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Foreword

On behalf of the Department of Bioengineering, I am happy to present the second issue of the ninth volume of the UIC Bioengineering Student Journal. This journal continues to strive to provide both graduate and undergraduate students an opportunity to gain experience writing research articles for an academic publication. This is a great opportunity for students to take the knowledge and skills learned in their coursework and research and apply it to write a paper relevant to the field of bioengineering. Students who participate in this student-led journal go through a rigorous review process in which students receive multiple peer-reviews and go through several rounds of editing until receiving final approval from the editorial board. As a result, students can improve their technical writing skills as well as their intercommunication skills, which will benefit them in their future careers.

I would like to thank our Faculty Advisor, Dr. Magin for his continuous support in helping us organize and further develop the journal. Also, I would like to thank our 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 consistently put their best effort forward to contribute to the completion and success of both issues of this year’s journal.

Jaqueline Rojas Robles
Editor-In-Chief
Undergraduate Volume.

Senior Associate Editor
Graduate Volume
ADVANCED VISUALIZATION IMAGING TECHNIQUES AND THEIR APPLICATIONS IN MEDICAL IMAGING

Abhinav Subramaniam
asubra7@uic.edu

Abstract
The interdisciplinary relationship emerging between medical and engineering professionals has led to innovative technological advancements. In particular, the medical imaging field has been steadily growing with the emergence of advanced visualization methods, such as 3D printing and virtual reality. By taking two-dimensional images from traditional volumetric imaging techniques it becomes possible to construct a three-dimensional model. 3D printing and virtual reality allow physicians to have tangible and explorable landscapes of patient anatomy. By incorporating virtual reality techniques, many companies, for example 3D Systems, have been able to create training simulations that are geared towards better educating the future class of health care professionals. These advanced visualization techniques are becoming commonplace for pre-operative planning and for patient education.

Keywords: Medical Imaging, Advanced Visualization, 3D-Printing, Virtual Reality, Patient Education, Simulation Training

1. Introduction
With the creation of virtual reality (VR) and 3D printing came promise of advancements in engineering and entertainment. However, these technologies have also found uses in the improvement of traditional medical imaging practices. Physicians are adopting 3D printed models and VR landscapes to better understand patient specific data and reduce any spatial recognition barriers. Advanced Medical Visualization Imaging provides the healthcare community an opportunity to experience traditional imaging data in a new light.

By using medical imaging methods that contain volumetric data, such as Computed Tomography (CT) or Magnetic Resonance Imaging (MRI), one can create three-dimensional representations of the imaged area. MRI and CT scans provide radiologists with multiple cross-sectional images taken at various angles to better diagnose patients. By taking these two-dimensional images and constructing a three-dimensional model, physicians will be better able to spatially understand the extent of their patients’ situation.

Engineers must work directly with physicians in order to interpret two-dimensional imaging data and construct the model correctly. Cohesion between medical anatomy and engineering digital construction must be present. Various steps are necessary to construct a three-dimensional model from two-dimensional MRI or CT scans. The engineer must first read the Digital Imaging and Communications in Medicine (DICOM) files, segment the anatomy, create a surface mesh, and confer with physicians to better refine the model. Figure 1 accurately depicts the construction of a three-dimensional model from two-dimensional imaging scans; the ability to grasp the information spatially via the three-dimensional model compared to the two-dimensional scans is evident.

Figure 1. Construction of three-dimensional model from two-dimensional imaging scans. From [5], reprinted by permission from Springer Nature

From here physicians are able to print the model as well as view it in a virtual reality device. Having the ability to physically disassemble a three-dimensional model of patient specific anatomy has provided surgeons with an opportunity to plan an operation ahead of time and to better avoid complications [12].
Many large companies, such as General Electric and Microsoft, are branching into virtual reality to help better educate future physicians and patients [4, 6]. Having the ability to relate an MRI or CT scan in terms of an interactable three-dimensional model allows patients to better relate to their condition, and provides physicians a new method of understanding traditional imaging data.

The purpose of this review is to introduce emerging methods of analyzing, visualizing, and incorporating traditional two-dimensional MRI and CT data in three-dimensional representations. Topics covering the different types of visualization methods, creation of such modalities, applications of these technologies, and future path will be presented.

2. Advanced Visualization Imaging Techniques- Virtual Reality and 3D Printing

Virtual reality and 3D printing are two of the emerging advanced medical imaging methods that are soon to be available at a physician’s disposal. The term “advanced” is used in this case to indicate the progress that has been made in constructing three-dimensional models from “traditional” two-dimensional image slices. The use of technologies like 3D printing and VR in medicine are still being explored.

As more research about the potential applications of advanced visualization is done, the incorporation of them into common practice will increase. The construction of such three-dimensional models, the operating principles of 3D printing and virtual reality, and their applications to the medical field are discussed in this section.

2.1 What is 3D Printing

3D printing, alternatively known as additive manufacturing, is a rapid prototyping process of creating three-dimensional solid objects from a digitally constructed model. The 3D printer creates such solid models by layering individual two-dimensional sheets of metal, powders, or plastics atop one another, as specified by its digital rendering. After a curing process interaction with the physical model is possible.

Medical 3D printing is an application of additive manufacturing that utilizes volumetric data from medical scans to create three-dimensional models in the anatomical plane. Each layer of material corresponds to the slices of the medical image being printed. Thus, the anatomical model is formed using the cross sections of the digitally rendered model of the medical scan.

2.1.1 Creation of 3D Printed Models

It is necessary to use volumetric data from traditional imaging methods, such as computed tomography (CT) and magnetic resonance imaging (MRI) scans, to construct three-dimensional models. The creation of such three-dimensional models requires the collaboration of an engineer and physician to accurately construct. 3D Models are constructed through a four-step process: image acquisition, image segmentation, verification, and 3D printing [10]. The main steps of this process and the manipulation of the image at each stage are summed up in the diagram in Figure 2.

![Figure 2. Workflow of creating a 3D printed model from volumetric data. From [13], reprinted by permission from Springer Nature](image-url)
organs are segmented out. This segmentation process can be automated on the basis of edge detection, thresholding, and region growing, but manual segmentation is also required \[10\]. Once the image has been appropriately segmented, it is converted to the Standard Tesselation Language (STL) file type in order for 3D printers to process the information. STL files only carry geometry information that defines surfaces using triangles. However, the image may acquire errors during the file type conversion process.

**Verification.** This is an intermediary step that allows for engineers to validate their work with radiologists. At this point the radiologist can view the STL format of the 3D model and verify that all of the anatomies are properly ordered, the region of interest is appropriately highlighted, and all necessary information is correctly described by the rendering. The engineer must also double check the STL to make sure that the model is 3D printer compatible. There can be no openings or inversions and all components must fit properly together. Struts may also be added to provide greater stability.

**3D Printing.** The final step of the creation of a 3D model is the 3D printing of the constructed STL model. Materials that can be used include ABS, PLA, nylon, resins, and even metals. The material is loaded into the printer, heated, and then deposited according to the data from the model. 3D printers operate on the principle of “additive manufacturing processes,” where two-dimensional layers of material are placed atop one another and fused by heat. The benefit of 3D printing is its low cost, relatively rapid production, and ability to create intricate designs. The disadvantage is that 3D printers are limited by space; only objects of certain size can be created.

### 2.1.2 Scope of 3D Printed Models in Medicine

3-D printed models of patient-specific MRI and CT scans allow physicians to physically disassemble and study their patient’s anatomy. This has been proven to be especially useful in preoperative planning, individualized implant design, and in the education and training of both patients and practitioners \[13\].

The use of 3D printed models in surgical planning provides physicians with the ability to interact with patient-specific anatomy prior to operating. Many hospitals have already incorporated 3D printing into their workflow. Figure 3 describes the top five medical disciplines that incorporate 3D printing technology for planning, visualization, and education purposes.

Craniofacial surgeons have often studied three-dimensional patient skull models prior to performing the surgery. A study conducted by a group of physicians analyzed the effectiveness of stereolithographic (a form of 3D printing) models in achieving clinical and aesthetic results for the preoperative planning of cranial reconstruction and neurosurgeries. Out of the 26 total patients in cases of corrective cranioplasty, the authors stated that for one patient the stereolithographic model provided no additional information, and that for cases of bone fragment reassembly the models were not necessary. In the case of reconstructive cranioplasty physicians concluded that the usefulness of the stereolithographic models is directly related to the size of the defect; planning for operations on larger defects would be aided by stereolithographic models. All of the patients undergoing skull base procedures benefited from the use of stereolithographic models in planning. Their results conclude that the stereolithographic models provide better understanding of patient anatomy, knowledge from pre-surgical simulation, intraoperative accuracy in localization of lesions, creation of accurate implants, and improved education of trainees \[7\].

![Figure 3](image-url)

Figure 3. Top five medical disciplines that incorporate 3D printing technology for planning, visualization, and education purposes (Input data from \[2\]).

Not only will the application of 3D printed models allow for physicians to decrease the risk of intra-operative complications, but the use of 3D printed models to create tailored implants have also been proven to reduce operation times and decrease the cost of operating room usage. For example, a study conducted on the usage of 3D printed models in the case of craniofacial trauma showed that the pre-formation of implants for 12 patients suffering from orbital fractures resulted in reducing operating times by 15 to 20 minutes \[3\]. Additionally, the use of rapid prototyping resulted in fewer trial fittings as well as more precise fit and
repara[3]. 3D printing provides a cost-effective way to
create customized implants that can provide individual
patients with anatomically matching prostheses.

Additionally, 3D printed patient-specific models can be
used to bridge the knowledge gap between practitioners
and their patients. Most patients lack the technical
knowledge to be able to fully grasp the anatomy
presented in an MRI or CT image even when explained
by a physician. However, by creating a physical model
of their scans a physician will be better able to explain
to their patient. This educational tool can be used not
only to educate patients, but also to prepare medical
school students for the variability in real life cases that
their textbooks may not present.

2.2 What is Virtual Reality

Virtual reality (VR) is a computer-generated
environment that can be interacted with and explored.
By incorporating VR goggles, motion sensors, and
infrared beams VR devices are able to correlate user
movements with the virtual environment. This allows a
user to physically turn their head and move around to
manipulate their avatar in the virtual environment as
well. With the inclusion of haptic controllers there is an
added layer of tactile feedback. These features serve to
provide the user with the most immersive virtual
environment possible. VR was originally developed for
its entertainment value, however, it has become clear
that there are boundless applications for this
technology.

Applications of VR in the medical field have become
commonplace. This technology allows physicians to
create a virtual model of their patients’ data that they
can interact with in three dimensions. Physicians are
already embracing this modality by using the features
of virtual reality as a form of pre-operative planning.
Future physicians can also better learn from three-
dimensional interpretations of imaging scans and can
can better develop their spatial reasoning skills via VR
learning. Additionally, by reducing spatial reasoning
barriers this allows for users to better relate to
traditional imaging data.

2.2.1 Creation of Virtual Reality Models

There are many similarities in the construction of 3D
models that are prepared for printing and those prepared
for virtual reality. However, VR models require more
processing prior to use. This is due to the fact that the
model must be able to be manipulated in real-time while
maintaining the shading and surfaces of a physical
object. The production of virtual reality models can
thusly be broken into the following categories: image
acquisition, data processing, image processing,
coordinate determination, and the compatibility with
tools for manipulation[15].

Image acquisition. As aforementioned in section 2.1.1,
three-dimensional models are created using volumetric
data sets from imaging methods like CT and MRI.

Data processing. During this phase of processing the
two-dimensional scans from volumetric imaging
methods are stacked upon each other sequentially and
rendered. From here the radiologists help identify
structures of the image that are unnecessary and the
engineers remove them from the data set.

Image processing. With the three-dimensional model
having been created, the next step is to refine the image.
Much like the validation step in 3D printing, there are
certain discrepancies that modelers must be weary of.
For example, engineers must make sure that the shading
of surfaces are true for all angles viewed, the surfaces
render quickly, and that the anatomy is properly
represented at all angles.

Coordinate determination. Because viewing angles
play a huge role in the efficiency of virtual reality
models, it is essential to determine and apply a universal
3D coordinate system for the image. The user must
perform spatial calculations to account for any
movement of the patient in the images[15]. This
coordinate system provides the image an appropriate
axis for manipulation. A structure can be manipulated
with respect to a newly defined coordinate system.

Compatibility with tools for manipulation. A variety of
tools are available for use in medical VR simulations
including: VR goggles, haptic feedback gloves, motion
cameras, motion controllers, and VR pens. The object
must be verified to be compatible with the
functionalities of these extensions. The use of tools such
as motion controllers and VR pens allow for the user to
directly interact with the model via gesture controls,
allowing for the virtual reality model to be used in
academic scenarios. VR goggles, motion cameras, and
motion controllers promote the immersive experience
of virtual reality beyond the computer screen. Such
environments can be effectively used in surgical
simulators.

2.2.2 Scope of Virtual Reality in Medicine

Virtual reality provides one key advantage in surgical
planning over rapid prototyping methods. Having the
ability to create VR simulations allow surgeons to not
only visualize their patients, but also to be able to walk
through a mock surgery prior to actually conducting it.
“Conceptually, surgical simulation is to perform "virtual surgery" completely in the computer and to
compute an image or three-dimensional visualization of the post-surgical appearance of the patient” [15]. Having the ability to undergo simulated surgeries can provide a new depth to medical education in a cost efficient and effective manner.

A recent study sought to create a virtual reality simulation of orthognathic surgeries for the correction of maxillofacial deformities using a personal computer and affordable VR devices. The study stated that “the understanding of specific anatomic geometry in cross-sectional CT images relies on the expertise of the viewer” [15]. Thus, by converting CT and MRI data into three-dimensional anatomical images they are able to appeal to a broader audience. They have concluded that the use of virtual reality is useful in complex cases and where the cost of administering a CT to a patient is justifiable, both in price and radiation exposure [15].

3. 3D Printing vs. Virtual Reality

Both 3D printing and virtual reality have been discussed as viable options for physicians to gain information, however, each has its own benefits. 3D printing is a relatively low-cost and quick method to create a tangible object. VR, on the other hand, provides a much more immersive environment, but requires much more expensive virtual reality technologies and processing to fully appreciate. Both 3D printing and VR allow users to create a patient-specific anatomical model that can be used for pre-operative planning and education. Virtual reality is able to take things one-step further by employing surgical simulators that allow surgeons to practice surgeries as well. 3D printing has been shown to assist in the creation of customized implants [3]. Both methods are able to take traditional two-dimensional data and represent them in a 3D form that is better understandable by both healthcare practitioners and their patients.

4. Currently in Practice

Many large firms, such as Microsoft and Medtronic, as well as several startups, have been developing methods to bridge the gap between two-dimensional MRI and CT scans and three-dimensional models. Many medical schools are adopting VR as a teaching method. Surgeons are turning to 3D printed models to assist in preoperative planning.

Case Western Reserve University (CWRU) Medical School has partnered with Microsoft to employ their Hololens, an augmented reality device, to better educate their students. Researchers and radiologists at CWRU have created “virtual cadavers” using real patient MRI data and have incorporated it into lab-based learning. CWRU representatives have stated “students who had used the Hololens devices reported that 15 minutes with the three-dimensional images “could have saved them dozens of hours” in their traditional anatomy labs” [1].

Companies like Materialise have taken 3D printing into the hospital itself by creating software, Mimics, to help healthcare practitioners convert patient data into 3D models. This allows physicians to create custom implants, plan surgeries, and educate their patients. This shows that the majority of the world’s top hospitals have an in-house 3D printing facility.

4.1 Opportunities for Growth

Although there have been increasing studies conducted on the usage of rapid prototyping and virtual reality in medicine a lot of these concepts have yet to be employed. There are a few reasons behind this but some of the important ones include: cost, employment of technical personnel, and necessity.

In order to create these 3D models hospitals must purchase the appropriate equipment: 3D printers, virtual reality devices, and segmentation software. All of these can be initially costly. Additionally, there is a steep learning curve associated with the creation of 3D models, so the employment of technical personnel is necessary. Many hospitals and physicians have been using traditional imaging methods for so long that they question why these advanced visualization methods are useful. In order to change their perception advanced visualization techniques must be demonstrated and the process must be simplified.

5. References


PHOTOACOUSTIC IMAGING AND ITS BIOMEDICAL APPLICATIONS
Cassandra Steffey
csteff2@uic.edu

Abstract
Ultrasound imaging is a technique that uses sound waves to visualize the tissues in the body. The images created are of high resolution (spatial resolution in millimeters) but they do not have high contrast. This is one of the major downfalls of ultrasound imaging. In order to get an image with better contrast, research was conducted into photoacoustic imaging. Photoacoustic imaging is an up and coming medical imaging technique that utilizes the photoacoustic effect discovered by Alexander Bell. The photoacoustic effect occurs when light or radio frequency signals are generated and absorbed into the tissue. The absorption of these waves produces an ultrasound wave that propagates to the surface. Photoacoustic imaging combines the two modalities and creates an image of both high resolution and high contrast. This type of imaging is very useful in both research and medicine. The images that are reconstructed can show structural, chemical, and functional properties of the tissues being imaged. This allows for the research and observation of the body’s many processes including looking at hemoglobin, water, lipids, and proteins. This technique has some limitations such as being dependent on the ultrasound receivers as well as other assumptions maintained during reconstruction algorithms. However, this technique is still beneficial in that it generates a great image, but it is also non-ionizing. The low frequency of the signals creates a safer technique than those of higher energy like x-ray and computed tomography. The goal of this paper is to explain the photoacoustic effect, give an overview of the photoacoustic imaging technique, examine the types of images that are constructed, and talk about the possible clinical and nonclinical applications.

Keywords: Photoacoustic, Ultrasound, Fluorescence, Medical Imaging, Biological Imaging

1. Introduction
1.1 History of Photoacoustic Imaging
Photoacoustic imaging is a method of imaging that combines both optical and ultrasound imaging [14]. This method started with the discovery of the photoacoustic effect. In 1880, Alexander Graham Bell discovered the photoacoustic effect while observing the generation of sound waves due to the absorption of sunlight [14]. This phenomenon was not well studied until the 1960s with the invention of the laser. The laser was an important contribution to photoacoustic imaging because it allows the light to have a designated amount of power and directionality that is needed in imaging [14]. Photoacoustic imaging was used initially in industry and in research up until the 1990s when it was considered for biomedical imaging purposes [14]. Photoacoustic imaging will advance medical imaging because it provides an image that has both high resolution and high contrast [11]. This method is also low risk because it involves non-ionizing radiation.

Photoacoustic imaging combines two different imaging modalities; ultrasound and optical imaging. Ultrasound imaging utilizes sound waves to produce a real-time image. Soundwaves are considered a very safe approach because they involve non-ionizing-radiation is used and there are no strong magnetic fields. Ultrasound waves are produced by a transducer and sent into the body in very short pulses. When a signal reaches a boundary (i.e. when layers of fat and tissue connect) some of the signal is reflected back toward the transducer. These reflected waves can be detected by the transducer and then with the use of computer algorithms an image can be created. The image is formed based on the time it took for the echo to be detected. The waves travel through tissue very quickly allowing for real-time pictures. In ultrasound imaging, the images have high resolution, but the contrast is not ideal. This is because the contrast is dependent on the mechanical and the elastic properties of the tissues which do not have enough variability to provide high contrast [1]. Ultrasound imaging is currently used in gynecology, obstetrics, cardiovascular applications, and for measuring blood flow. These applications do not necessarily need a high contrast image to get a usable image which is why ultrasound is a good imaging modality.

Optic imaging or fluorescence imaging, uses light properties to construct an image. Light imaging is based on the reflection and absorption of light in different tissues. In fluorescence imaging, there is high contrast due to the different chemical compositions and
corresponding absorption, but it has low spatial resolution [11]. This is because there is much more scattering in the tissues with fluorescent signals than that with ultrasound signals [11]. Photoacoustic imaging combines the two modalities creating both a high resolution and high contrast image.

The purpose of this review is to discuss the photoacoustic effect and how it can be used as a biomedical imaging modality. The background and technique of photoacoustic imaging will be presented briefly, and different biomedical applications will be discussed.

2. Photoacoustic Imaging in Tissue

2.1 Absorption

![Absorption Coefficients for Different Tissue Components](image)

Figure 1. This plot shows that absorption coefficients are different for different endogenous tissue chromophores. Oxyhemoglobin (red), deoxyhemoglobin (blue), water (black), lipid 80% by volume (brown), lipid 20% by volume (pink), melanin (black dashed), collagen (green), and elastin (yellow). From [12], reprinted by permission from Springer Nature

When optical waves or radio frequency waves are absorbed into tissue, that absorption produces ultrasonic waves (MHz). The production of these ultrasonic waves is due to local heating and corresponding thermoeelastic expansion that occurs when electromagnetic waves of lower frequencies are absorbed [10]. The different tissues in the body have different absorptions due to their individual properties as can be seen in Figure 1. These differences can be detected and converted into an image of the system.

2.2 Optical Properties of Tissues

The use of visible and near infrared waves in photoacoustic imaging allows for deeper penetration, better absorption by contrast agents, and good image contrast [11]. Tissue has many different molecular components. These different components have different electronic and vibrational structures that create variances in optical scattering and optical absorption [10]. The amount of optical scattering can show the changes in architecture of the tissue [10]. The optical absorption can reveal the metabolism of the tissue and the formation of blood vessels in the tissue. One example of how the absorption change can be seen is with hemoglobin. When hemoglobin is oxygenated, the absorption is two orders of magnitude higher than other molecules such as melanin or deoxyhemoglobin [10].

2.3 Radio Frequency Properties

Radio frequency is the range of frequencies from 20 kHz to 300 GHz in the electromagnetic spectrum. At a radio frequency signal of 0.3-3(GHz), electromagnetic waves can be transmitted through the body [10]. This signal can also be absorbed or reflected by different components of the tissues. The two properties that affect the radio frequency absorption the most are ionic conductivity and vibration of dipolar molecules [10]. Small differences in ionic composition, water content, or protein amount will greatly increase the absorption of radio frequency signals [10].

3. Photoacoustic Imaging Technique

3.1 Nonionizing Waves

As mentioned earlier, photoacoustic imaging is a non-ionizing technique. This means that there are very little risks with this procedure especially in terms of radiation. Imaging such as x-ray and CT are considered ionizing radiation techniques. This means that the imaging can cause ionizing radiation in the subject. Ionizing radiation occurs when high energy particles are absorbed into the tissues. The high energy can excite particles, damage DNA, and cause free radicals in the body. This has many health issues especially when introduced to areas that undergo constant cell development. The signals used in ultrasound, MRI, and photoacoustic imaging are non-ionizing because their energy levels are too low to cause such levels of damage in the tissues.

3.2 Photoacoustic Wave Generation

There are many different mechanisms for generating ultrasound signals in tissues. The process used in medical imaging uses electromagnetic pulses [11]. One mechanism to generate photoacoustic signals is diagramed in Figure 2. In this figure it can be seen that a pulsed laser aimed at the target tissue from the outside
of the body results in ultrasonic waves produced inside the body. These ultrasonic waves can be detected and analyzed in the same manner as the ultrasound imaging currently used. To explain in more detail, the electromagnetic pulses cause the tissue to experience a slight increase in temperature and thermoelastic expansion. This change in temperature can be computed with Eq. (1) [11].

\[
\Delta T = \eta \frac{\Delta E}{\rho V C_v} \approx \eta \frac{\Delta E}{A} \frac{1}{\rho \rho C_v}
\]

(1)

Here \(\eta\) is the fraction of absorbed energy that goes into heating, \(\rho\) is the density of the tissue, and \(C_v\) is the specific heat capacity of the tissue [11]. The expansion caused by the increase in temperature will produce ultrasound waves that propagate through the body [10]. These pressure waves can be detected on the surface using acoustic microphones [11]. The change in pressure increase due to the rapid heating is computed by using Eq. (2) [11].

\[
\Delta P = \beta K_T \cdot \Delta T
\]

(2)

Here \(\beta\) is the thermal expansion coefficient and \(K_T\) is the bulk modulus [6]. There are two conditions that must be met for this to occur. The first condition is related to the thermal confinement and the second condition is related to the stress confinement. The thermal confinement is dependent on the heat diffusion which itself is dependent on the geometry of the heated volume [10]. When tissue absorbs the radio frequency or fluorescent pulse, there is an excited period. During this time period, there is little dissipation of heat and the thermal confinement condition is met [10]. For the stress confinement condition to be met, the time for the stress to transmit the heated region must be larger than the pulse width. This allows for the thermoelastic pressure to build up and it releases as an acoustic wave [10].

![Illustration of the mechanism for the photoacoustic effect](image)

**Figure 2. Illustration of the mechanism for the photoacoustic effect [2]**

### 3.3 Propagation and Detection

The acoustic wave is generated by the excited and high-pressure region created by the radio frequency or fluorescent signal. These acoustic waves travel to the tissue surface and are detected by the receiver [1]. This is similar to the propagation in ultrasound imaging. The waves travel deep into the tissues with very little scattering due to the low frequency range. Attenuation in the tissues is dependent on temperature and frequency [10]. In general, the attenuation increases with frequency, but penetration decreases. To explain, if the frequency was high, there would be more absorption and scattering which would cause a decrease in penetration [10].

In ultrasound imaging, the transducer operates both as the emitter and the receiver. This is important because in ultrasound imaging, the emission efficiency is important to calculations and reconstruction. In photoacoustic imaging, the emission efficiency is not important. This allows for the detector to be highly specialized for sensitivity [10]. In most medical applications the detector is piezoelectric based. There are some detectors that are optical detection based but the piezoelectric ones have less noise and better sensitivity [10].

### 3.4 Contrast

Contrast can be defined as the relative difference of signal intensities in two adjacent regions of an image. In photoacoustic imaging the contrast is dominated by the optical absorption [1]. This means that the anatomical features that contain hemoglobin, lipids or water are very easily identified. This is because they have a high level of optical absorption. Hemoglobin has a high absorption which is why the vasculature has such high contrast [1]. The oxygenated and deoxygenated blood can be determined as well; allowing the functional component of the tissues to be seen. Hemoglobin is one of the most looked at chromophore because it can show bleeding, blockages, and other functional information.

Melanin is another high absorption molecule. This allows images of areas that are pigmented like on the skin or retina. The last area that is looked at is lipid content [1]. There is a small range where water is predominating over hemoglobin. In this range, localized lipid deposits can be viewed. This is important in atherosclerosis [1].

Even though chromophores like hemoglobin and melanin are predominate over the majority of the visual spectrum, there are ways to view the chromophores that are weakly absorptive [1]. The use of spectroscopic inversion or contrast dyes can help visualize the areas that are normally hard to view.

### 3.5 Contrast Agents

One of the benefits of photoacoustic imaging is the ability to use contrasting agents. Contrasting agents are
chemicals added to the blood that change the density of targeted areas. Contrasting agents can target specific components such as proteins. When a contrasting agent binds to a protein it changes the density of that tissue. If the density changes, the amount of reflected or absorbed waves changes. This allows for the differentiation of different tissues. Contrasting agents are very useful for targeting specific organs because protein concentrations vary in different tissues. Figure 3 is an image taken of a melanoma using contrasting agents. The most common contrast agent is gold nanoparticles. Gold nanoparticles are strong and have a tunable optical absorption [10]. This is due to the surface plasmon resonance effect. This effect occurs due to the oscillation of free charges on the surface of gold nanoparticles. These free charges oscillate with the electromagnetic field and lead to an optical absorption much greater than organic dyes [10]. This property makes gold nanoparticles, nanorods especially, applicable for in vivo imaging [14]. Due to the many structures of gold nanoparticles (nanospheres, nanorods, nanoshells, nanoprisms, nanocages, nanostars, etc) there is a broad range of resonant frequencies that enable a wide range of targeting and applications [10]. The image in Figure 4 shows how gold nanoparticles were used to identify tumor structures.

3.6 Photoacoustic Tomography

Photoacoustic Tomography is the traditional mode for photoacoustic imaging [1]. An example of a photoacoustic tomography machine is shown in Figure 5. The image is constructed by taking the time-–varied detections of the acoustic waves at the tissue surface [1]. These acoustic signals can be back projected into a three-dimensional image based on the speed of sound [1]. Spherical, cylindrical, and planar geometries are used for acoustic wave detection [1]. The first two geometries are only appropriate for areas like the breast or for small animals because it requires access from all angles. The planar geometry is the most applicable for all other anatomical targets [1].

There are many methods for the reconstruction of the photoacoustic image. The earliest methods are like those involved in ultrasound imaging: delay-and-sum receive focusing and beamforming. These methods are not the most accurate. A few of the other methods that are employed are filtered back projection, serial summation, Fourier transform, and time-reversal methods [13]. The filtered back projection can create an exact reconstruction however, it is computationally intensive. The time-reversal method is the least restrictive method due to the fewest assumptions but is also computationally intensive [13]. One common used method is the Fourier transform method. Fourier transforms are the time-dependent pressure data. This method works best for planar geometries and is a fast and computationally advantageous method [13]. The reconstruction formula in the Fourier domain can be written in the form in Eq. (3) [13].

\[
p_0(r) = \frac{1}{4\pi^2} \int_{-\infty}^{+\infty} dx_0 dy_0 \int_{-\infty}^{+\infty} dk \hat{p}_k (r_0, k) \times \\
\int_{p-|k|}^{p+|k|} dudv \exp[-izsgn(k)\sqrt{k^2 - p^2}] \exp[iu(x_0 - x) + iv(y_0 - y)]
\]

The reconstruction consists of three steps: (1) Find the Fourier decomposition by taking the two-dimensional Fast Fourier Transform, (2) compute the relationship between the source distribution and the measured data, and (3) take the inverse Fast Fourier Transform of the relationship to find the initial pressure [13].

Figure 3. This is an image of gelatin phantoms containing cells and two types of coated nanorods. Image above is an ultrasound image, image below is an ultrasound and photoacoustic image. From [4], reprinted by permission from Springer Nature

Figure 4. This shows the MRI and Photoacoustic images of a rat cerebral cortex before and 2 hours after the injection of gold nanocages. These images show clear tumor visualization. From [7], reprinted by permission from Springer Nature

Figure 5. Pulsed light enters a liquid filled cavity that rotates continuously during data acquisition. The wavelength and pulse power are measured by a spectrometer during data acquisition. From [8], reprinted by permission from John Wiley and Sons
4. Biomedical Applications

4.1 Oxygenation

One of the more common uses of photoacoustic imaging is to use it to determine oxygen uptake. This is because oxygen can be observed in endogenous chromophores like hemoglobin and deoxyhemoglobin [14]. Due to their differences in wavelength-dependent optical absorption properties, photoacoustic imaging can be used to assess total hemoglobin and blood oxygenation [11]. This process has been used to look at hypoxia during cholangitis, murine tumors, and in cholangiocarcinogenesis [9]. Before photoacoustic imaging, the oxygen uptake could be monitored using radioisotopes. The use of photoacoustic imaging makes this process less dangerous and non-invasive [9].

4.2 Inflammatory Arthritis

Inflammatory arthritis is a condition that can cause significant activity limitation and reduced quality of life. Early diagnosis is the key to better and more personalized treatment [6]. There are two conditions that support the diagnosis of inflammatory arthritis; increased hyperemia and increased hypoxia. Hyperemia can be determined by looking at the distributed hemoglobin and hypoxia can be determined by looking at the oxygenation of that hemoglobin [6]. Using photoacoustic imaging with a single laser wavelength, the hemoglobin distribution can be observed. When performing photoacoustic imaging with two laser wavelengths, the hemoglobin oxygenation can be seen. This process has shown that photoacoustic imaging could be a non-invasive and objective medium for diagnosing inflammatory arthritis [6].

4.3 Peptide Uptake

Another application of photoacoustic imaging is to observe the uptake of different substances into cells. One example of this was the use of photoacoustic imaging to monitor the uptake of peptides in xenograft breast tumors. Breast cancer is one of the most common carcinomas [3]. In Figure 6 below, photoacoustic images were used to observe the expression of ErbB2 in cancer cells. ErbB2 is an epidermal growth factor receptor that is expressed in 30% of all breast cancers [3]. This is an important application because it allows for better detection of the location of tumorous cells without being invasive.

4.4 Gut Microbes

A new application for photoacoustic imaging is for observing bacteria. One example of this was for the observation of the distribution of gut microbiota in the gastrointestinal tract [5]. In order for photoacoustic imaging to detect the bacteria, the bacteria were labeled with near-infrared dyes. With the dyes present, photoacoustic imaging was able to detect the live bacteria in the gastrointestinal tract [5]. This is important because the treatment of different diseases is dependent on the distribution of bacteria [5]. In order to better diagnose and treat such diseases, the non-invasive approach of photoacoustic imaging presents an exciting alternative to current methods like biopsy.

4.5 Prostate Cancer

Prostate cancer is the most prevalent cancer in men. The current diagnosis of prostate cancer involves prostate-specific antigen blood tests and digital rectal examinations [2]. Malignant prostate tissue has approximately three times more blood flow than normal prostate cancers. This is a great property for photoacoustic imaging because of the difference in chromophore concentrations [2]. This makes photoacoustic imaging a good imaging modality for the detection of prostate cancer and it was shown that it was able to differentiate between the two tissue types [2].

5. Conclusion

Photoacoustic imaging utilizes the photoacoustic effect. This phenomenon occurs when tissues absorb light or radio frequency signals. These signals cause an increase in temperature of the tissue. The tissue then experiences thermo-expansion and a subsequent increase in pressure. The increase in pressure releases an acoustic wave that propagates to the tissue surface where it is detected. This type of imaging is non-ionizing. This means, due to low energy, there is no harm in terms of ionizing radiation when using this technique.
The biomedical application of photoacoustic imaging uses visible light, near infrared light, or radio frequency signals. The combination of both fluorescence and acoustics allows for a high resolution and high contrast image. In ultrasound alone, the image has good resolution due to the propagation depth and mechanical properties of the tissues. When combined with optical signals, the image improves in contrast. This is due to the chemical properties of the tissues. Radio frequency signals are used to better understand the functional properties of the tissues because of their conductivity properties.

The process of recreating an image depends on the detection geometries and the information that is being observed. However, the final image can reveal the structural, chemical, and functional properties of the area being imaged. This is due to the abundant optical absorption of hemoglobin which is responsible for the high contrast. The other types of chromophores can still be detected with the help of computation and/or dyes. This technique has many applications that will expand the medical imaging field as well as research, diagnostics, and medicine. There is a lot that is being researched and worked on in this field that will bring an exciting future and a better insight into many aspects of science.

6. References


AN OVERVIEW OF ECHOCARDIOGRAPHY FOR EXAMINATION OF CARDIAC STRUCTURES
Christine Lee
Clee146@uic.edu

Abstract
Echocardiographs were first utilized in the 1950s by examining waveforms that would indicate the anatomy of the mitral valve in the heart. By the 1970s, echocardiography was recognized as the main cardiac diagnostic method. The purpose of echocardiography procedures is to diagnostically examine the anatomy of the heart using cardiac ultrasound. Several types of echocardiographs exist, such as transthoracic, transesophageal, fetal, doppler, and three-dimensional echocardiographs, all of which serve a different diagnostic purpose. These tests result in live cardiac images, an echocardiogram, that are utilized to detect defects in the heart. This technology can detect weak heart muscles, holes, clots, or tumors in the heart, but has some limitations and risks involved. However, the risk associated with these procedures is minimal, as most methods are non-invasive and do not require radiation, unlike other imaging techniques. Although transesophageal echocardiography can result in patient discomfort or other complications due to its invasive nature, studies have shown that only about 5% of these procedures result in these complications, making this procedure generally low risk. Despite the cost of approximately $1,000 to $3,000 per procedure, echocardiograms are beneficial in preventing the progression of life-threatening diseases or complications. Overall, echocardiography is a beneficial method for examination of cardiac structures and provides the healthcare provider and patient with accurate information that may be used to diagnose a patient. These diagnoses are crucial in treating cardiac complications efficiently before they are advanced to more complicated forms. This paper will give a brief overview on the functions and applications of echocardiography.

Keywords: Echocardiography, Cardiac, Heart, Structures, Defects, Examination

1. Introduction
Methods of echocardiography were first utilized in the 1950s by examining waveforms produced at the mitral valve [6]. This first application of two-dimensional echocardiography was utilized by the “Father of Echocardiography”, also known as Inge Elder. Elder used the M-mode, or time motion, method to analyze a patient suffering from mitral stenosis [12], which occurs when the mitral valve narrows in the heart [1]. Two-dimensional echocardiography was popularized in the 1970s when it was demonstrated with a linear transducer array in Rotterdam [6], which converts electrical signals into rectangular images [18]. By the 1970s, echocardiography was recognized as the main cardiac diagnostic method [12].

Previous methods to measure electrical activity of the heart such as electrocardiograms faced difficulties measuring the cardiac output and functionality of the heart. On the other hand, echocardiography procedures can accurately measure the morphology and function of the heart, paving the way for it to become recognized as the main cardiac diagnostic method.

Electrocardiography is a test utilized to examine cardiac structures by producing live cardiac images that display defects in the heart. The images obtained with this test are referred to as echocardiograms [12] and are obtained by reflecting ultrasound waves on the heart [8]. The resulting images provide data on cardiac function, morphology, and hemodynamics which can be utilized for detection and monitoring of heart diseases [12].

Cardiac function assessments can detect and monitor different heart diseases, both minor and major, such as heart valve disease, coronary artery disease, and pericarditis [8]. Echocardiograms are also useful in providing information to determine required treatments for heart diseases, as well as monitoring changes or improvement in the heart [21]. This procedure can also detect abnormal morphology, such as abnormally sized hearts through the presence of larger or thicker ventricles [21]. There are several echocardiograph procedures that are minimally invasive and used for different diagnostic purposes. These procedures are beneficial in providing crucial information for both health care providers and patients.
The purpose of this review is to provide a brief overview of the physical principles behind electrocardiography, introduce some of the several echocardiography procedures used for various diagnostic purposes, describe the typical procedure setup, and provide a discussion on some of the benefits and limitations of electrocardiography.

2. Physical Principles

Depending on the elastic properties or density, various tissues in the human body are differentiated with sound waves during an echocardiography procedure [11]. Sound waves are both reflected and refracted off tissues of varying densities, and the transducer, the probe placed against the chest of the patient, converts and amplifies these reflected waves into electrical energy [11]. This electrical energy is then displayed for the sonographer to examine for abnormalities in the cardiac morphology [11].

For these readings, the frequency \((f)\), wavelength \((\lambda)\), and speed of transmission \((c)\) determines the resolution of the image obtained [11].

\[ c = f \times \lambda \]  

Eq. (1) can be utilized to determine that a higher resolution can be obtained when a smaller wavelength is produced by a high frequency transducer [11]. However, larger cardiac structures cannot be penetrated by small wavelengths, ultimately limiting high-frequency transducers [11]. Therefore, the focal plane, size, and frequency of the transducer must be carefully determined to obtain a high-resolution image [11].

3. Types of Echocardiography Techniques

The transthoracic echocardiogram (TTE) is the most standard method of echocardiography, due to its minimally invasive and radiation-free procedure [8]. As shown in Figure 1, this procedure is performed by placing an ultrasound transducer on the chest, which emits high frequency sound waves [8]. Figure 1 also shows the process of the transducer generating sound wave echoes that are then displayed as a picture on the computer monitor for the sonographer to interpret [21]. These sound waves reflect off the cardiac structures and produce images that can be analyzed to detect cardiac complications, such as disease or damage [8]. Due to its minimally invasive nature, similar technology is utilized to examine a fetus’s health prior to birth [8].

Doppler echocardiography is another method of echocardiography that was first clinically utilized in the 1970s to examine valvular regurgitation [12], which occurs when the heart contracts and blood leaks back into the atrial cavity [16]. This method of echocardiography aids in the discovery of obstruction in the cardiac muscles by calculating flow rates [9]. Its ultrasound method provides information on the blood flow rates throughout the heart [21]. Bernoulli’s equation is utilized to identify pressure changes throughout the valves of the heart with these flow rates [9]. Doppler echocardiography is normally used with transthoracic echocardiography to simultaneously examine flow velocity with cardiac functions [9]. As can be seen in Figure 2, the resulting Doppler echocardiograph images display blue and red sections that indicate cardiac flow [14].

Another form of echocardiography is the transesophageal echocardiograph (TEE), which was first utilized in the 1980s when a fiberoptic endoscope was used in conjunction with a two-dimensional transducer [12]. The most modern TEE procedure can output detailed images of the heart, including the vessels and pericardium [9]. These images are obtained by inserting an ultrasound transducer orally.
into the esophagus, shown in Figure 3, which takes several pictures of the cardiac vicinity [8]. As shown in Figure 3, sound waves are utilized to capture pictures of the hearts structures, including the ventricle and atrium [19]. Since the esophagus is located near the heart, the procedure does not interfere with the lungs or chest and produces detailed images of the cardiac structures [8].

![Figure 3. A transesophageal echocardiogram (TEE) procedure. A probe is inserted into the esophagus to emit sound waves which produce pictures of the cardiac structure [19]](image)

Apart from the other methods, two-dimensional echocardiographs are useful in obtaining 2-D images of the cardiac structures and vessels. This procedure was developed in the 1950s [6] and it produces images of the heart that can be viewed at three different angles: long-axis, short-axis, and four-chamber views [22].

Following the development of the two-dimensional echocardiograph, three-dimensional echocardiographs were developed in the 1970s by utilizing the reconstruction technique [12]. This reconstruction technique gathers images obtained at different transducer locations and constructs the images together to create a three-dimensional image of the cardiac structures as shown in Figure 4 [12].

![Figure 4. Three-dimensional echocardiographs produce 3-D images of the cardiac structure. This figure displays a three-dimensional view on the left atrium (LA) and ventricle (LV), as well as the aortic root (AR). From [22], reprinted by permission from Elsevier Spain](image)

Although the varying forms of echocardiography function differently, these methods all provide crucial cardiac information that can be beneficial in the medical field.

4. Patient Procedure and Associated Cost

Echocardiograph ultrasound procedures are generally minimally invasive and radiation-free, and accurately evaluate the condition of the cardiac structures including the valves and muscle [8].

4.1 Associated Cost

Consultation with a cardiologist before an echocardiograph procedure usually ranges between $200 to $300 [3]. The cost of a screening procedure ranges between approximately $1,000 to $3,000, and health insurance only covers the cost when there is an existing cardiac complication that needs to be examined [3]. This means that the cost of an echocardiogram procedure is not covered for patients who are receiving a routine screening examination [3]. However, for qualifying patients, health insurance can cover between 50 to 90% of the costs [3]. Therefore, with most of costs covered by insurance, an echocardiograph is recommended for cardiac examinations.

4.2 Procedure

Prior to the procedure, patients consult with a doctor to determine if an echocardiogram is needed. The patient will sign a consent form and inform the doctor if they have any allergies or outstanding conditions, such as heart diseases or pregnancy [19].

As the procedure proceeds, all clothing, disruptive jewelry, and oral inserts are removed, and the patient’s bladder must be emptied [19]. The patient will have an intravenous line inserted to provide medication and sedatives, and their heart rate will be monitored with an electrocardiogram [19]. To decrease discomfort caused by the inserted probe, the patient’s throat is sprayed with a local anesthetic [19]. Following these procedures, the lights are turned off to better examine the echocardiogram monitor, and the probe is inserted down the throat [19]. Once the probe is inserted down the esophagus, the camera at the end of the probe obtains pictures of the cardiac structures. Then, the doctor carefully withdraws the probe from the throat to complete the procedure [19].

Following the echocardiogram procedure, the patient’s blood pressure, heart rate, and oxygen levels
will be watched to ensure the patient’s recovery. Then, all equipment used in the procedure is removed, and the patient will be dismissed. It is advised for the patient to avoid intense physical activity following the procedure because the chest or esophagus area may feel tender depending on the procedure [19].

5. Advantages of Echocardiography

Echocardiography techniques tend to be characterized with high sensitivity and high specificity for different applications. For example, a study that utilized Doppler echocardiography to examine cardiac pressures of one hundred and ten patients revealed a sensitivity and specificity of 73.5% and 57.8% respectively [15]. Another study used transesophageal echocardiography to examine the morphology of the aortic valve in seven hundred and ten patients. Results found the sensitivity of the procedure to be 87% and the specificity to be 91% [7], indicating the reliability of this imaging method.

In another study conducted by Boston University School of Medicine, thirty-one already diagnosed cardiac amyloidosis patients were tested with a two-dimensional echocardiograph for amyloidosis. The test gave results with a specificity and sensitivity of 87% and 81%, respectively [2]. In another study conducted, the ability of a two-dimensional echocardiogram to detect the defected function of the left ventricle was examined. The sensitivity, specificity, and predictive accuracy of an echocardiogram were tested and yielded the results of 81%, 100%, and 100%, respectively [4]. Therefore, the high sensitivity and specificity rates obtained from these two studies are examples of how echocardiography is an accurate way for obtaining cardiac information.

With its accuracy, echocardiograms provide detailed information pertaining to the heart, including the movement, size, and structure of the cardiac walls, valves, and septum [21]. Images of cardiac regions that cannot be examined with a precordial ultrasound can be obtained with echocardiographs [20]. These images are high quality and unobstructed, thus making this procedure more beneficial for patient care [8]. Echocardiographs are useful for patients who require an overall assessment of their cardiac functions [8]. These assessments can detect and monitor a range of different heart diseases such as heart valve disease, coronary artery disease, and pericarditis [8]. Echocardiograms are also useful in providing information to determine required treatments for heart diseases, whether surgical or medical, as well as monitoring changes or improvements in the heart [21].

This procedure can detect abnormally sized hearts through the presence of larger or thicker ventricles [21]. This abnormality can be the cause of valve regurgitation, hypertension, and in more serious cases, heart failure [21]. Echocardiographs can also detect weak heart muscles, holes, clots, or tumors in the heart [21]. Early detection can prevent life-threatening diseases or complications such as coronary heart disease, heart attack, or stroke [21]. This technology is beneficial because it provides information that is crucial in early detection and diagnoses.

6. Disadvantages of Echocardiography

Although echocardiograph procedures are beneficial, drawbacks exist that prevent this method from being entirely accurate and can also cause minor discomfort to patients.

6.1 Practical and Theoretical Limitation

Echocardiograph procedures come with several limitations, either practical or theoretical [13]. For example, Doppler echocardiographs cannot obtain images of the pulmonary artery that are as clear compared to images taken with a two-dimensional echocardiograph. Despite improved image quality, the two-dimensional echocardiography produces a mitral valve area that is below accurate measurements [13]. This drawback occurs in patients that experience mitral regurgitation, but accurate data can be obtained when two-dimensional echocardiography is used in conjunction with Doppler echocardiography [13].

It was found in a study led by Miltiadis A. Stefadouros, that features of the complex left ventricle cannot be measured through echocardiography. For example, the volume of the left ventricle cannot be accurately determined with solely an echocardiogram. The volume can be determined by using formulas but can only provide accurate results when the patient’s left ventricle shape follows the standard form. This means that if the left ventricle of a patient is abnormally shaped, then the volume cannot be accurately computed [17].

6.2 Risk and Discomfort

When operated correctly, standard echocardiograph procedures are minimally invasive and low risk. Transesophageal echocardiography, on the other hand, can potentially result in patient discomfort due to its semi-invasive procedure [20]. A risk factor exists when the procedure is performed by an inexperienced cardiologist, especially if the patient has an existing
cardiac complication [20]. Also, executing the procedure without an optical control could be dangerous during the insertion of the probe [20].

Transesophageal Echocardiograph Procedure Complications

Figure 5. Complications encountered by 90 of 10,419 patients during a Transesophageal Echocardiogram procedure (Input data from [20])

A study conducted in Safety of Transesophageal Echocardiography found that 1.9% of 10,419 transesophageal procedures were unsuccessfully completed due to the inability to insert the probe down the patient’s esophagus. This complication was commonly encountered because of either an inexperienced cardiologist or patient discomfort [20]. Patients commonly experienced increased heart rate and blood pressure during or following the insertion of the probe into the esophagus. Therefore, the patient may require sedation to prevent further complications during the procedure. From the same study, complications were also encountered in 90 of 10,419 procedures because of several reasons. The most common complication was due to patient discomfort once the probe was inserted into the esophagus. Other complications resulted from bleeding, and cardiac or pulmonary complications in the patients [20]. However, in the study of 10,419 patients, less than 5% of the tests ran into complications, making this procedure generally low risk [20].

7. Conclusion

Echocardiography is an accurate method for obtaining information on cardiac structures and functions. It can be utilized to detect defects in the heart, both structural and functional. Cardiologists can utilize the information obtained to diagnose and develop a treatment plan for the patient’s cardiac illness. This method is crucial in preventing the progression of life-threatening illness.

There are several echocardiography methods that can be utilized to track cardiac health, including transthoracic, transesophageal, two- and three-dimensional, and Doppler echocardiography. These methods are used for different diagnostic purposes of the heart and are minimally invasive. However, transesophageal echocardiography involves the insertion of a probe down the patient’s esophagus, which may cause patient discomfort. Although patient discomfort is considered, these complications arise in only approximately 5% of procedures conducted.

With complications only arising in 5% of procedures, the echocardiograph procedure is generally simple and minimally invasive. Patients are usually discharged from the hospital on the same day as the procedure and can continue practicing their daily routines. Also, echocardiographs are generally low cost when covered by insurance. Insurance may cover between 50-90% of the costs for the echocardiogram when an existing cardiac complication must be monitored. Therefore, echocardiograph procedures are beneficial to patients and can provide crucial information in health diagnoses.

Future advancements in echocardiograph technology can reduce the number of cardiac complications that occur in patients. These advancements could include developments in the design of the device to ensure patient comfort or to provide more accurate data that can be used to diagnose patients. Echocardiographs can be improved to measure the complex left ventricle and provide information without the use of formulas to comprehend data. Doppler echocardiographs can also be improved to provide clearer images of the pulmonary artery. Two-dimensional echocardiographs can be improved to provide more accurate cardiac measurements. These advancements in technology will make echocardiograph procedures more reliable in providing crucial information for healthcare providers and patients.

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Abstract

Positron emission tomography and computed tomography are two separate imaging techniques. Positron emission tomography is a functional imaging technique which uses nuclear medicine enabling it to observe metabolic processes by detection of gamma rays. A positron emitting radionuclide is introduced into the body and this tracer moves to areas of higher chemical activity. The emission of gamma ray pairs is then detected. Computer analysis is used to construct three dimensional images of the radionuclide concentration. Computed tomography scans use multiple computer processed x-ray measurements to produce a cross sectional image. This allows for the technician and medical staff to non-invasively see an area of interest inside the patient's body. The combination of these two forms of medical imaging allows the mapping of a functional imaging technique onto a stationary image. With this projection, there is a more precise anatomical localization alongside the functional image. This allows for a more accurate diagnosis compared to previous methods in which positron emission tomography and computed tomography were taken separately. In this paper, a more in-depth overview of both positron emission tomography and computed tomography is provided along with advantages of the positron emission tomography-computed tomography compared to both techniques. Also, applications of the positron emission tomography-computed tomography are discussed and how it has opened a new frontier in the area of medical imaging.

Keywords: Positron Emission Tomography, Computed Tomography, Positron Emission, Radionuclide, Gamma Rays

1. Introduction

Positron Emission Tomography (PET) is a form of nuclear medical imaging in which radioactive material usually dosed in mSv (millisieverts) is delivered to the patient via injection or inhalation. The radioactive material doses are known as radiopharmaceuticals or radiotracers. The amount of radioactivity detected can give a physician an indication of the functionality and activity of different organs and can detect the presence of disease. The radioactive agent causes an emission of gamma rays which result from excess energy in the nucleus [13]. Pairs of gamma rays are then detected and show up on the rendering as brighter spots on the image.

The idea of emission and transmission tomography was introduced in the late 1950s. Using previously established work, as well as a growing field of nuclear medicine, a myriad of tomographic instruments were first created at the University of Pennsylvania. In the late 1960s the PC-I displayed in Figure 1 was created. This positron detecting instrumentation included two 2-dimensional arrays [11]. Inclusion of two separate arrays led to the creation of the current appearance, form, and function of current PET scanners.

X-Ray Computed Tomography (CT) is a nondestructive technique for visualization of interior features within a solid object, as well as for obtaining digital information on the three-dimensional geometries and properties of the object [2]. One CT image is referred to as a slice. It corresponds to what the object being scanned would look like if it were to be sliced along a plane. Images typically consist of pixels (picture elements) whereas a CT slice image is composed of voxels (volume elements). Tomographic imaging consists of directing X-rays at an object from multiple orientations and measuring the decrease in intensity along a series of linear paths [2].

Figure 1. PC-I, the first tomographic PET imaging device. From [7], reprinted by permission from Society of Photographic Instrumentation Engineers

Both PET and CT have their own advantages that when combined into one imaging modality allow for improved anatomical visualization. A brief overview
of PET, CT, and positron emission tomography-computed tomography (PET-CT) with a focus on hardware of the medical imaging systems then and now will be given in this review followed by advantages, limitations, and the potential future of PET-CT.

2. PET Scanners

2.1 Comparison of PC-I to Current Scanners

Current PET scanners include a circular detector placed around the table the patient lays on. This circular detector detects gamma rays more accurately as all incidents are captured on the detector and do not scatter around the room. By having a circular detector, this allows for the volume of the radioactive concentration to be shown.

PC-I was the first tomographic PET imaging device and is shown in Figure 1. It was built in 1969. The intent of the PC-I was to obtain focused images on planes parallel to the detector planes as well as obtaining tomographic images on transverse planes [7]. PC-I was the first to incorporate rotation and translation of the two detector banks as well as interpolative motion of the detectors to improve sampling and image quality.

Improving on the PC-I design, the next logical steps that followed included incorporating a circular or cylindrical array of detectors illustrated in Figure 2. James Robertson and Zang-Hee Cho are the first ones credited with constructing a ring detector system for a PET scanner in 1974 [7]. Current PET scanners include the ring of detectors and decreased imaging times as well as increased image quality since the first reports completed with the PC-I [11].

2.2 PET Quality Control

PET scanners are validated and controlled through a Jaszczak Phantom. An example of one such testing device is displayed in Figure 3. It consists of a main cylinder or tank made of plastic with several inserts. The phantom responds similar to how human tissue and organs should during a scan. This allows for testing, tuning, and maintenance of a device providing more accurate results [7]. Another benefit of a phantom is that it is more easily accessible and available than a human subject or cadaver to test a device.

Figure 3. Jaszczak Phantom used for quality control of nuclear imaging scanners [14]

3. X-ray Computed Tomography

3.1 Mathematical Theory

Beer’s Law is shown in Eq. (1) where $I_f$ and $I_0$ are radiation power, $c$ is absorption density, and $l_0$ is the path length. It measures the decrease in X-Ray intensity. Beer’s Law describes intensity reduction as a function of X-ray energy, path length, and the linear attenuation coefficient of the material. After scanning, an algorithm reconstructs the distribution of X-ray attenuation in the imaged volume.

$$I_f = I_0 e^{-cl_0}$$

Tomographic reconstruction then records the intensities and creates the images seen on the CT. The Radon transform developed by Austrian mathematician Johann Radon in 1917 showed mathematically that a function could be reconstructed from an infinite set of its projections. Later in 1937, Stefan Kaczmarz developed a method to find an approximate solution to a large system of linear algebraic equations [2]. This discovery led to the reconstruction method called ART (algebraic reconstruction technique) adapted by Sir Godfrey Hounsfield when he developed the first commercial CT scanner. An HU (Hounsfield Unit) is a quantity
named after Sir Hounsfield. Hounsfield unit (HU) scale is a linear transformation of the original linear attenuation coefficient measurement into one in which the radiodensity of distilled water at standard pressure and temperature (STP) is defined as zero Hounsfield units (HU), while the radiodensity of air at STP is defined as -1000 HU [12].

3.2 X-Ray Computed Tomography

Hounsfield invented the first commercial scanner in the United Kingdom at the EMI Central Research Laboratory. An image of the EMI scanner can be seen below in Figure 4. On October 1, 1971, the first brain scan was conducted at the Atkinson Morley Hospital in Wimbledon. The original 1971 prototype took 160 parallel readings through 180 angles, each 1° apart, with each scan taking a little over 5 minutes. The images from these scans took 2.5 hours to be processed by algebraic reconstruction techniques on a large computer [2].

Figure 4. An early version of the EMI scanner [3]

It is claimed that the revenue from record sales of The Beatles in the 1960s funded the development of the CT scanner at EMI. The first production X-ray CT machine was limited in making tomographic sections of the brain but acquired the image data in about 4 minutes. The computation time was about 7 minutes per picture. This scanner required the use of a water-filled Perspex tank with a pre-shaped rubber "head-cap" at the front, which enclosed the patient's head. The water-tank reduced the dynamic range of the radiation reaching the detectors (between scanning outside the head compared with scanning through the bone of the skull). The images were relatively low resolution, being composed of a matrix of only 80 × 80 pixels [2].

The first CT system that could make images of any part of the body and did not require the "water tank" was the ACTA (Automatic Computerized Transverse Axial) scanner designed by Robert S. Ledley, DDS, at Georgetown University, pictured in Figure 5. This machine had 30 photomultiplier tubes as detectors and completed a scan in only nine cycles, much faster than the EMI-Scanner. It used a minicomputer both to operate the servo-mechanisms and to acquire and process the images. Pfizer acquired the prototype from the university, along with rights to manufacture it. This unit produced images in a 256×256 matrix, with much better definition than the EMI-Scanner's 80×80 [2].

Figure 5. Robert Ledley with the ACTA whole-body CT scanner [9]

As the technology became more widespread, CT scanners also evolved. The 1990s saw a split into two major groups. Scanners were either portable, or fixed. Currently, scanners have vastly improved in all areas compared to the original EMI unit. Manufacturers have created scanners which take an image in less than 1 second. This is fast enough to allow for clear images of beating hearts and coronary arteries. Resolution has increased from 80 x 80 pixels to 1024 x 1024 or even 2048 x 2048 [4].

4. PET-CT

PET-CT combines the two imaging modalities discussed previously into a single gantry. Several sequential images from both devices are collected and combined into one single superposed image. This allows for the functional aspect of PET to be positioned on the anatomical aspect of the CT image. Figure 6 and 7 contain a side by side of a CT and PET...
image along with a PET-CT image below of the same body.

Figure 6. On the left a whole body CT scan. On the right a whole body MRI [6].

Figure 7. A PET-CT image of the same body from the previous figure [6].

David Townsend and Ronald Nutt initially proposed PET-CT systems. The National Cancer Institute funded the first PET-CT prototype for clinical evaluation and installed it at the University of Pittsburgh Medical Center in 1998. The first commercial systems were available by 2001. As of 2010 there were approximately 2,000 PET-CT scanners being used in the United States [1]. PET-CT scanners are becoming more common as two devices are replaced by one. PET-CT scanners can also be used as a standalone PET or CT scanner if only one modality is required for the desired image.

4.1 PET-CT Advantages

Using a PET-CT system is more beneficial than a standalone PET or CT scanner. One reason is that it allows for anatomic localization instead of relying solely on a contrast which is visible in CT or PET. Another benefit of the PET-CT scan is that the patient undergoes two exams in one sitting rather than at two different times. Depending on the scanner, some contain the CT and PET scanner elements in the same tube. Others contain the CT and PET scanners on opposite ends of the gantry and the patient simply has to be moved on a motorized bed to have the other exam administered. PET-CT scanners are replacing conventional PET scanners because the anatomical localization provides better diagnosis in oncology, radiation therapy, cancer staging, and surgical planning [1].

PET-CT has also helped in biopsy localization by allowing the physician a better view of questionable tissue, which increases the probability of the specimen collected for the biopsy to have a better representation of the patient’s ailments. There are examples of a standard PET not identifying tumors due to low radiotracer uptake. If the tumor does not uptake enough radiotracer on the PET it can display as a lesion on the CT. PET-CT scans also offer the ability to characterize radiotracer lacking abnormalities and incidentalomas, or unanticipated findings such as aneurysms or renal masses [5].

4.2 Limitations of PET-CT

One problem of the combined device is it is much more expensive than the standalone devices. Most new generation PET-CT machines with 128 detectors cost between $1.5 million and $2 million. A 128 slice CT scanner costs between $250,000 and $800,000 [14]. Another problem is also seen with standalone PET devices. The difficulty and cost of producing and transporting the radiopharmaceutical used for PET imaging impedes the widespread availability due to manufacturing processes. One tracer used to trace glucose is Fluorine-18, however it only has a half life of 2 hours and requires a very expensive cyclotron to be produced [4].

Patient comfort and safety is also very important to consider with medical imaging. One such consideration is that most PET-CT scanners are a long tube, claustrophobia may be a problem with some patients. Radiation exposure is also a problem with any form of nuclear imaging. A regular PET scan gives between 3 to 5 times the regular radiation exposure a person experiences over an entire year. For PET-CT it is often 5 to 10 times the annual rate.

5. Discussion

Despite the aforementioned problems with PET-CT, prices for scanners will continue to drop as vendors develop lower cost options and technology becomes more widely available. Furthermore, continued development of new radiotracers will lead to a growth in clinical applications of the PET-CT scanner.
enabling it to improve the fields of nuclear and radiological imaging.

One potential future for PET-CT lies in the growth and influence of machine learning. As the process of machine learning collects data from scans and images, it may help identify problem areas or aid in diagnosis. The aspect of machine learning may also suggest other areas to scan to aid and improve the quality of the imaging procedure. Another potential impact could be the rise of organ specific scanners. By making organ specific scanners, the patient can be exposed to less radiation, a shorter imaging time, and allow identification and diagnosis more quickly [8].

Although the outlook for PET-CT and medical imaging in general is very exciting, the progress from the origins of nuclear imaging and CT is tremendous. Exam times have been cut down significantly, and imaging quality has vastly improved. The millions of lives saved or improved by both standalone modalities greatly increase with the increased presence and future of PET-CT.

6. References


THE COMBINATION OF ARTIFICIAL INTELLIGENCE AND BIOMEDICAL IMAGING: IMPROVING THE EFFICIENCY OF DIAGNOSIS

Kevin Zeng
jwzeng2@uic.edu

Abstract
Due to lack of disease identification for developing countries, the combination of artificial intelligence and biomedical imaging can assist clinicians for diagnoses. On the other hand, combining artificial intelligence with traditional imaging techniques can highly improve the efficiencies of diagnoses from mammography or magnetic resonance imaging by using the learning abilities of systems from examples by applying algorithms involving deep learning. The aim of this paper is to analyze the possible algorithms and outcomes of the combination of artificial intelligence and traditional biomedical imaging techniques. By building the integrating system of medical imaging visualization and quantification system using technique of deep learning, the rate of error in diagnosis, such as human error, decreases rapidly. Also, machine learning can perform some tedious work, such as lesion recognition, anatomical region segmenting, and characterization of abnormality. The samples that are obtained from patients can instantly be compared with other cases from enormous databases to determine the symptoms of cancer earlier. More importantly, the techniques of artificial intelligence are efficient for some diseases, such as diabetic retinopathy, that need fast diagnosis and diagnoses in the emergency rooms. Furthermore, the techniques of artificial intelligence are beneficial to different groups of people. From the perspective of patients, they can obtain the results more quickly and accurately, and potential personalized treatments are generated automatically for them. From the perspective of clinicians, the required time of reading the films is reduced. The probabilities of side effects for different treatments can be generated easily, and different potential treatments can be compared in a short time to determine the best treatment solution for patients. Several algorithms that involve machine learning, such as Computer Aided Diagnosis, support vector machine, relevance vector machine, and brain mapping techniques, will be used to analyze the incorporation of artificial intelligence to biomedical imaging.

Keywords: Artificial Intelligence, Biomedical Imaging, Deep Learning, Machine Learning

1. Introduction
Currently, lack of disease identification causes many problems of diagnosis for patients in developing countries. According to the statistics from Fair Lawn Imaging, two third of humanity is not able to obtain the basic medical imaging modalities [17]. Some problems can be severe, such as late detection of cancer.

Biomedical imaging helps physicians by using different imaging modalities, such as x-ray, magnetic resonance imaging (MRI), and ultrasound. These kinds of techniques are common in the United States and diagnosis can be effectively made from the images obtained. However, developing countries still need more knowledge of using these kinds of imaging techniques. Educating staff in the hospital sometimes is unrealistic due to lack of resource, funding and staff, so the combination between AI and traditional bioimaging techniques can save time instead of teaching every individual staff and increase the degree of correct diagnosis. Recently, there has been a lot of research to combine artificial intelligence (AI) with biomedical imaging because AI can offer predictive algorithms with the application of deep learning, which can reduce the mistaken diagnosis and reduce problems of wrong diagnostic results.

In the past few years, AI has become a hot topic in the applied science field, including machine learning, deep learning, and artificial neural networks. The applications of these techniques can highly reduce the percentage of diagnosis. Deep learning is a technique that allows the system to identify the specific patterns that are learned from examples, such as inputting the scanning data into the predictive algorithm for the recognition of disease location [10].

The current situation of biomedical imaging involving AI highly depends on deep learning for recognizing patterns of disease. The core factors that make the
system of AI and biomedical imaging possible are the storage of data and the combination of data including electronic x-ray, MRI, ultrasound images, waveforms, and diagnostics determinations [10]. The algorithms that have been programmed into the system can recognize patterns of diseases, changes of the organ parameters, and trends of patients’ illness. The data in the system is obtained from recent electronic images from the hospital and imaging data that was obtained from patients in the past to make comparisons [10].

The purpose of this review is to give a brief overview of several AI algorithms such as Computer Aided Diagnosis (CAD), support vector machine (SVM), relevance vector machine (RVM), latent Dirichlet allocation (LDA), principal component analysis (PCA), and common spatial pattern (CSP). Then, examples of AI application to biomedical imaging will be presented. Furthermore, a discussion of comparing various AI algorithms will be given with the purpose to emphasize the importance of AI integration into medical imaging.

2. Logic behind AI algorithms

In this paper, several algorithms will be used to analyze the advancement of AI applied to biomedical imaging. Basically, the concept behind AI covers three areas, which are input, predictive models, and output. The simple logic behind the system is that the data of the images is input into the system (Figure 1) [19]. The images are converted and analyzed by algorithms that involve deep learning to perform tasks, such as pattern recognition and diseases characterization. The output of the algorithms can be shown directly on the display. The input x is input to the predictive model, and the predictive model manipulates the input variable to generate the output y [19]. The algorithm, or predictive model in this case, is formed by learning from enormous amounts of data with known input and output [19].

![Figure 1. Logic behind artificial intelligence. From [19], reprinted by permission from IEEE](image1.png)

In order to apply AI techniques to large data sets, the system needs to know what to find from a specific image. Learning from examples is a way to allow the system to “memorize” characteristics of the images; this kind of technique is called supervised learning and is the basic concept behind deep learning [10].

3. Examples of AI Applications to Biomedical Imaging

There are a lot of AI applications that are used for medical imaging, and the AI applications that are shown on this paper are the commonly used. A common method that applies AI is CAD.

![Figure 2. Logic behind Computer Aided Diagnosis (CAD). From [14], reprinted by permission from Elsevier](image2.png)

For example, CAD can highly improve the diagnosis for mammography. Normally, two observations of two radiologists of mammography can increase the accuracy of the diagnostic results but applying CAD can reduce time for comparison of results between radiologists and increase accuracy from human errors [19]. Basically, there are two steps for performing CAD for mammography analysis: the first step is it to apply an automated image analysis tool to identify the category of the image, and the second step is to characterize patterns for potential lesions [19].

The techniques of computer-aided detection (CADe) and computer-aided diagnosis (CADx) are also combined with CAD [19]. CADe is used to recognize the appearance of possible lesions on the image, and CADx is used to characterize the features of the lesion, the bright white spots on MRI images, that may come up in the future [19].

The indication of breast cancer is the detection of bright white spots that appear on mammograms. AI can aid in prevention of severe situations such as misdiagnosis because spotting localized areas or characteristics is a powerful strength of AI. The diagnosis of breast cancer from mammogram should be quick in order to avoid the appearance of severe situations. The indication of breast cancer is the detection of localized microcalcifications (MCs), which are small white areas that can appear on mammograms [19]. Due to the fact that radiologists sometimes may miss locating these white areas on the
images, the techniques of AI may highly improve the detection of MCs. Also, MCs are small, and the brightness and direction can be different among mammograms \[19\].

The AI tools which are used to detect these areas are SVM and RVM \[13, 15\].

The mammogram region contains a mixture of health areas and MC areas. Having the ability to separate values of different groups from a mixture, such as grouping point A, point B, and point D away from point C from Figure 3, is an important technique for the AI system. Using the traditional manipulation technique Fisher Linear Discriminant does not show the separations of different groups completely due to a failed assumption for the model, assuming the wrong distribution that eventually causes misclassification between point B and point D from part (a) of Figure 3 \[19\]. In part (a) of Figure 3, the outlier value D from Class 2 causes value B to pass the boundary between Class 1 and Class 2 \[19\]. Separating the wrong values for different groups can result in severe problems. For example, it can be wrong diagnoses for patients.

In order to prevent defining the wrong boundary between groups, an advanced technique called SVM can be used to generate the boundary only based on examples from training \[19\]. In part (b) of Figure 3, the situation becomes more satisfactory. The boundary T is shown diagonally in the middle between two groups and can successfully separate Class 1 and Class 2.

The concept of using SVM follows three steps. The first step is to form two groups by connecting the data points between each other. Two closest data points are selected by using constrained optimization and connected with a line for the second step. The final step is to generate the boundary that is perpendicular to the closest line from the second step \[18\]. By applying AI to mammography, AI can be used to discriminate between areas of healthy tissues and lesions.

The technique of RVM can also be used to discriminate different groups of data. RVM is a simplified version of SVM, and the advantage of this method is to reduce the manipulation steps, time, and cost for the system \[1, 19\]. The cost of applying RVM can be reduced to 35 times less than the SVM approach \[19\]. This approach is similar to SVM with the exception of using Bayesian technique. It starts with a model, which is shown in Eq. (1) below.

\[
f(x) = \sum_{i=1}^{N} w_i K(x, x_i)
\]

where \(f(x)\) is a kernel model, \(K\) is a kernel function, and \(w_i\) is kernel weight with assumption of Gaussian distribution and this model involves t-distribution \[19\]. By using t-distribution, most terms in the summation equation give zero terms, resulting in few nonzero terms to provide relevance vectors \[19\]. This approach, RVM, also avoids the accumulations of outliers that appear on the SVM to better generate the classifications of data points, which provide a more efficient technique for discriminating healthy tissues and lesions \[19\].

In the mammogram from Figure 4, part (a) shows the MCs mixing with other white areas, so radiologists have difficulty finding the MCs in the mixture. Part (a) serves as the input to the algorithm, SVM, to be analyzed. Part (b) shows the result of using SVM. This
image shows the whiter spots instead of localized white area, and the cloudy areas from part (a) disappear. Part (c) shows more clear results with yellow circles indicating the lesion positions.

Since the computational steps and time of RVM are reduced, the areas without MCs will quickly be excluded in the first step using the computational method of group classification [19]. Then, the algorithm of RVM only focuses on finding MCs in the potential areas [19]. Also, the yellow circle that indicate MCs, which are shown on Figure 4, can efficiently list the potential areas of lesions in a short time.

Since comparison between SVM and RVM is mentioned above, the applications of SVM and RVM for mammography will also be compared here. As shown on part (a) of Figure 5, even though the SVM is applied to discriminate the MCs, the results are still not clear to radiologists [19]. By comparing the results of SVM to RVM, the results of RVM show the MCs more clearly [19]. Especially for the results that are shown at the bottom right on part (b) of Figure 5, potential MCs should be indicated by a bright area and dark background.

![Figure 5](image.png)

Figure 5. (a) Comparison between the existence and absence of MCs using SVM (b) Comparison between the existence and absence of MCs using RVM. From [2], reprinted by permission from MIT Press

Another concept that is discussed in this paper is AI application to brain imaging data. The common method that is used for functional magnetic resonance imaging (fMRI), electroencephalography (EEG), and magnetoencephalography (MEG) is LDA with sparse Fisher [11]. LDA is a latent factor model to reduce dimensionality for classification and filtering through Dirichlet random variable [3]. LDA should be a better classifier due to the formation of covariance structure that is similar to Gaussian structure [3,6,9].

The problem with analyzing fMRI is that the input dimensions are high with low number of samples [4,12,16]. Brain mapping has the problem of using small number of samples to illustrate the spatial representation of the brain [19]. The important factor in generating the map of brain is to utilize the useful features on the examples with lowering the degree of dimension [11].

In order to perform dimensionality reduction, PCA or non-negative matrix factorization can be used to manipulate, without using features of class, in an unsupervised way [2,5,8,20]. Using PCA or non-negative matrix factorization can also reduce the source of noise to increase the signal-to-noise ratio (SNR), and the situation that is not nonstationary will also be removed [11].

Again, the supervised method can also be involved in brain mapping, and it is a way to exclude the information that is not related to brain mapping and extract useful information [11]. Here, the algorithm for extracting characteristics for brain mapping is CSP [7].

CSP utilizes the information that is marked to find the spatial filter of separating signal and is used to maximize signal with the reduction of the class that is not relevant to the signal [9].

Using Eq. (2), the dimension can be reduced efficiently [11].

\[
\Sigma_1 w = \Sigma_2 \lambda w \tag{2}
\]

Here \(\Sigma_1\) and \(\Sigma_2\) are signal covariance matrices and \(w\) and \(\lambda\) are eigenvectors of the system [11].

As Figure 6 shows, the green ellipsoid and the blue ellipsoid indicate two different sample classes [11]. The left side of the figure is the original input data, the middle portion is the illustration after using whitening, and the right portion is the result after using the Eq. (2) [11]. The right portion of Figure 6 also rotates the directions of the two sample classes. The dimensionality also is also reduced by using this technique.

![Figure 6](image.png)

Figure 6. Process of using CSP. From [11], reprinted by permission from Elsevier
Classifier can also be trained with a dimensionality reduction algorithm [19]. When the raw data is input to the model that incorporates the desired characteristics, then the brain map can have different features if different substances are introduced into the brain with different levels of voxel [19]. Figure 7 indicates the spatial activation pattern after using placebo and drug, and the color of the voxel indicates the level of drug and placebo separation [19]. One can realize that the effective areas become more obvious as the algorithm runs iteratively.

Figure 7. Illustration of using drug and placebo in the brain. From [19], reprinted by permission from IEEE

4. Discussion

As various algorithms have been compared, one should realize that finding good fitting models for traditional biomedical imaging techniques is one of the most important factors in the combination system of AI and biomedical imaging. Also, having simplified algorithms for processing imaging data is another important factor because the time to disease detection highly depends on the computational steps of the algorithms. If less computational steps are required for the system to process the imaging data, the system can make the detection or decision more quickly.

By comparing SVM to RVM, one can realize the advantage of having simplified algorithms. SVM has more computational steps comparing to RVM, and it still produces images that are not clear to radiologists. The images from SVM are still in low resolution comparing to the RVM. The images from RVM have better contrast compared to RVM. The MCs on RVM images are more recognizable.

After reducing the dimensionality of fMRI image data, the nonlinear models can be applied to the imaging data. So, one can realize that dimensionality reduction is the most important factor for classification on MRI.

There are various weaknesses of traditional biomedical imaging techniques. For example, the processing time of traditional biomedical imaging techniques are slow for high resolution images, and the processing time is fast for low resolution images. AI algorithms can better improve these weaknesses. Less computational steps algorithms need to be developed to minimize the time to detect diseases.

5. Conclusion

In the next few years, the integrated system of AI and biomedical imaging should be an important tool to assist clinicians with the determinations of diseases and diagnoses, and the integrated system will not replace the job of clinician, which is to determine potential disease of patient. The applications of AI for medical imaging still stay at the basic tasks, such as classification. Higher levels of diagnostic tasks, such as characterizing anatomical structure for more imaging modalities, still need to improve to better help the clinicians in the developing countries.

6. References


Abstract:
Orthopedic casts have been used for centuries, yet the research is still far from optimizing this basic medical device. While supplement devices, such as splints, have made their way into the market to aid the fracture healing process, the cast still plays a vital role in the recovery process for most patients. The most commonly used types of cast cause many secondary injuries, as the skills of the applier are a critical necessity to ensure that the patient heals properly. It is essential to understand current setbacks of the modern cast to properly create a plan of innovation. With technology developing rapidly, the use of 3D printers and scanners may revolutionize the orthopedic casts we are familiar with, for one which optimizes the child patient’s experience and decreases the healing process duration.

Keywords: Orthopedic, Cast, Fracture, 3D, Printed, Splint

1. Introduction
Fractured bones are one of the most common causes for Emergency Room visits, especially in children. 26% of all hand and forearm fractures cases are children, between the ages of 5-14 years old [14]. The purpose of a cast is to immobilize non-displaced fractures, maintain reduction of displaced fractures, and to protect operatively treated fractures. Techniques of casting seem to be less emphasized in many current orthopedic training programs which results in more complications from improper casting methods [10]. These injuries are on the rise for two reasons, increase in athletic participation and an increase of child obesity [14]. For the purposes of this paper, we will focus on casts utilized for the forearm and wrist, with a focus on children.

To properly understand current orthopedic cast developments, it is important to first understand the history behind it. The first orthopedic cast dates to the ancient Egyptians. While the currently used orthopedic cast has come a long way from its original development by the Egyptians, it has gone practically unchanged for the past hundred years.

The Ancient Egyptian design for the orthopedic cast used a bark tree splint that was tightly wrapped in linens. This was the earliest known method of treating bone fractures. Common issues might have been infections and blood circulation. An ancient Greek physician, Hippocrates of Cos, would later go on to write about the importance of casts and develop the basis of physical therapy. He often wrote about the importance of these exercises, which we now know prevents muscle atrophy. The cast was constructed from common natural ingredients, which were mainly animal-based products. To create that hardened outer shape, casts would be made from flour, animal fat, and eggs. To construct the shape of the cast itself, wax, cardboard, cloth, and parchment would be used. Arabian doctors used lime derived from sea shells and albumen from egg whites to stiffen bandages. All these designs had many hygiene concerns along with high possibilities of infections due to the materials used and the low frequencies of showers taken [13].

Between the Arabian design and the modern plaster design, many more casts came in play, all being produced from animal by-product and being susceptible to the same issues. The derivative of the plaster cast of Paris is the cast design still used worldwide today. It originally involved a patient putting their leg or arm in a wooden box. This box would later be filled with plaster, which results in an extremely restrictive cast, forcing the patient to be bed bound for months. That is when Antonius Mathijsen, a doctor in the Dutch army, had a revolutionary idea in 1851 and decided to dip linen in the plaster and wrap it around the patient’s fracture. This allowed the cast to be light enough to go about daily activities and was, in a sense, individualized to fit an individual’s unique fracture. For the same design, in the past few decades, materials like knitted fiberglass bandages with polyurethane or thermoplastic have been used, with little difference in the experience of the wearer. Modern medicine coupled with bioengineering insight is developing at a faster rate than ever before. Thus, it
is important to innovate a more cost productive and efficient model of a cast.

2. Associated Injuries with Fractured Bones

When trying to understand the function of a device, such as the orthopedic cast, it is essential to fully comprehend the circumstance that the device is being used in. The wearer of the cast may not only be suffering from a broken bone but may also be dealing with associated injuries. The purpose of a cast is to aid the healing procedure of the bone and is a key aspect on whether the patient will have long term damage. When an individual break a bone, there are some common associated injuries that go along with the actual fracture(s) such as: internal bleeding, neurapraxia, vascular injuries, compartment syndrome, and infections. Most fractures can lead to osteomyelitis. In more serious, but not rare, cases the following injuries might occur: hemorrhagic shock, axonotmesis, neurotmesis, distal limb ischemia, fat embolism, rhabdomyolysis, hyperkalemia, infections, contractures, sensory deficits, paralysis, amputation, and osteomyelitis. For a more detailed description on some of these fractures see section 10.

The job of a cast is to prevent movement of the joint or bone while it heals, which quickens the recovery process. Yet, often there are complications both due to the cast design and healing process overall. Some long-term complications of breaking a bone include: joint instability, this can increase the chance of osteoarthritis; stiffness/impair range of motion, this is the cause of misaligned articular cartilage and prolong immobilization; nonunion or delayed union, this is when the fracture has not yet healed and can be due to incomplete immobilization, partial disruption of the vascular supply, or personal patient health issues; malunion, when the bone heals but with deformities which is usually due to inadequate stabilization during the recovery process; osteonecrosis, when part of a fracture fragment can become necrotic; and osteoarthritis, this disrupts the surface of the joint and causes joint malalignment and cartilage degeneration [8]. Many of these long term, and in many cases, permanent, health issues are due to the restraints in the plaster cast design [1].

3. Flaws in Current Traditional Cast Design

The question of how a cast can help solve all these issues is hard to answer because many of these issues can’t be solved by correcting flaws in the plaster design but rather are due to current cast limitations. There are some ways the cast design can address the problems patients face and seven possible solutions are listed here.

1. Increasing movement to aid physical therapy
2. Providing ventilation to the skin surface to prevent bacterial or fungal growth
3. Creating a cushioned interior to prevent pressure on bones (especially for thinner patients who may have a more delicate frame)
4. Ability to measure synovium fluid
5. Being able to constantly check and have a medical professional re-adjust the cast if needed
6. Creating casts with lighter materials, increasing ease of daily hygiene
7. Providing needed support without restricting blood flow

However, these problems of hygiene, ability of re-adjustment, and needed ventilation tend to be more prevalent in third world countries where material standards are lower and medical regulations are not up to par.

Wearers of the modern cast design have complained for years about common issues like the ‘stuffiness’ and heat inside, itchiness, keeping the cast dry, cleaning themselves with a cast on, weight of the cast, pain of the cast chipping inside, and inability to move muscles inside easily, amongst others [8]. This leads to increase number of follow-up visits to the hospital. There are multiple cast related issues that patients visit the ER for, but the breakdown for patient visits is as follows: 29% due to a wet cast, 10% due to a damaged cast, 23% due to having a tight cast, 13% due to a loose cast, and 10% due to a new or different pain [10]. There are many small details that factor into the cause of these ER visits. There are a few types of complications that can occur, such as pressure-induced complications, heat-induced complications, water-induced complications, and friction-induced complications [10].

Pressure-induced complications occur when there is a focused pressure over a small surface area. This focused pressure often leads to pressure sores which are caused by lowered areas of perfusion. This issue can be avoided by insuring proper hand positioning and avoiding uneven edges or wrinkles in the lining when applying the cast. It is especially important to be aware of pressure and tightness when applying a fiberglass. The medical official should insure that the index layer is properly molded to prevent tightness which can lead to vascular and soft tissue damage.
The second type of complication known as heat-induced complications are usually caused by thermal injuries that occur when the cast is improperly cured, or the cast exceeds 24-ply in thickness. The main cause for these complications is usually the dip water. Often the dip water is too warm, as temperature regulation prior each application is not feasible for many clinical settings. Another mistake which is made is placing an unhardened cast on a pillow. The heat produced from exothermic reactions in the material will trap the heat, increasing the probability of a thermal injury.

The next mentioned complication is water-induced complications. When a cast encounters a liquid substance, in most cases water or juices, the number of complications rises dramatically. Wet casts usually cause skin infections, maceration, and disrupt the structural integrity of the cast. Patients often overlook small water exposure, hence most damage isn’t noticed till after the cast is removed. This is where preventive methods are essential, such as the availability of commercially sold products, such as cast protectors and waterproof liners.

Finally, friction-induced complications can be due to improper cast application, which can result in multiple types of skin complications. These complications can be minor, such as skin excoriations, to more severe issues, such as pressure ulcers which can require surgery. The issues are usually caused specifically due to poor padding. Increasing the amount of padding can dramatically reduce the amount of pressure from certain areas.

4. Choosing the Type of Cast

Currently, the two types of casts typically used in hospitals are made from either plaster or fiberglass. A plaster cloth’s advantage is that they are easier to mold, in comparison to fiberglass counterparts; however, there are drawbacks of plaster too, such as its poor resistance to water and its low strength-to-weight ratio which makes it heavier than a fiberglass cast [14]. Due to this reason, being lighter and a less bulky fit, fiberglass is often chosen for children. When applying a cast, there are a few things medical professionals must keep in mind: type and amount of material used, type of soft roll, presence of absence of stockinet, final cast shape, and position [14].

For forearm injuries, two forms of casts are usually placed upon patients, above-the-elbow (long) and below-the-elbow casts (short). While most professionals prefer to give above-the-elbow casts when dealing with a forearm fracture, both types of casts show the same amount of displacement of the bone. The below-the-elbow casts resulted in lower costs, pain, swelling, complications, and higher patient day-to-day comfort. In comparison, the short cast only compares well to a long cast if it is well-molded by the applier [1]. Hence the cast type should technically be chosen upon cast-applier’s experience for optimal healing results.

5. Cast Removing Issues

Cast saws are usually the tool used to cut the cast open. Caution is taken to ensure the patient’s skin is not damaged in the process. But no matter how safe the tool, with improper use it can result in complications, such as thermal injuries and abrasion. For example, adding four layers of padding instead of two, can drastically decrease the temperature, by about 8 degrees Celsius [10]. Safe removal of a cast requires many key factors, such as thickness of the cast, experience of cast saw user, and dullness of the blade amongst others [14]. The saw often also causes fear amongst children and trauma. Due to this fear, children often have more movement during the process which can increase likelihood of injury.

6. Splints as an Alternative to the Cast

In 2006, the medical industry had a “break through” with removable splints, which started to become used in higher frequency rather than the typical cast. Splints are defined as ‘rigid or semi-rigid, non-circumferential material used to reinforce a soft dressing or provide additional support for immobilization of the body part being treated’. They are usually made of a rigid material, such as metal, plastic, wood, plaster, or even folded newspaper [13]. These splints would be custom made to properly aid the individual’s bone structure but they can only be used for well-align fractures with low risk of displacement. They are removable and adjustable (usually with straps). This allowed individuals to clean themselves by removing the cast and being able to do physical therapy exercises. Other benefits include: cost saving, comfort, room for physiologic swelling, can be removed for redressing of soft tissue wound, grants ability to scratch itches, grants ability to attend occupational therapy, benefits patients with sensory integration dysfunction, and higher patient satisfaction compared to cast [14].

When regarding forearm injuries, there are a few common types of splinters used: aluminum; coaptation, where two plaster slabs are put on opposite sides of the forearm and held together using dressing; velcro; and thermoformable, a material which is heated and shaped to fit the patient’s forearm. They are
usually reserved for buckle and non-displaced fractures, as they produce the same results with the same risks as a cast [14].

While this idea seems good in theory, it doesn’t always work well in application because when used on children, they would often remove it. Due to the thick and dense material of the cast, it would retain heat and irritate the skin upon long wear. While this did remove the issue of cleanliness and infections, casts would often be taken off for a longer duration of time and this negatively affected bone healing. This ‘medical trend’, as the design is often described by medical professionals, did not continue for long and while occasionally used, most doctors choose to give the old-school cast.

7. Future Technology: 3D Printed Casts

As 3D printers become more readily available, technology has found new ways to advance the current design of a cast. A graduate of Victoria University in New Zealand did just that by developing a scanner and 3D printing a cast [5]. The design mimics small honeycombs, the same design that can be found inside your bones. Due to this structural design, there is plenty of air ventilation, which prevents the stuffy feeling. Many of the skin problems patients face can be eliminated due to the decreased amount of surface area covered up [5].

The cast is 3D printed, which gives a new direction for customized casts. While the prototype used a hacked Kinect, an X-box gaming device which scans the player, a more sophisticated scanner is currently being built to better serve its purpose and get approved for professional use. The cast design has been said to cut down time of healing, by around 70%, and reduce the chances of an infection by three-fourths [5]. Since the cast is individualized, it brings up the initial cost until 3D printers become readily available not only in medical facilities in the United States but also internationally. This could be why the design has not progressed much since 2014, although many others have tried to copy the design and improve upon it. While a great design, it cannot be replicated on a larger scale with the technology and supplies hospitals currently possess [7].

8. Orthopedic Cast Market

While there has not been a new applicable invention in the orthopedic cast industry in the past few decades, the market is very large and is continuously growing with the prevalence of obesity and osteoporosis, due to the diabetes and easier access to proper medical intervention. Per Transparency Market Research, there is an expected increase in the global casting and splinting market value from $1.8 billion USD in 2015 to $3.1 billion USD by 2024 [11]. With the increase in health problems, there is a projected increase in the healthcare sector investments. Geographically, the global orthopedic braces/supports and casting/splints market is currently the largest in North America, but Asia is quickly catching up as countries start to modernize with better medical facilities [9]. This means a new cast design can be scaled on an international basis rather than just nationally [11]. There is a higher demand than ever before for innovation in this field.

9. Conclusion

The current cast design, a stem from the plaster cast of Paris, is decades behind other medical devices used in the medical field, especially in orthopedics. Demands for casts are on the rise as medical facilities improve internationally, resulting in easier access to such devices for many individuals. Health concerns like obesity are playing a huge role in the projected growth of the industry.

The current orthopedic cast is not changing to modern needs and is causing medical problems that can be prevented. Many secondary injuries are caused by limitations of the cast and improper care. Innovations such as the 3D printed casts are pushing the glass ceiling of this field. Children are often the victims of improper casting methods, processes that can be completely prevented with the use of a 3D printed cast.

As engineering continues to reduce the cost of facilitating secondary devices such as scanners, CAD design programs, and printers, it is possible to see a drastic increase in accessibility of such designs. Other designs continue to be researched on the daily but as we attempt to revolutionize the cast, it is important to factor in cost, current resources, and scalability. The demand for plaster casts is growing and so should research in plasters and bandages respectively.

10. Glossary

1. Axonmtesis: Nerve injury characterized by disruption of the axon and myelin sheath by with preservation of the connective tissue fragments, resulting in degeneration of the axon distal to the injury site; regeneration of the axon is spontaneous and of good quality.
2. Compartment syndrome: A condition in which increased pressure in a confined anatomic space adversely affects the circulation and threatens the function and viability of the structure therein.

3. Contractures: The chronic loss of joint motion due to structural changes in non-bony tissue. These non-bony tissues include muscles, ligaments, and tendons.

4. Distal Limb Ischemia: Caused by embolism or thrombosis, or rarely by dissection or trauma. Thrombosis is usually caused by peripheral vascular disease (atherosclerotic disease that leads to blood vessel blockage), while an embolism is usually of cardiac origin.

5. Fat Embolism: A process by which fat tissue passes into the bloodstream and lodges within a blood vessel.

6. Hyperkalemia: Describes a potassium level in blood that's higher than normal. Potassium is a critical nutrient to the function of nerve and muscle cells, including those in the heart.

7. Neurapraxia: Failure of nerve condition in the absence of structural changes, due to blunt injury, compression, or ischemia.

8. Neurotmesis: Partial or complete severance of a nerve, with disruption of the axon and its myelin sheath and the connective tissue elements.

9. Osteomyelitis: An infection that can affect any bone in the body. Most often affects long bones (leg and arm), the spine, and foot bones. The infection can be bacterial (usually from Staphylococcus) or, more rarely, functional.

10. Rhabdomyolysis: Caused by direct or indirect muscle injury. Results from the death of muscle fibers and release of their contents into the bloodstream. This can lead to serious complications such as renal failure.

11. References


THE USE OF MEDICAL IMAGING TECHNIQUES IN DIAGNOSIS OF ALZHEIMER’S DISEASE
Yaseen Saleh
yasaleh2@uic.edu

Abstract
Alzheimer’s disease is currently the sixth leading cause of death and disability in the United States, directly killing close to 100,000 people each year. Yet, unlike other leading causes of death such as heart disease, which have been subject to successful treatment campaigns, mortality due to Alzheimer’s disease has increased substantially over the last decade. One major barrier to the treatment of Alzheimer’s disease has been the lack of effective biomarkers for diagnosis. Currently, the only definitive method of determining if a patient has Alzheimer’s disease is a post-mortem evaluation for Amyloid-beta plaques and Tau tangles. Instead, diagnosis is often made in light of perceived cognitive decline, and more recently, information from different medical imaging techniques. The primary imaging technique used is magnetic resonance imaging for structural visualization. Magnetic resonance imaging can be used to rule out other possible causes of dementia such as a tumor. Furthermore, it can also be used to visualize shrinkage in certain brain regions like the hippocampus that is typical in Alzheimer’s disease. Scientists, however, have not agreed upon a threshold normal volume for these structures, making it difficult to make a diagnosis based off of this information. Positron Emission Tomography has also emerged as a useful tool to aid diagnosis. Some studies have suggested that Alzheimer’s disease is associated with reduced glucose metabolism in areas key to learning, making fluorodeoxyglucose- positron emission tomography scans an attractive option for diagnosis. Recently, several radiotracers have been shown to associate with Amyloid-beta plaques, allowing for live visualization of plaques during a positron emission tomography scan (although plaques are not necessarily indicative of Alzheimer’s disease). As indicated previously, the lack of definitive biomarkers has hindered the use of these imaging technologies in diagnosing Alzheimer’s disease. However, the use of multiple modalities in tandem has allowed for better sensitivity in diagnosing Alzheimer’s disease than purely the use of cognitive examinations.

Keywords: Alzheimer’s Disease, Medical Imaging, Magnetic Resonance Imaging, Positron Emission Tomography

1. Introduction
Alzheimer’s disease (AD) is the most common form of dementia, accounting for 60 to 80 percent of all cases. It is currently the sixth leading cause of death in the United States, resulting in the deaths of close to 100,000 people each year. More than 5 million Americans are currently living with AD and suffering from its effects, characterized by significant loss in memory and cognitive abilities due to neuronal degeneration [1]. This suffering is exacerbated by the lack of a cure, as only short-term palliative treatments are available today.

Over the last few decades, other leading causes of death, like heart disease, have been subject to massive campaigns that have resulted in drastic reductions in mortality rates. However, despite AD’s devastating impact, less research and resources have been devoted to its study, and its impact is expected to rise. By 2050, it is estimated about 50 million Americans could suffer from AD, while healthcare costs due to AD (currently at $259 billion) could rise to $1.1 trillion [1].

1.1 Symptoms and Pathology of AD
Alzheimer’s disease is typically described in three stages, outlining progressive deficiencies in memory and cognition. In the earliest stage, the mild stage, it can be difficult to notice differences as changes may be restricted to a person having trouble coming up with the words they want. In the later moderate AD stage, a person may experience consistent memory loss that disrupts an individual’s daily life, such as an inability to remember important events. This is accompanied by subsequent complications in problem solving and familiar task completion. Mood changes are also frequently observed. In the final stage, a person with AD loses their ability to interact with the environment
and communicate, often requiring 24-hr care for the remainder of life [1].

The two hallmarks of AD are the presence of extracellular amyloid plaques and intracellular neurofibrillary tau tangles in the brain (Figure 1). Amyloid plaques are formed from the extracellular aggregation of amyloid-beta (Aβ) peptide, a product of amyloid precursor protein (APP) processing, into a quaternary storage structure. Tau tangles form as a result of hyper-phosphorylated tau proteins dissociating from microtubules and aggregating intracellularly. Pathology in AD begins with amyloid deposition followed by tau neurofibrillary tangles and eventually neuronal loss, which can be seen on the organ level through a reduction in brain volume. Furthermore, amyloid deposition is believed to begin in the hippocampus, spreading eventually to the deep layers of the frontal cortex and then the rest of the brain, explaining the disease progression from memory loss to general loss of cognitive function.

Currently, there is no cure for AD and the causes are fervently disputed. In the past, amyloid plaques have been touted as neurotoxic, but plaques have been shown to have poor correlation with neurotoxicity, explaining the failure of numerous vaccine trials targeting amyloid [2]. The leading theory in AD research is that Aβ peptides possibly in oligomeric or monomeric form are the proximal neurotoxins leading to numerous new studies.

Figure 2. Silver stain of brain tissue from an AD patient. AD is diagnosed post-mortem through the presence of extracellular amyloid plaques (red, left) and intracellular neurofibrillary tau tangles (black, right) [2]

1.2 Diagnosis of AD

In addition to the absence of a cure, AD treatment has been severely hindered by the lack of conclusive diagnostic methods. There are no definitive biomarkers like blood sugar levels that can be measured to diagnose hyperglycemia and diabetes. The only definitive way to diagnose AD is a post-mortem analysis of brain tissue illustrating the presence of plaques and tangles. Instead, diagnosis of AD in vivo is often made in light of perceived cognitive decline and memory loss. The issue here is that observing such cognitive decline requires attentive longitudinal observation and can be very subjective. Accordingly, patients may only seek a physician’s evaluation after family members notice a significant loss in function and memory. By this time, the disease has likely progressed into its later stages, and the patient may have suffered significant neuronal loss, limiting the available treatment options. Even if a treatment were developed that could stop the progression of AD, there is still no way to regenerate lost neurons, as tissue regeneration in the brain is very limited.

Recent advances in medical imaging have allowed for visualization of brain tissue in ways that were previously impossible in vivo. Accordingly, these medical imaging techniques have been adopted to help diagnose AD. For instance, MRI is often used to visualize the neuronal atrophy discussed previously, while new radiotracers that associate with amyloid have allowed for PET scans to view plaques within the brain [3]. These techniques provide new insight into disease diagnosis. However, the lack of understanding of the causes of AD and the lack of biomarkers have prevented these techniques from being used as definitive diagnostic methods because the information they give is believed to be largely correlative and subjective. Accordingly, medical imaging is currently used to provide secondary confirmation to the principal criteria of cognitive decline used traditionally to diagnose AD. The information given by medical imaging (specifically PET and MRI) and its limitations in diagnosing AD are the subject of this article.

2. Magnetic Resonance Imaging in AD Diagnosis

One of the primary medical imaging techniques used in AD diagnosis is magnetic resonance imaging (MRI) for structural visualization. MRI’s utility lies in its ability to produce images of the brain with high contrast between different soft tissues, which can allow the physician to look for atrophy of gray matter as well as rule out other possible causes of dementia.

2.1 How Does It Work

MRI depends on a property known as nuclear spin, which is the rotational movement of a subatomic
particle like a proton or neutron around its axis. The spin of a particle is given a quantum number that is either $\pm \frac{1}{2}$. Accordingly, nuclei with equal numbers of protons and neutrons cancel out their overall spin. Rather, it is the nuclei with an unequal number of protons and neutrons, like hydrogen’s most common isotope protium, that is important to MRI because these nuclei have unpaired spins. Because of the abundance of hydrogen nuclei in the body (whether in water or lipid molecules), this provides a useful property to target for differential tissue properties [4].

Because these nuclear spins represent a moving charge, these nuclei also have magnetic moments. Thus, when a strong magnetic field is applied, the magnetic moment will attempt to align itself with the magnetic field. However, since the nuclear moment is restricted to certain orientations, it is not possible for the nuclear moment to align parallel with the magnetic field. Instead, the interaction between the field and the misaligned moment generates a torque, causing the proton (in the case of protium) to precess around the axis of the magnetic field at a characteristic frequency, known as the Larmor frequency. The sum of individual magnetic moments and the slight preference of protons aligning themselves in the lower-energy parallel spin to the magnetic field give rise to an overall longitudinal magnetization in the direction of the field [4].

To generate the MRI image, a short radiofrequency field pulse is applied to the region of interest at a 90-degree angle to the external magnetic field, resulting in a magnetization perpendicular to the original field axis and a torque that causes the overall nuclei magnetization to precess around the original field axis (Figure 2). This precession leads to the variation of magnetic flux with time, inducing a voltage in MR detectors, which consist of conductive loops like copper wires [4].

After the end of the pulse, the overall magnetization will relax to its original longitudinal orientation. Measurement of the recovery of the longitudinal magnetization is known as the T1 recovery time, while the loss of the transverse components is known as the T2 recovery time. This is where the tissue contrast is generated in MRI, because different tissues show differential recovery times, allowing for high contrast and high-resolution images. For example, water protons and lipid protons have drastically different resonant frequencies, leading to different recovery times, and subsequently good resolution between grey and white matter (where myelin is abundant) in the brain [4].

### 2.2 Uses of MRI in AD Diagnosis

MRI provides a useful method of visualizing structural integrity and volume within the brain. Alzheimer’s disease is characterized by significant neuronal atrophy and reduction in brain volume due to compromised synapses and neuronal degradation. This can be visualized with the use of MRI in progressed forms of the disease (Figure 3).

Pathology in AD is believed to begin in the hippocampus before spreading to the cortex, explaining the loss of memory as a primary symptom. Accordingly, visualization of such drastic cortex shrinkage as in Figure 3 may only be possible in advanced stages of the disease. This is problematic because even if there were a treatment to stop the progression of disease, there is no method of regenerating lost neurons nor their functions. Accordingly, some studies have focused on using MRI to measure hippocampal volume reduction, as this may be a method of early diagnosis. Focusing on brain volume, however, is hotly disputed because of the significant baseline variation among people [3].

Another prominent use of MRI in AD diagnosis is to rule out other possible causes of dementia. For instance, if an older patient comes to a physician with significant memory loss, the physician might order an MRI to rule out the possibility of a tumor in the
hippocampal region. In addition to the hippocampus, there are numerous regions in the brain that are associated with memory, meaning that a tumor pushing on one of these regions, fluid buildup in the brain, or even a stroke can result in memory loss. MRI can resolve many of these, as tumors often show differential magnetization recovery times from normal tissue. Because of the lack of established biomarkers for AD, this role of MRI is critical, because physicians may not be able to definitively determine AD, but they can at least rule out other common causes of dementia that have established treatment protocols. A brain tumor, for instance, might require surgical removal.

2.3 MRI Sensitivity and Specificity

Questions have been raised regarding the sensitivity and specificity of MRI in diagnosing AD. Sensitivity here is defined as the ability to diagnose AD in all the patients who actually have AD, while specificity is defined here as the ability to avoid diagnosing patients without AD. Sensitivity and specificity are measured using Eq. (1) and Eq. (2) respectively.

\[
\text{Sensitivity} = \frac{\text{True Positives}}{\text{True Positives} + \text{False Negatives}} \quad \text{(1)}
\]

\[
\text{Specificity} = \frac{\text{True Negatives}}{\text{True Negatives} + \text{False Positives}} \quad \text{(2)}
\]

As part of the recent Alzheimer’s Disease Neuroimaging Initiative, several studies have been done to measure the sensitivity and specificity of using brain volumes measured with MRI to diagnose AD through a computer software, constructing receiver operating characteristic (ROC) curve plots such as the one in Figure 4. Both the sensitivity and specificity have proven to be quite poor with both being often below 70% when diagnosing a cohort containing cognitively normal individuals and AD patients [6,7]. This trend can be even worse when attempting to diagnose in a cohort comprising of individuals with Mild Cognitive Impairment (MCI) and AD patients. Individuals with MCI can often convert into AD patients, but this is not always the case. In general, measuring brain volume in the hippocampus fared better than other regions, but this advantage was lost in studies that attempted to discriminate between AD and MCI. Overall, this means that if diagnoses were made purely based off of MRI volume measurements, diagnoses could miss more than 30% of AD patients and misdiagnose similar numbers as well. Recent studies have attempted to use machine learning involving large cohorts to predict conversion from MCI to AD. These studies, seem to be more promising, reaching predictive accuracy of up to 90% [8]. However, such techniques are still under development.

2.4 Complications with MRI Diagnosis

As discussed previously with the ROC data in Figure 4, the predictive capabilities of diagnosing an individual with AD based off of brain volume of different regions measured through MRI is extremely lacking due to the poor sensitivity and specificity. This results from an inherent issue with structural-based diagnosis: there are no agreed upon volume standards for a cognitively normal individual. In other words, humans have a wide variability in terms of brain volumes and the volumes of different structures, meaning “shrinkage” is largely dependent on a
person’s baseline as well as their age. Unless the physician has access to longitudinal MRI data over the course of the patient’s life, it is difficult to determine what qualifies as too small for a normal individual. Structural-based diagnoses can also be hindered by the relatively poor knowledge of the mechanisms behind different neurodegenerative diseases. Such mechanisms may not be seen on a macro level in terms of shape and volume, meaning it would be impossible to rule out other neurodegenerative diseases with similar symptoms based off of an MRI measurement.

3. Positron Emission Tomography in AD Diagnosis

Positron Emission Tomography is another technique used to improve AD diagnosis accuracy. PET scans have been used in different ways depending on the tracer. For example, using a fluorodeoxyglucose-PET scan provides contrast with areas with reduced glucose consumption. Other tracers co-localize with amyloid making in vivo plaque visualization possible. However, once again the lack of biomarkers damages the utility of PET in diagnosing AD.

3.1 How Does It Work

Positron Emission Tomography is a nuclear imaging technique. In PET, a radioactive isotope like $^{18}$F is generated using a cyclotron and injected into the patient. This isotope will undergo radioactive decay, such as is shown in Eq. (3), resulting in the emission of a positron (a positively charged electron) and a neutrino.

$$ ^{18}F \rightarrow ^{18}O + e^+ + \text{neutrino} \quad (3) $$

This positron will travel through the tissue before annihilating with an electron, resulting in the emission of two antiparallel 511 keV gamma rays perpendicular to the collision. Once the gamma rays leave the body they are detected by scintillation crystal detectors that convert the signal into visible light, which is then translated into a computer-generated image. Depending on the radiotracer used, PET scans can provide contrast based both off of differential tissue attenuation and the body’s metabolism of the radiotracer. In other words, different tissue types will attenuate the gamma rays within the body differentially because of variations in density and other properties, while using a radiotracer that is metabolized by the body will lead to localizations of signal from the area the body is metabolizing it [4].

3.2 $^{18}$F-Fluorodeoxyglucose-PET Scans

A commonly used radiotracer for PET scans that is also used in AD is $^{18}$F-Fluorodeoxyglucose (FDG). FDG is very similar to glucose, differing only by a fluorine in place of one of glucose’s hydroxyl groups. Like glucose, cells that are metabolically active will uptake FDG and phosphorylate it in the first step of glycolysis to keep it in the cell. However, unlike glucose, FDG cannot be further catabolized in the remaining steps of glycolysis, resulting in a radiotracer that is taken up by cells undergoing glycolysis and remains there without being metabolized. FDG is often used to image tumors because cancer cells have a higher rate of metabolism, resulting in a higher localization of FDG in these cells, and subsequently a higher signal intensity. It is used for similar reasons in AD diagnostics. Studies have shown in AD patients that brain tissue associated with memory and learning have reduced glucose metabolism [3]. Accordingly, FDG-PET is often used to look for decreased rates of glucose metabolism compared to a cognitively normal individual (Figure 5).

3.3 Pittsburgh compound B (PiB) – PET scan

![Image of PiB-PET scan](image)

Figure 6. PiB-PET scan of an AD patient (left) and cognitively healthy individual (right). Red indicates an area of high amyloid deposition while blue indicates an area of low amyloid deposition [2]
The other prominent use of PET scans in AD diagnosis is to visualize amyloid plaque deposition. The blood-brain barrier has been an obstacle to this, but recently radiotracers have been found that have a high permeability in the BBB. Pittsburgh compound B (PiB) is one-such radiotracer that has been shown to co-localize with amyloid-beta structures in the brain (see Figure 6). Fluorbetaben, Fluorbetapir, and Flutemetamol are three other new radiotracers that have also been shown to co-localize with amyloid-beta structures in the brain. These radiotracers allow for visualization of one of the two hallmarks of AD in vivo, an unprecedented advance for the use of medical imaging in AD diagnosis. Radiotracers that co-localize with tau-proteins and neuroinflammation are also currently under development [3].

3.4 PET Sensitivity and Specificity

![ROC plots for diagnostic accuracy of predicted short-term AD conversion from MCI using (a) FDG-PET and (b) PiB-PET.](image)

Studies have also been underway to measure the diagnostic accuracy using PET techniques. So far, FDG-PET has showed similar levels of sensitivity and specificity to MRI-based diagnostic techniques in predicting conversion from MCI to AD. Using FDG-PET to predict this conversion has a sensitivity of close to 78% and a specificity of 75%. This is an improvement compared to the MRI-based predictions, but still not accurate enough to be the main source of diagnostic prediction. PiB-PET has shown to be far more sensitive in predicting conversion of MCI to AD reaching sensitivities of 94%. However, PiB-PET struggles with a very low specificity of 56%, meaning the number of false positives using PiB-PET is just as high as the number of true negatives [9,10]. Accordingly, both these techniques struggle to reach the accuracy needed for regular diagnostic use, although ROC data for PET are limited because it is still a relatively new technique in the field.

3.5 Complications with PET Diagnosis

As discussed previously with the ROC data in Figure 7, the predictive capabilities of diagnosing an individual with AD based off of either reduced FDG uptake or the presence of amyloid plaques is still not at an accurate enough level to be the main diagnostic tool in the field. PET runs into similar problems as MRI. While there is a general pattern of reduced glucose use in AD, there is no definitive measure, making FDG-PET a largely correlative technique. Furthermore, as stated previously, while amyloid plaques are a hallmark of AD, they also have poor correlation with neurotoxicity, disease progression, and cognitive decline. It is not unusual for an elderly individual to have amyloid plaques and be cognitively normal. Moreover, AD patients with similar levels of amyloid plaques can be at entirely different stages of disease progression, making PiB-PET another technique that suffers from the lack of understanding with respect to AD mechanism.

4. Conclusion: MRI? PET?

Both MRI and PET provide useful information that can help a physician diagnose AD. MRI can help the physician to see neuronal atrophy and complications with structural integrity within the brain. PET techniques allow the physician to measure abnormal tissue function as well as visualize a major hallmark in AD. However, both of these techniques are severely lacking when it comes to predictive power and diagnostic accuracy. These techniques only seem to be accurate when comparing AD patients in advanced stages of the disease to control patients, which renders the techniques somewhat less useful because by that time the patient will have significant cognitive and behavioral deficits that are irrecoverable and blatantly apparent to the physician. The main appeal of medical imaging in AD diagnosis is the desire for early
detection so that intervention can be done prior to significant neuronal loss. Furthermore, it is not clear that these issues in accuracy will be resolved in future development because they do not result from computer processing power or the resolution of the techniques which will likely be improved. Rather, the failures of these techniques result from the fact that they measure “trends” relating to AD that are quite subjective and have no agreed upon thresholds. The issue seems to be not the techniques, but the understanding of the mechanisms behind AD. Once the causes and mechanisms are understood better, it will be easier to find a technique that can target those mechanisms for early detection. Currently, it does not seem like MRI will be the way forward, but PET could have a future if a radiotracer can be developed that co-localizes with causative elements of AD.

That being said, while these techniques may not have the desirable diagnostic accuracy to revolutionize AD diagnosis, they still can and will provide useful correlative information in vivo that can serve as affirmation of more definitive diagnostic techniques. Currently, research is underway to find possible AD biomarkers in the CSF or plasma, such as oligomeric Aβ quantities, that can provide a threshold for diagnosis. If such a biomarker can be found, then the combination of a spinal tap, cognitive examination, and PET scan for amyloid or tau pathology could provide the diagnostic certainty that has eluded physicians in the past.

7. References


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).
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 Italic 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.

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.

\[ E_{(\rho_{0})} = m^a(s-h) + P_o + A(t)^a * \Sigma(s) \]  

Note: Equations must be entered using equation editor.

4. Page Limit
Maintain a page limit of 5-10 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)


