Future studies should examine this finding systematically.

5. Acknowledgments

Howard University
Amen Scholars Program
Mentors - Angela Cole, Ph.D., Joneis Thomas, Ph.D., Denee T. Mwendwa, Ph.D.

6. References


   <http://www.nationalmottep.org>


Mission Statement and Bylaws - Spring 2016

Mission
The mission of the journal is to develop the art of scientific writing among bioengineering students. Students may submit articles that describe original research or that review existing research (with proper credit listed in the references) that has been published elsewhere. Students may also submit papers that have been submitted for a grade in a UIC class. The journal also provides an opportunity for all bioengineering students to be involved as editors and reviewers. Thus, working on the publication of the journal will provide students with an overall appreciation of the processes involved in submitting, editing, and disseminating scientific findings. Additionally, through the publication of each issue, the journal serves to expose the authors, reviewers, and readers to current trends in the bioengineering field.

Scope
Submissions can range from original research articles and technical reviews to book or software reviews relevant to bioengineering. Letters to the editor are also welcome. Completed research projects are not necessary for publication. It is expected that some of the articles that appear in the journal will later be expanded into full-length studies and published elsewhere. Publication in the UBSJ does not preclude later publication of the results in a copyrighted technical journal.

Bylaws
1. Editorial Board
   The UBSJ shall elect one Chief Editor, one Editor-Elect, and one or more Associate Editors during the final week of classes. Editors shall be elected based on a vote of the current editorial board, reviewers, and authors. Editors must have at least one semester of experience participating in the journal, and must display qualities desired of an Editor such as active participation and timely completion of deadlines, and the Chief Editor must have held the position of Editor for at least one semester. When a new Chief Editor is chosen they shall receive control of the UBSJ Google Drive folder. The Editor-Elect shall continue in the position of the editor in the following semester. If the performance of the Editor-Elect is deemed unsatisfactory, including such factors as level of participation and interpersonal skills, the rest of the editorial board may choose a different editor to be Chief Editor the following semester.
   It is the responsibility of the Chief Editor to keep in regular contact with the Faculty Advisor and Department head about developments in the journal as well as update and maintain the Google Drive folder. Questions and concerns should be brought to the attention of the Faculty Advisor before anyone else. Finished journals and any funds raised should be sent to Jay Lin (jlin13@uic.edu).

2. Meetings
   The UBSJ shall have general body meetings, to be held throughout the semester. One meeting must be held within the first two weeks of the semester, and at least once monthly afterwards. Meetings should introduce the journal to interested students and update members on paper statuses. Meeting times are to be finalized during the third week of school between 1:00pm-6:00pm on a day when the highest possible amount of board members can attend.
3. **Articles**

Papers must follow the UBSJ article template, available on Blackboard and the Google Drive folder. Content may include original research, technical reviews, book reviews, or software reviews. Other subjects may be allowed on a case-by-case basis. In the event that a paper authored by more than one student is submitted, names shall be listed in alphabetical order and each student must be involved in the review process. Papers shall be limited to two authors. No member may be the author of more than one paper per publication.

4. **Membership**

Only bioengineering students may participate in the UBSJ. In the event that a student from another major submits a paper, it shall be accepted on a case-by-case basis, depending on the quality of the paper and the number of previously submitted papers. To become a member, either as a reviewer or an author, interested students may email any of the editors, or the UBSJ email account (bioejour@uic.edu).
TITLE OF THE ARTICLE

Author Name
e-mail

Abstract

The title should be 14pt, bold, Times New Roman all capitals. The author name must be in 12pt, Times New Roman, and email in 11pt Italics Times New Roman. The abstract should be displayed in a 10pt, italic, Times New Roman font, justified, single column, with an additional left and right indentation of half an inch from the margin. Limit abstract to 300 words.

Keywords: Template, UIC, Bioengineering, Student, Journal

1. Introduction

This document represents the format for submissions to the student journal. The two column format is followed for the body of the article. Text font should be 10pt Times New Roman, justified, single-spaced.

A single empty line should separate paragraphs, the end and beginning of different sections, and must be inserted above and below figures, tables, and equations.

2. Example of Numbered Heading

Each heading must be numbered and be in 12 point, bold, Times New Roman font, with the first letter of all words capitalized except for prepositions and conjunctions.

Figure 1. Figure captions are to be below the figure in 9pt Times New Roman, Justified

2.1 Example of Subheading and Table

Subheading must be in 11pt, bold, Times New Roman. Tables should be numbered in the order they appear.

Table 1. This table descriptor is 9pt Times New Roman, Justified

<table>
<thead>
<tr>
<th>Column 1</th>
<th>Column 2</th>
<th>Column 3</th>
<th>Column 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Row 1</td>
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<td>is</td>
<td>Times</td>
</tr>
<tr>
<td>Row 2</td>
<td>New</td>
<td>Roman</td>
<td>10pt</td>
</tr>
</tbody>
</table>

3. Equation

Equations should be centered on separate lines with a single space above and below. The equation number should be indicated in parentheses at the rightmost of the last line of the equation.

\[ E_{(a)} = m^a(s-h) + P_o + \Lambda(t)^s * \Sigma(s) \]  

4. Page Limit

Maintain a page limit of 4-5 pages for your entire submission.

List and number all references in 10-pt Times New Roman, single-spaced, at the end of your paper. When referenced in the text, enclose the citation number in square brackets, for example [1]. For multiple references separate using comma(s) [2, 6]. Where appropriate, include the name(s) of editors of referenced books. Arrange all references in alphabetical order of the ‘Last Name’ as demonstrated in the examples below.

5. References

(Use format from Annals of Biomedical Engineering)


