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Foreword

I am happy to present the ninth volume of the *UIC Bioengineering Student Journal* on the behalf of the Department of Bioengineering. This is a great platform for both graduate and undergraduate students to enrich their technical skills by serving as an author, reviewer or being a part of editorial board, since last two years I have been involved as an editor, author and Editor in Chief. It gives me great pleasure working with talented Bioengineering students who give their best to publish highest quality journal.

I am also happy to share that, this year we came up with two volumes, graduate and undergraduate volume which was due to huge number of article acceptance and participation by the authors, which happened for the first time since the start of UBSJ. I am also sure that each new issue would come up with great innovations and would be of better quality than last.

I would like to thank our Faculty advisor Dr. Richard L. Magin for his constant support to create a student-led journal. I would also like to thank our Department Head Dr. Thomas Royston for continually supporting the journal with sufficient finances and giving us freedom to host release parties every year. Lastly, I extend my heartfelt thanks and congratulate all the authors, reviewers and the editorial board for their dedication and working tirelessly to make this year’s issue a success.

Mounica Bandela.
Editor-In-Chief
Graduate Volume.

Senior Associate Editor
Undergraduate Volume
Abstract
This paper reviews the uses of Optical Tweezers concerning biological and biomedical areas. After a brief description of the basic principle of operation and of the most relevant technical aspects, the most significant advancements that led to the growing popularity of this technique are illustrated. The advantages and limitations of the technique and a comparison with other methods are discussed. Some examples of relevant or novel experiments using Optical Tweezers are presented, along with hybrid techniques in which Optical Tweezers are used in combination with other methods.

Keywords: Optical Traps, Microscopy, Lasers, Micro-manipulation

1. Introduction
1.1 Brief Description
Optical Tweezers (OTs) refers to a device that exploits the optical radiation pressure of tightly focused laser beams to hold microscopic dielectric particles in place for manipulation. The name is also used with reference to the numerous variants in the more comprehensive apparatus shown later, and to the different techniques which employ the basic trapping components. OTs are one of the three most popular force spectroscopy techniques together with Atomic Force Microscopy (AFM) and Magnetic Tweezers (MTs). The basic principle underlying OTs was introduced by A. Ashkin in the 1970s, and was developed later on by Ashkin and S. Chu, during the 1980s. Chu was eventually awarded the Nobel Prize in 1997 for his work with OTs. Different setups, such as Holographic OTs (HOTs), Optical Stretcher (OS), non-Gaussian OTs, can be exploited to achieve numerous degrees of manipulation. The trapped particles can be also used as “handles” to move other objects in the experimental stage. OTs nowadays allow precise measurements of forces, torques and displacements in the order of pN and angstrom (Å) resolution [2,16,18].

1.2 OTS in Biomedical Applications
In recent years, OTs have gained an increasing popularity in biological and biomedical applications for a number of reasons:

a) Low level of invasiveness [6,19].
b) Easy combination with other techniques [6].
c) Recent developments allow for time and spatial resolution to include the natural biological systems’ scale [8,20].
d) High resolution in terms of force and displacements in the order of Å and pN [6,8,19].
e) Contact-less interaction with living cells.
f) As a single molecule technique, allows for the particular phenomenon to be observed, and avoids rare events being masked by the population averaging typical of other techniques [10].

These factors explain why today OTs are a state-of-art technique used to investigate properties of single cells [1,12,18,19], down to single molecules [6,12], sort cellular populations [17], create experimental environments for simulations or perform cellular micro-surgery, cell positioning and optical guiding [19].

A few other examples of OTs applications in the biological field:

a) Quantitative study of molecular motors proteins.
b) Investigation of the mechanical properties of biopolymers.
c) Quantitative assessment of forces developed during chemical reactions and cellular structures’ properties.
d) Study of adhesion and inter-cellular interactions.
e) Cell microsurgery [17], sorting, transportation and positioning.
f) Tissue engineering, stem-cell study and in vitro fertilization.

In other fields, OTs are used for microfabrication, study of colloidal solutions properties, micro-rheology, non-equilibrium thermodynamics [8], investigation of artificial polymers’ properties and microstructure and nanostructure characterization.
2. Rationale

2.1 Physical Principle

For the sake of simplicity, only the ray optics description of OTs working principle will be provided here. This corresponds to the case in which the particle’s diameter is much larger than the working wavelength ($d \gg \lambda$). In the case in which the particle’s diameter is much smaller than the working wavelength ($d \ll \lambda$), we are said to be in the Rayleigh regime (dipole approach, [19]), or—as it is often the case—we are in the intermediate situation in which $d \approx \lambda$.

![Figure 1. Ray optics representation of OTs working principle, focused trap [4]](image)

OTs rely on a simple physical principle in which the momentum transmitted by the incident beam to the particle will change direction because of the different refractive index of the material. These different entering and exiting momentum will result in a net force, which, by Newton’s third law, will correspond to an equal and opposite force onto the particle. In the presence of a strong gradient of beam intensity and of a tightly focused geometry, the total force will be null (equilibrium condition) only if the particle is placed in the middle of the beam, slightly downstream respect to the waist. Any displacements from this position will result in a net force pulling the particle back in place, called trapping force (see Figure 1).

Also, note that to achieve a stable trapping along the axial direction, a tight focus is required [19], so that the axial trapping force can compensate the scattering force that would push the particle downstream (see Figure 1). Therefore, OTs require a focusing lens with a high numerical aperture (NA).

2.2 Trap Stiffness

It is often convenient to schematize the trapped bead behavior as an ideal spring in 3D. Provided that we stay quite close to the focus region (more specifically, when displacements are smaller than half the radius of the particle within the focal region, according to [19]), the relationship between trapping force and distance from focus will be linear. This up to a certain extent where the bead escapes the trap. Once the trap stiffness is determined or given, the relation between trapping force and displacement will be of direct proportionality, as in Hook’s spring law given by Eq. (1) [6,8,10,12,19] (see Figure 2).

$$\vec{F} = -k\vec{x}$$

(1)

The constant $k$ is called trap stiffness and it is usually of the order of pN/µm. To compute $k$, we must calibrate the system. Trapping forces, and therefore trap stiffness, depend on:

a) Laser source intensity (although for biological applications it is customary not to exceed order of 100mW, to avoid photodamage), see [6,19].

b) Particle characteristics (shape and refractive index difference respect to the medium).

c) Laser focus mode.

![Figure 2. Hookean spring OTs model [11]](image)

2.3 Trap Calibration

There are two main ways of calculating $k$ to calibrate the trap, which are drag force and Brownian motion methods. Drag force method relies on measuring the displacement induced by a known flow of fluid in the specimen chamber [6,12,19]. Brownian motion method instead uses displacements caused by thermal vibratory motion. The power spectrum ($S_x(f)$) of the displacements has a cutoff frequency directly related to stiffness [6,10,19].
2.4 Setup

Apart from the very optical trap, there are other elements that are crucial in designing the system to achieve optimal performance. In Figure 3 the reader can observe a schematic of the various system components. A more detailed discussion can be found at [9]. The main components are:

i. **Laser beam**: Usually NIR or IR range for biomedical applications. The most popular is diode-pumped Nd:YAG for single cell applications [12,18,19].

ii. **Beam expander**: To exploit all the collimator width.

iii. **Beam steering**: Moves the trap (and so the trapped particles) in the scenario. It can be done also with multiple traps in the most sophisticated systems.

iv. **Dichroic mirrors**: Directs the laser beam to the sample plane and to the position detector.

v. **Microscope objective and condenser**: Creates collimated beam and gathers light, respectively.

vi. **Position detecting device**: e.g. A Quadrant Photodiode (QPD), detects particle displacements.

vii. **Light source and camera**: Acquires a video recording.

Furthermore, other aspects need to be considered to properly perform experiments. These aspects are environmental conditions, position detection method, and trap steering method [6]. They are important in that they affect the repeatability, resolution and accuracy achievable.

Environmental conditions such as temperature, microfluidics, and chemical composition of the specimen chamber are of particular relevance when dealing with biological substrates (see Discussion section). The environment must be carefully controlled to avoid external influences (vibrations, refractive index fluctuations due to gas movements).

Position detection method must be carefully chosen according to the specific requirements (real-time, space and time resolution, cost), the most appropriate method for lateral position detection: QPD (as in Figure 3), image processing techniques, laser interferometry are the most common techniques. The most popular and precise one is back-focal plane interferometry, where the Position Sensitive Detector (PSD) is placed in a plane which is optically conjugate to the back-focal plane (BFP) of the condenser [10]. Regarding axial position detection, fluorescence or laser interferometry could be used or image processing techniques. For a more complete discussion see [9].

Trap steering method can be achieved in many ways. The most appropriate one will depend on the number of traps, range of deflection, scanning velocity, one could choose among simple lenses system (as in Figure 3), galvo-mirrors [12] or Optical Deflectors (ODs) (both acousto-optic (AOD) and electro-optic (EOD)) and Spatial Light Modulators (SPL). The last method is known as Holographic OTs (HOTs), because it relies on the creation of holographic patterns from diffractive elements [19].

3. Rationale for OTs Advancement in Biomedical Applications

3.1 OTs technical advancements

Nowadays OTs enjoy a growing popularity for biomedical applications, that can be largely attributed to some key advancements that integrated the most basic setup presented in 2.4.

a) The improvement of Position Sensitive Devices (PSDs).

b) The creation of multiple types of beam profiles and multiple traps.

c) The growing number of integration possibilities of OTs and other techniques.

The improvement in the PSDs is mainly technological and related to a general development of the sensor’s performances such as accuracy, noise immunity, response bandwidth and will not be discussed here in detail. The most critical aspect concerning OTs is the improvement of resolution. For a more complete discussion on the topic, see [8].

![Figure 3. Basic OTs setup.](image-url)
Non-Gaussian Beam Profiles have been introduced instead of traditional Gaussian profile (TEM\(_{00}\)) and allow for customizable number of trapped particles and modalities [19]. In particular, we point out: Bessel Beams (allow for simultaneous particle trapping in the transverse plane), and Laguerre–Gaussian Beams (or optical vortex, allows 3D trapping as well as torque application).

Multiple Beams can be either dual (only two beams) or properly multiple. They can be created by: splitting the initial beam, using computer generated holographic images (CGH), or by rapidly scanning the scene with a single beam (multiplexing or time sharing) [19]. For a list of the methods used to achieve multiplexing, see 2.4. Dual beams can be classified in parallel (to create interference patterns, as in [2]) or counter-propagating, used to perform the so called Optical Stretching, as in [13].

### 3.2 Integration with Other Techniques

According to [6], ease of integration is one of the most relevant characteristics that led to the present popularity of OTs. OTs can be easily and naturally integrated with other single-molecule and single-cell techniques, and with other optical imaging methods. OTs' flexibility is also one of their most peculiar advantages that makes them a good alternative respect to other force spectroscopy techniques [10]. In the following section the reader can find a more detailed list of the techniques that have been used in combination with OTs.

### 4. Examples of Applications

In this section are briefly listed some classes of experiments that have been performed using OTs.

i. **Motor Protein Strength**: A typical setup is depicted for measuring the strength of the myosin head pulling the actin filament in Figure 4 [15]. Similar setups have been exploited for kinesin and more complex structures such as cilia and flagella [6,8]. For more on this topic see [14].

ii. **RBC Mechanical Characterization**: Red blood cells (RBC) membrane properties are greatly different among healthy and sick individuals. To quantify these differences, various setups exploiting OTs have been experimented. For a complete list of RBC experiments featuring OTs, see [19]. One interesting experiment is the one performed by [18]. Here, OTs were exploited to study how the stiffness properties of RBC change between healthy and tumorous cells. This is potentially useful in finding new advanced diagnostic tools for cancer.

iii. **Cell Rotation**: In [1] an experiment is reported in which a mammalian cell was stably rotated using HOTs and generating two traps. This controlled manipulation may be very useful for tomographic sectioning of single cells.

iv. **Cell Transportation**: In [17] an application is reported in which a robot-aided HOTs system can automatically position groups of cells in micro-surgery scenario. The work combines both multiple OTs with simultaneous and continuous manipulation and some predictive tracking, based on image processing. This can be exploited for lab-on-chip devices and high throughput micro-fluidic instruments.

v. **Bio-polymer Mechanical Characterization**: OTs can be successfully employed to study mechanical properties of bio-polymers such as DNA or RNA [8]. The setups can be passive, meaning we simply record the trapped bead displacement derived from conformational changes that the molecule is undergoing (such as enzymatic transform or folding/unfolding), or active, measuring the tensile or torsional stresses and thus the rigidity of the nucleic acid. A well-known experiment of this kind is described in [16].

![Figure 4. Myosin head force measurement (upper part showing OTs apparatus, lower part showing binding sites vs. observations). From [15], reprinted by permission from Springer Nature](image)

### 5. Technique Limitations

Despite their numerous advantages, OTs have some limitations, and only some can be partially overcome by future developments, as pointed out in [8].
5.1 Noise

Sources of noise can be experimental or Brownian [8]. Experimental noise is noise deriving from the setup. These can be fluctuations in the specimen stage or other instruments that cause motion of the trapped bead, fluctuation of the optical trap itself and of laser power source. All these problems can be addressed through better instrumentation, always according to [8]. The two main methods used for reducing their effects are: noise subtraction from the signal (whether through noise estimation or feedback), and setup immunization (customarily archived through careful construction of the stage). Brownian noise is noise deriving from the thermal agitation. This kind of noise can never be completely eliminated, and depends on a variety of factors, not all of which can be varied to meet the requirements. Therefore, it represents the ultimate resolution limit of the OT system. Nevertheless, the effect of Brownian noise can be reduced by adjusting some other experimental parameters such as bead diameter [8].

The Signal to Noise Ratio (SNR), is the most popular measure for determining the acceptability of the noise level. In the case of a single optical trap with a bead connected to a single biological substrate (the tether), SNR can be described by Eq. (2) [8].

\[
SNR \leq \frac{k_{\text{tether}} \Delta l}{\sqrt{4k_B B W T y}}
\]  

Here, \(y\) = drag coefficient of bead, \(k_B\) = Boltzmann’s constant which is equal to 1.38*10^{-23} m^2·kg·s^{-2}·K^{-1}], BW = measurement bandwidth [Hz], T = temperature (in K), \(k_{\text{tether}}\) = stiffness of the biological substrate [Pa], \(\Delta l\) = displacement. For example, increasing substrate stiffness and reducing bead size both decrease the influence of Brownian noise on the results. Contrarily to what one may expect from the thermal origin of Brownian noise, little can be done by manipulating the temperature, since biological systems operate in a narrow range of temperatures.

5.2 Photo-damage, Heating, Opto-mechanical Interplay

There are three main drawbacks in the use of OTs. Heating and photo-damage are potentially damaging effects on the substrate. They can be caused by high irradiances from laser beams (up to MW/cm², [19]). Opto-mechanical interplay is a possible source of error that is almost always neglected that may undermine the reliability of certain experiments if not properly quantified. Photo-damage (or opticution) refers to the breaking of molecular bonds caused by laser absorption. The heating effect concerns the temperature increase induced in the environment by laser and can range from 1-2 °C for a typical 100mW laser beam [19]. To avoid opticution, one should take care to use wavelengths to which biological structure are transparent (such as IR), and limit direct exposure. Also, it seems that working in anaerobic conditions decreases the incidence of photo-damage [19]. Another option would be to use counter-propagating laser beams. To avoid heating, one could use an experimental environment rich in heavy water D₂O [19], that absorbs less at IR range, so that the temperature rise is modest. For a damage-less method for trapping single cells, see [12].

Opto-mechanical interplay [19] refers to the deformation deriving from the radiation pressure applied by the photonic flux of the laser onto membranes, that is usually neglected, but that may affect the reliability of the results – especially when such membrane properties are under examination.

5.3 Need for Controlled Environment

In addition to what was discussed in 2.4, additional care must be taken when employing OTs for biological specimens. The reasons for this are that biological specimens can survive only in a relatively narrow range of chemo-physical conditions such as temperature, pH, and ionic concentrations, and are sensitive to the smallest changes in the parameters mentioned above (e.g. enzyme properties typically vary according to temperature and pH). Therefore, if we do not set the environmental conditions such that they match the physiological ones, the results may be unreliable, [19].

Another aspect linked to what was said above in regard to intercellular interactions is that when dealing with OTs, we’re often manipulating few cells at a time, so we lose information from complex cellular interactions [6]. Most recent techniques allow for manipulation of more complex biological systems, but there is still room for more advancement in this sense.

6. Discussion

K. C. Neuman and A. Nagy report a comparison between OTs and other common methods used to investigate single cells or molecules, shown in Figure 5. Following the discussion of [10], only the comparison between Atomic Force Microscopy (AFM), OTs and Magnetic Tweezers (MTs) will be presented here.
All three techniques rely on the attachment of the specimen to intermediate objects, that are directly manipulated. The assessment of the forces depends critically on the ability to detect the displacements of one of the two ‘handles’. All the techniques share some of the problems affecting the ‘measures’ reliability such as mechano-acoustic vibrations, electric noise, and temperature drifts.

 OTs are the most versatile of the techniques here discussed, and one of the most precise [10]. MTs have a much more restricted range of manipulation, lacking the ability to measure very fast or small movements [10]. AFM is simple to implement, but the range of forces typical of biological events is most often out of the capabilities of the system, namely because of the high cantilever stiffness [10].

Table 1. Comparison between single cell investigation methods. From [10], adapted by permission from Springer Nature

<table>
<thead>
<tr>
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<th>Optical Tweezers</th>
<th>Magnetic (electromagnetic) tweezers</th>
<th>AFM</th>
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<tbody>
<tr>
<td><strong>Spatial resolution (nm)</strong></td>
<td>0.1-2</td>
<td>5-10 (2-10)</td>
<td>0.5-1</td>
</tr>
<tr>
<td><strong>Temporal resolution (s)</strong></td>
<td>10^{-7}</td>
<td>10^{-6}-10^{-7}</td>
<td>10^{-2}</td>
</tr>
<tr>
<td><strong>Stiffness (pN)</strong></td>
<td>0.005-1</td>
<td>10^{-4}-10^{-4}(10^{-5})</td>
<td>10-10^{4}</td>
</tr>
<tr>
<td><strong>Force range (pN)</strong></td>
<td>0.1-100</td>
<td>10^{-5}-10^{5}(0.01-10^{6})</td>
<td>10-10^{4}</td>
</tr>
<tr>
<td><strong>Displacement range (nm)</strong></td>
<td>0.1-10^{2}</td>
<td>5-10^{5}(5-10^{6})</td>
<td>0.5-10^{4}</td>
</tr>
<tr>
<td><strong>Probe size(µm)</strong></td>
<td>0.25-5</td>
<td>0.5-5</td>
<td>100-250</td>
</tr>
<tr>
<td><strong>Typical applications</strong></td>
<td>3D manipulation Tethered assay Interaction assay</td>
<td>Tethered assay DNA topology (3D manipulation)</td>
<td>High-force pulling and interaction assays</td>
</tr>
<tr>
<td><strong>Features</strong></td>
<td>Low-noise and Low-drift dumbbell geometry</td>
<td>Force clamp Bead rotation Specific interactions</td>
<td>High-resolution imaging</td>
</tr>
<tr>
<td><strong>Limitations</strong></td>
<td>Photodamage Sample heating Nonspecific</td>
<td>No manipulation (Force hysteresis)</td>
<td>Large high-stiffness probe Large minimal force Nonspecific</td>
</tr>
</tbody>
</table>

Despite the advantages OTS offer, there are some drawbacks associated with respect to other methods such as AFM or MTs. First of all, they rely on purely optical principle. Therefore, they need highly pure and homogeneous environment, precise and stable beam generation and steering methods to ensure good precision and resolution [10]. While the latter can simply be a matter of good quality instrumentation, the first one may imply a radical change in the experimental environment that may affect the reliability of the results (i.e. rarely biological samples in their native condition meet these requirements, and so we cannot truly test them in their most authentic form). The need for controlled environment has been also introduced in 5.3. Also, they are highly non-specific, meaning there is no way to prevent any other dielectric particle to be trapped by the beam, creating false signals and spurious potentials [10]. This is not a problem with other techniques. Moreover, the range of forces is limited to 0.1 –100 pN [10], because for lower values we would lose stability, and for higher values too high power would be required. Also, the range of measurable displacements can be very small (only 150nm) if more sophisticated techniques such as dynamic position control are not employed. Finally, another crucial disadvantage are the heating effects and opto-mechanical interplay, which were further discussed in 5.2. A summary of different features for OTS, MTs, and AFM is shown in Table 1.

One of OTs most remarkable features is the possibility to naturally integrate them with other techniques so to create new inspecting instruments. OTs are easily used in combination with fluorescence microscopy [3,5,19], atomic force microscopy (AFM), Raman spectroscopy [19], micro-fluidics, lab-on-chip devices [19]. According to [8], the invention of an ever-growing number of hybrid techniques employing OTs was one of the crucial points needed to bring this method to a state-of-art status.

7. Conclusions

OTs basic principle dates back to the 1970-1980s but is one of the leading single cell and single molecule techniques in the current biological and biomedical repertoire. OTs nowadays enjoy growing popularity, thanks to some specific technologic advancements, especially in beam modalities, steering methods (including multiplexing/timesharing), active feedback methods to control traps and reduce noise, position detection strategies (both in the sensor and processing parts), integration with other methods to achieve a growing number of hybrid techniques that can better meet the demands of the scientific community.

The basic principle of OTs is very simple, but nonetheless almost endless variations of the basic setup are possible (number and modality of beams, number of trapped objects, trapping configurations, steering methods, calibration, position detection and processing method, combination with other techniques). This allows OTs for an extremely wide range of possible uses in the biological and biomedical fields and explains the great diffusion they have today. Although the method has some disadvantages (deriving mainly from the exclusively optic nature of the technique), much works has also been done to
overcome such limitations. Nowadays OTs can effectively compete with other popular techniques such as AFM and MTs and stands out for flexibility and adaptability. There is no doubt that future developments could improve the technique further. According to Nobel Prize winner Steven Chu: ‘I would not be surprised if in the coming decade there could be a truly great discovery using optical tweezers, or some other single-molecule technique’ [7].

8. References


TRANSCRANIAL DOPPLER SONOGRAPHY: EARLY DIAGNOSIS OF STROKE IN ASYMPTOMATIC PATIENTS
Josephine R. Masandika
jmasan3@uic.edu

Abstract:
Transcranial Doppler Ultrasound is a non-invasive imaging method used to visualize cerebral arteries. It is performed by placing a low frequency (<2MHz) transducer on thin parts of the cranial bone in order to visualize blood flow in the brain including flow in carotid arteries. Carotid stenosis is the cause of 85% of ischemic strokes, caused by a blood clot blocking a blood vessel and depriving parts of the brain of blood. Dr. Pandya et al. conducted a study using Transcranial Doppler Ultrasound to investigate cerebral vascular reserve to identify carotid artery stenosis and evaluate stroke risk in asymptomatic patients. There are multiple treatment options for carotid stenosis that leads to transient ischemic attack. The American Heart Association recommends revascularization procedures such as carotid endarterectomy and endovascular stent placement. Such procedures are controversial for asymptomatic patients because of their cost, the invasive nature of procedures, and potential complications (~35% fatal). Identifying risk factors in asymptomatic patients before they experience transient ischemic attacks will minimize invasive medical intervention and minimize stroke fatalities over time. The focus of this paper is to explore how the non-invasive, convenient, and low cost of Transcranial Doppler Ultrasound will help identify carotid stenosis through cerebral vascular reserve in asymptomatic patients. The low cost and relatively straightforward Transcranial Doppler Ultrasound method will identify patients who could benefit from extreme intervention as well as those who could benefit from medical therapy alone.

Keywords: Transcranial Doppler Ultrasound, Cerebral Vascular Reserve, Stroke, Carotid Artery Stenosis

1. Introduction

Stroke is the number five cause of death and the leading preventable cause of long-term disability in the United States [1]. The highest mortality for strokes occur outside of the hospital, particularly because most people do not know the symptoms of stroke. Stroke is particularly dangerous in women because the symptoms present differently in women than in men. In a study by Pandya et al., asymptomatic patients were evaluated for stroke risk through investigation of Cerebrovascular Reserve (CVR), specifically blood flow in the Middle Cerebral Artery (MCA), a common artery in the brain used to identify patients who are at high risk of carotid stenosis. Carotid stenosis is the cause of 85% of ischemic strokes, caused by a blood clot blocking a blood vessel and depriving parts of the brain of blood. In this study, CVR impairment was determined by measuring cerebral blood flow velocity before and after vasodilatory stimulus. Patients who showed CVR underwent immediate revascularization, while those who did not have any impairment underwent medical therapy [2, 4].

The imaging techniques used to assess the degree of carotid luminal narrowing in both asymptomatic patients and patients who have undergone stroke include Positron Emission Tomography (PET), Computed Tomography (CT), and Magnetic Resonance (MR). Although all these methods are reliable, PET and MR perfusion use radioactive tracers while CT uses x-ray. Transcranial Doppler (TCD) Ultrasound (US) is the only imaging modality that carries no radioactivity risk and has no long-term damage. In addition, TCD US can be used bedside and takes a very short time to generate an image compared to PET, CT, and MR. Using a low-cost imaging modality such as TCD US will allow doctors to identify the patients for whom invasive medical intervention such as revascularization outweighs the risk of complications (high risk) as well as patients who will benefit from medical therapy (low risk) [4, 6].

In addition, studies have shown that TCD US has 100% specificity and 93% sensitivity in identifying landmarks in the MCA. These are high values compared to MR which has 74% specificity and 46% sensitivity [2, 6]. Because of these properties TCD US is the first imaging techniques used in emergency rooms if a patient has symptoms that indicate stroke.

Considering that the highest mortality for strokes occur outside of the hospital, identifying risk factors
early on may increase the accuracy of diagnosis and reduce mortality rate. The use of TCD US will also allow doctors to decide which treatment option is both cost-effective and gives the patient the best health outcome. In addition to becoming a preventative measure for asymptomatic patients, TCD US can be used bedside which makes it easier for doctors to detect changes in cerebral blood in real time and prevent stroke reoccurrences, which improves prognosis for stroke patients.

The purpose of this review is to highlight the importance of TCD US in diagnosing strokes in asymptomatic patients thus reducing the high mortality rate for strokes [7]. I will focus on TCD US as it is used to analyze CVR impairment in patients with varying levels of luminal flow narrowing. I will also discuss the effects of treatment methods based on methods of diagnosis and determine the optimal diagnostic method for strokes.

2. TCD US Methodology and Diagnostics

TCD US is performed by placing a low frequency (≤2MHz) transducer on thin parts of the cranial bone in order to visualize blood flow in the brain, including flow in carotid arteries. Physically, the signals from the transducer are reflected back by the erythrocytes in the blood. When ultrasounds hit a moving object, the reflected waves show a shift- Doppler shift (f) that is directly proportional to the velocity (v) of the object. The time difference between the time of the signal to time of reflection is proportional to the depth that the initial signal reached.

The formula used to determine Cerebral Blood Flow Velocity (CBFV) is derived from the general Doppler principle is shown in Eq. (1).

\[ v = \frac{(c \times f)}{(2 \times f_0 \times \cos \theta)} \]  

(1)

In this equation c is the speed of the US wave emitted from transducer, f_0 is the emitted wave pulse frequency, and \( \theta \) is the angle formed by reflected wave relative to the initial US emission beam [2]. CBFV is estimated by Eq. (2).

\[ \text{Mean CBFV} = \frac{[PSV + (EDV \times 2)]}{3} \]  

(2)

Here PSV is peak systolic velocity and EDV is end diastolic blood flow velocity.

For the purposes of this paper, CBFV is synonymous to CVR. Higher mean CBFV values indicate arterial stenosis disease or vasospastic reaction which is a stroke measurement. A low CBFV value may indicate increased intracranial pressure (ICP) useful for Traumatic Brain Injury (TBI) management, or brain stem death. "By the Bernoulli principle, the correlation between velocity and pressure exerted by blood flowing, is characterized by a decrease of pressure exerted by the fluid as the velocity of flow increases" [2]. This means TCD US can estimate the diameter of the arteries using blood velocity as well as the location of any obstructions which helps assess whether a patient is at risk for stroke.

3. Brain Anatomy and CVR

The most frequently observed intracranial vessel is the MCA. The Internal Carotid Artery (ICA) and the External Carotid Artery (ECA) make up the terminal branch of the common carotid artery. The ICA divides into the MCA and the Anterior Cerebral Artery (ACA). Roughly 60-70% of the ICA blood is sent to the MCA; therefore, blood in the MCA accounts for a majority of the blood in the ipsilateral hemisphere of the brain [2, 4]. If blood flow is occluded for any reason, the brain is at risk of experiencing a Transient Ischemic Attack (TIA). If the blockage bursts the arteries, then a hemorrhagic stroke has occurred. Smaller emboli may travel to the heart and lead to Myocardial Infarction (MI), brain aneurysm, and in some cases multiple TIAs that lead to brain death.

TCD US estimates CVR by noninvasively analyzing blood flow in the MCA. A patient is considered at risk for stroke if blood flow through the MCA is compromised.

4. TCD US-Informed CVR Assessment Stroke Model

To assess whether Cerebral Vascular Reserve (CVR) determined by TCD US is the best diagnostic option for patients at risk for stroke, I will consider a study by Pandya et al., which uses TCD US as a diagnostic tool compared to medical therapy and revascularization therapy. It is important to note that the use of TCD US as proposed in this paper is relatively new. There are currently few to no viable studies that compare current imaging modalities to TCD US for stroke diagnosis. The study presented here [4] uses TCD US-informed CVR assessments to determine the optimal diagnostic tool for stroke as well as the most efficient treatment method. Findings from this study are an important first step in considering the efficacy (financial, quality of life, and otherwise) of TCD US as a diagnostic tool for asymptomatic patients.
A recent study by Pandya et al., used a computer-simulated model that projected stroke events, life expectancy, quality-adjusted life years (QALYs), and lifetime health care costs for a group of asymptomatic patients. The model considered five degrees of luminal narrowing for patients with carotid stenosis ranging from minimal narrowing (0-49%) to 100% narrowing-complete CVR impairment (Figure 1) [4].

The annual probability of progression to greater luminal flow narrowing was 5.2%, while the annual probability of regression to lower luminal flow narrowing was 4.5%. Patients with 100% luminal flow narrowing had no chance of regression. This means patients are more likely to get worse than get better. As indicated in Figure 1, 100% luminal flow narrowing only led to stroke or death (related or unrelated to a stroke). In this study, probability statistics were based on previous stroke studies that focused on luminal flow narrowing. Patients who progressed through two categories within a year were placed at a higher risk of stroke, and patients in advanced categories of luminal flow narrowing (90%-99% or 100%) were assigned immediate revascularization. For this model, stroke occurrence increased risk of death by 14%. CVR-based revascularization led to regression from the highest narrowing degree down to 0-47% narrowing. However, patients still had a 3% probability of experiencing restenosis [5].

Cost-effectiveness analysis showed that the CVR strategy was optimal with a cost effectiveness threshold of $100,000 per QALY) for all ages, except for in patients starting at age 60 years, when immediate revascularization was optimal [4]. It should also be noted that patients over 60 have unstable life years even without considering stroke risks. However, for the purposes of this study, the life years only considered the risks that come with stroke events, and cost estimation only considered the cost for stroke treatment and management.

Table 1. Lifetime per-person cost-effectiveness results for patients in a simulated study. From [4], reprinted by permission from The Radiological Society of North America

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Stroke Events</th>
<th>Life Years</th>
<th>QALYs</th>
<th>Costs ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Starting population aged 70 years (base-case analysis)</td>
<td>0.141</td>
<td>12.481</td>
<td>9.456</td>
<td>14.597</td>
</tr>
<tr>
<td>Medical therapy</td>
<td>0.109</td>
<td>12.727</td>
<td>9.924</td>
<td>16.953</td>
</tr>
<tr>
<td>Immediate revascularization</td>
<td>0.087</td>
<td>13.017</td>
<td>9.940</td>
<td>20.850</td>
</tr>
<tr>
<td>Starting population aged 60 years</td>
<td>0.200</td>
<td>18.337</td>
<td>13.942</td>
<td>19.240</td>
</tr>
<tr>
<td>Medical therapy</td>
<td>0.160</td>
<td>18.698</td>
<td>13.208</td>
<td>20.372</td>
</tr>
<tr>
<td>Medical therapy</td>
<td>0.129</td>
<td>18.982</td>
<td>13.246</td>
<td>23.643</td>
</tr>
<tr>
<td>Immediate revascularization</td>
<td>0.099</td>
<td>7.740</td>
<td>6.813</td>
<td>9.947</td>
</tr>
<tr>
<td>Immediate revascularization</td>
<td>0.058</td>
<td>7.961</td>
<td>6.850</td>
<td>13.618</td>
</tr>
<tr>
<td>Starting population aged 60 years</td>
<td>0.054</td>
<td>8.252</td>
<td>6.838</td>
<td>18.502</td>
</tr>
</tbody>
</table>

* Discounted at 3%

5. Optimal Treatment Model

A two-way sensitivity analysis by Pandya et al., on the average annual risk of stroke and probability of complication from revascularization procedures shows that CVR-based treatment has the lowest probability of complication during revascularization (Figure 2).

These findings further support the hypothesis presented here that CVR-based strategy using TCD US is a very good method of assessing stroke risk for asymptomatic patients. The use of TCD US as a “preventative” diagnostic tool does not apply to patients who are at 100% luminal flow narrowing because they have a higher probability of death, and therefore, the probability of complications may be low as shown in Figure 2 because patients in this group do not survive for very long after the procedure. TCD US is most helpful in patients with luminal narrowing from 0 - 99% as presented by the model because there is still a reasonable probability of regression back to
lower luminal flow narrowing and lower probability of complications during revascularization procedures.

Medical therapy is usually the first recommended therapy for patients who have undergone a stroke, especially if the stroke is a TIA and not hemorrhagic. Since TIAs are usually caused by blood clots, tissue Plasminogen Activator (tPA) is administered to dissolve the clot and the patient remains under observation. Multiple imaging studies may be conducted during this time to observe blood flow in the brain. If blood flow does not improve after medical therapy, revascularization is then performed. However, due to the time delay between tPA administration and revascularization procedures, TIA patients may have higher complication risks, shown by the sharp incline of complications associated with medical-based therapy as shown in Figure 2.

Figure 2. Two-way sensitivity analysis showing that CVR-based treatment is optimal as it leads to the lowest probability of complications from revascularization procedures. From [4], reprinted by permission from The Radiological Society of North America

Generally, as the risk of stroke increases, as well as higher luminal flow narrowing, the need for revascularization increases as well. But the increase in narrowing also increases the probability of stenosis and death; therefore, the probability of complications appears lower. CVR-based treatment is able to continuously monitor blood flow, so if there are any changes in luminal flow narrowing, immediate action can be taken, reducing the probability of complications during revascularization procedure.

6. Discussion and Conclusion

Although the focus on TCD US use here was based on CVR impairment, other diagnostic measurements can be used with TCD US to assess stroke risk. In addition to CVR, TCD can also detect micro-embolic signals (MES) or high-intensity transient signals (HITS) which can signal vulnerable atherosclerotic plaque in the carotid artery [3, 4].

It is important to note that Pandya et al., focused on a single risk factor for stroke, i.e., CVR. Ideally, the decision on whether or not a patient should go through revascularization procedure depends on other factors, not only degree of luminal flow narrowing. Factors such as age, sex, and the structural characteristics of the plaque play an important role in determining whether or not revascularization procedures will be beneficial [3]. Recent studies on stroke all agree that carotid stenosis is an important factor to study in determining individual stroke risk factors [1, 3, 5, 7]. The common recommendation is that multiple imaging studies are needed in order to not only identify luminal flow narrowing but to identify plaque morphology in order to have as much information as possible before deciding on treatment. Therefore, despite its many advantages, TCD US should not be used on its own in diagnosis and management of strokes. Higher imaging modalities such as Positron Emission Tomography (PET), Computed Tomography (CT), and Magnetic Resonance Imaging (MRI) play an important role that TCD cannot fill. For example, TCD has poor tissue contrast compared to CT and MRI therefore, it cannot show surface ulceration for the targeted regions. This is unfortunate since plaque morphology is an important risk factor for ischemic strokes.

Like any imaging modality TCD US has strengths and weaknesses. The recommendations presented by myself and Pandya et al., focus on preventative and emergent care for otherwise healthy patients. TCD US remains the only portable, noninvasive, and cost-efficient method to assess luminal flow narrowing in patients who have yet to experience a stroke. TCD US has proven very accurate in imaging the most widely used tool in stroke diagnosis, luminal stenosis flow [2,3,4]. Based on Pandya et al., comprehensive study, treatment decisions (including revascularization) based on CVR assessment not only have the lowest probability of complications but may also help high risk patients (90-99% luminal flow narrowing) regress
as far back as 0-45% luminal flow narrowing (Figure 1) [4]. The ability to use TCD to continuously monitor changes in luminal flow gives doctors more information and improves both diagnosis and prognosis, which improve patient outcome.

Based on the studies presented here and stroke statistics presented by the America Heart Association, the future of stroke prevention lies in being able to 1. Educate people on stroke risk factors, symptoms, and what to do when one sees such symptoms. 2. Efficient imaging modalities that can identify both the level of luminal flow narrowing as well as plaque morphology in order to minimize the risk of recurring strokes and complications from revascularization procedures. Studies such as those done by Pandya et al., and Liem et al., are an excellent step towards achieving these two goals.

7. References


SPINE IMPLANTS: MATERIAL SELECTION TO AVOID FAILURE
Kirsten Sipek
ksipek2@uic.edu

Abstract
Spine implants are a treatment option for patients with spinal deformity or instability. The most utilized materials are cobalt chromium, titanium, and polyetheretherketone. The applied materials need to be stable and allow for osseointegration, in which the bone and implant become fused together. Sometimes, it is critical to modify the surface of the prosthesis to propagate osseointegration. This can be achieved by increasing surface roughness, using chemical treatments, or producing a porous material to create the implant. Even with the correct material selection and surface modification, spine implants are still at risk for failure. When dissimilar metals are used for the rods and screws of the implants, the risk of corrosion is increased. This will result in a required revision surgery to stabilize the prosthesis. The implant corrosion leads to metal particles entering the tissues surrounding the implant, increasing the risk of infection and inflammation. This paper will discuss the different material choices, and examine which materials are best for prosthesis success. When the implant is made of a titanium alloy, it fuses with bone. However, when polyetheretherketone is used, a fibrous connective tissue forms around the implant. These different biological processes result in varied immune responses. There is a decreased risk of inflammation with titanium alloy, but the fibrous tissue surrounding the polyetheretherketone implant increases the risk of inflammation and cell necrosis. This demonstrates that osseointegration is critical in reducing the inflammation which can lead to implant failure.

Key Words: Spine Implants, Osseointegration, Disc Degeneration

1. Introduction
In the past, spinal disc degeneration would have been treated with fusion, in which two or more vertebral discs are joined together. However, when knee and hip arthroplasties became successful, researchers aimed to expand the use of implants to the spine. There was some reluctance to replace intervertebral discs instead of utilizing fusion because osseointegration is crucial for implant success. Many patients suffer from osteopenia, or bone density loss, of the spine which poses challenges for proper prosthesis function. The first spine implant to be used in a human was done by Fernstrom in the late 1950s [13]. This design included a metal ball inserted between the discs. However, these implants failed due to the ball sinking into the surrounding vertebral bodies and endplates.

The location of the disc disease determines which treatments are most effective. The lumbar spine has the largest vertebrae and is responsible for the greatest load. This section of the spine has the most common occurrence of pain and injury due to the large loading. Along with spine implants placed between the discs, plates are used for spinal alignment. Some conditions that cause poor spine positioning are scoliosis, kyphosis, and lordosis. Scoliosis occurs when the spine curves to the sides. Kyphosis refers to the rounding of the upper back and is often called “hunchback”. Lordosis is the inward curving that mainly occurs in the lower back. These conditions are illustrated in Figure 1. Often, these diseases will be treated using rods and screws to straighten the spine and create proper alignment. However, these constructs can limit the range of motion for patients. Approximately 3,000,000 spinal fusions are completed each year in the United States [4]. Hence, it is critical to improve the devices used for these procedures.

Figure 1. Three most common spinal deformities

One of the possible improvements to be made is material selection. Material chosen for the spinal implant has a significant effect on the success and longevity. Titanium has a positive history in implant use, especially with hips and knees. However, polyetheretherketone (PEEK) has gained popularity due to properties similar to those of cortical bone.
The goal of this review is to give an overview of the failure types associated with both interbody spinal implants, as well as rod and screw constructs. Furthermore, current advances in the field of spinal implants will be discussed.

2. Material Selection

Interbody implants along with rod and screw devices most commonly use titanium and PEEK because of their biocompatibility [9]. However, stainless steel and cobalt chromium alloy have been used as well. Each of these materials has been studied to determine the advantages and disadvantages of the different applications.

2.1 Interbody Implant Material

Titanium alloys were introduced to spinal implants about a decade before PEEK [9]. This was due to the success in other orthopedic implants, such as the hip and knee. Titanium alloys are preferable because of the corrosion resistance and low density. Titanium alloys, however, need surface modifications to create a more stable bone-implant integration. The elastic modulus of titanium is also much greater than that of cortical bone, as shown in Figure 2. This can lead to implant stress shielding which occurs when the implant, rather than the bone, absorbs the body’s loads. This causes osteopenia due to the bone being underused. When combined with inflammation, stress shielding can result in implant failure.

Figure 2. Elastic modulus of PEEK, cortical bone, and Ti alloy. From [9], reprinted by permission from John Wiley and Sons

PEEK has a lower elastic modulus than cortical bone, which can be remedied by employing the use of carbon fiber reinforcements, which increases the elastic modulus in a mechanism similar to that of steel rebar in concrete. This allows the optimal material properties to be attained and diminishes the negative effect of stress shielding. Another factor needing consideration is osteoblast maturation, which was addressed in a 2012 study that looked at the comparison between titanium alloys and PEEK. The results showed that the titanium alloys provided a more optimal environment for osteoblast differentiation [7]. This resulted from the titanium alloy having a rougher surface than PEEK, which gives a more desired cell environment. This leads to a stronger bone and implant interface and propagates a more successful implant.

2.2 Surface Modification

The surfaces of titanium and PEEK can be altered to create the best implant interface for osseointegration. Surface modifications are common for materials used in biomedical applications to make them better suited for the biological environment. For titanium, an increased surface roughness allows better bone growth on the implant, while also increasing friction to limit micromotion. This roughness can be achieved by plasma spraying, in which the titanium is coated with heated hydroxyapatite (HA). The HA is porous and leads to an improved bone tissue growth, and also reacts with the body fluids to promote integration [5]. The rough surface is displayed in Figure 3. It works so well because natural bone contains HA particles along with collagen.

Like titanium implants, PEEK has also been coated with HA to help mimic natural bone and increase implant acceptance. There have been positive results with the creation of an HA/PEEK composite to more closely resemble the cortical bone mechanical properties. Because PEEK material has poor osteoblast differentiation, researchers employed a different method which involved coating the material with titanium, for ideal osseointegration. This technique is shown in Figure 4.
2.3 Rod and Screw Material

In spinal surgery, screws have a variety of uses which include attaching plates, stabilizing a fracture, or creating a rod and screw structure [4]. Some of the most common materials utilized for rod and screw devices are stainless steel, cobalt chromium, and titanium alloy. Of the three materials, titanium has the best corrosion resistance, while stainless steel is the most susceptible to corrosion. Although the failure of rods is not a common occurrence, it is important to utilize a material with ideal mechanical properties. These properties are stiffness, yield stress, and fatigue life [16]. Both stainless steel and cobalt chromium are stiffer than titanium, however, stainless steel has a shorter fatigue life. In addition, titanium has a lower yield stress. It was also determined that a larger diameter rod is stiffer and generates a greater spinal correction.

3. Failure Modes

As with implants in the joints of the hip and knee, there are risks of failure due to different causes. These can be attributed to material make-up, infection, or implant loosening. Research is being done to limit these complications and improve treatments.

3.1 Failure of Interbody Implants

One notable case report focused on the failure of a carbon fiber-reinforced polymer cage that was implanted upon the removal of a degenerated disc [11]. After 2 years of having the implant, the patient experienced pain down both legs and was unable to walk short distances. It was found that there was loosening of the screws along with narrowing of the spinal canal. This is not a common failure; however, it is important for the patient to be aware of the symptoms of possible implant loosening. Upon revision surgery, it was also found that the cage had broken into fragments which demonstrates the possible instability of polymer materials in spinal implants.

As with any surgery, interbody spinal implants have a risk of surgical site infection [6]. The course of treatment includes antibiotics and debridement. In more severe and persistent infections, removal of the suggested protocol procedure. A study completed in 2008 found an infection rate of 3.7% [3]. This was accompanied by symptoms such as pain, discharge, or swelling. The treatments also included antibiotics, and then implant removal if there was no sign of improvement. The majority of the implants included in this study were made of stainless steel which does not encompass the current most widely used material. Upon the implant removal, 50% of the implants had loosened, and 6% had fractured. These incidents can be correlated to the infection as well.

3.2 Failure of Screw and Rod Implants

To correct spine deformities, rod and screw constructs are utilized. The rods are bent intraoperatively to mimic the curvature of the spine and gradually create alignment. At the screw insertion points, the rod is notched, which shortens the fatigue life and leaves the rod more susceptible to failure. The bent and notched locations are the most likely to experience failure because of the weakened material [16]. The spinal rod bending is demonstrated in Figure 5.

A study completed in 2017 examined the use of dissimilar metals in spinal rods and screws [8]. Recently, two different metals have been used in spine implants, such as cobalt chromium rods and titanium screws. This has increased the incidence of galvanic corrosion, which occurs between two dissimilar metals. The implants of seven patients were studied microscopically and macroscopically for signs of corrosion. These implants consisted of cobalt chromium rods with titanium screws, and titanium rods using titanium screws. This allowed a comparison of similar and dissimilar metals. Upon macroscopic
inspection, 44% of the cobalt-chromium rods showed evidence of discoloration with scratches and pitting, while the titanium rods had a lower corrosion incidence of 33%. The microscopic studies presented similar findings. However, this was not a statistically significant difference to conclude that dissimilar metals are more prone to corrosion.

A failure that can occur with any implant is metallosis, or the presence of metal debris in the tissues surrounding a metal prosthesis. This complication was the subject of a case study in which a patient received a rod and screw device for scoliosis [10]. Four years after the implant surgery, the patient experienced symptoms of infection along with lower back pain and tingling in both legs. An affected screw was removed, however, the patient then presented with weakness below the knees. The patient was found to have a corrosive film on the screws and material inside the spinal canal, but no infection. Bloodwork showed that the levels of chromium eight times above the normal range. The implant was removed, and the patient reported no further issues. Metallosis can lead to metal debris in the bloodstream, causing toxicity. It can also cause inflammation of the soft tissue which may develop into implant loosening.

4. Implant Advancements to Prevent Failure

Spinal implants have been undergoing advancements to create an improved patient outcome. Some of the goals are less invasive surgery and more biocompatible materials. Portions of this research are outlined in this section.

4.1 Interbody Implant Advancements

To reduce the number of surgical site infections with interbody implants, a minimally invasive procedure has been recently developed. To treat degenerative disc disease, an expandable cage can be implanted where the diseased disc was removed [2]. Through the small incision, the PEEK cage is inserted and expands into a circular arrangement. Bone graft is injected to fill the cage outline. The height of the cage can be adjusted based on each patient. With the small incision, there is a lesser chance of wound infection and pain, postoperatively.

Currently, metal interbody cages used for spinal fusion can cause damage to the surrounding intervertebral discs. To prevent this, 3D printed cages can be produced [12]. This creates an implant designed to perfectly fit a patient’s specific anatomy. It can also lead to improved load transfer and less bone damage. These devices are coated with HA to ensure optimal bone growth. This shows promise in creating a more individualized and lighter approach to spinal fusion. See [2] for complete discussion of these 3D printed cages.

4.2 Rod and Screw Advancements

An experimental study looked at the use of a shape-memory metal rod to treat scoliosis [14]. The research was done using pigs, but there was no evidence of material rejection or adverse reactions. After 6 months of implantation, the device was covered in newly formed bone. The rod is composed of a nickel-titanium alloy and can correct scoliosis not only laterally, but axially as well. This is a benefit that is not available with the current treatments. This material, however, requires more extensive studies of the biomechanical properties, as high fatigue life and yield strength need to be achieved.

In children with scoliosis, expandable rods have been utilized to accommodate the growth of the child. However, surgery is required each time the rod needs to be expanded. Recently, a study was completed to determine the effectiveness of a rod that can be expanded using magnets [15]. This would eliminate the need for additional surgeries and minimize the risk of infection. The caregivers at home are also able to participate in the device expansion. Both presented cases yielded positive results and an improvement in spinal alignment. The device is shown in Figure 6.

5. Conclusion

Material selection is a critical step in spine implants. Titanium has better osseointegration properties, but PEEK has an elastic modulus closer to that of cortical
bone. Both PEEK and titanium would require surface modification to ensure optimal bone formation. This can be achieved by increasing surface roughness or applying a coating of HA.

To reduce the risk of galvanic corrosion in rod and screw constructs, it is ideal to use the same material for both the rods and screws. Metal ion blood levels should be monitored to diagnose metallosis which can lead to implant loosening or organ disease. Interbody cages created from 3D printing can be beneficial in reducing the risk of adjacent disc disease and creating a lighter, more individualized implant.

With future research and advancements, minimally invasive spine surgery would be ideal to avoid postoperative infections and stress on the body. This can be achieved with expandable interbody implants or magnetic growing rods. Each patient’s condition needs to be evaluated so that the treatment will be the most successful for the individual’s specific needs.

6. References


INTRODUCTION TO MOLECULAR COMMUNICATION
Matthew Klug
klug2@illinois.edu

Abstract
The importance of molecular communication is increasing as technology grows smaller. The ability to reliably communicate on the molecular scale is becoming a significant issue that information theory is trying to resolve. The general problem formulation has roughly been defined as well as the different modes of transportation these molecules use, but closed form expressions are still actively being researched. Beyond the movement of molecules, an optimum channel shape needs to be found to further augment the ability to communicate on this scale. An overview of these topics will be presented to provide a basis for understanding molecular communication and the problems that can arise.

Keywords: Molecular Communication, Active Transport, Passive Transport, Mutual Information, Channel Capacity

1. Introduction

The next up-and-coming field in communication studies involves the use of molecules to transfer information over very small distances known as molecular communication [5]. The desire for smaller portable handheld devices in industries ranging from medical to commercial is becoming the new standard. As the need increases for smaller and smaller devices, understanding communication on a molecular level is becoming of growing importance. Without the proper understanding of molecular communication, the needs of these industries will go unmet.

As with many forms of technology, as the size decreases, the complexity increases. This is increasingly true for molecular communication as traditional communication techniques cannot be applied to them directly. Currently, it is not even clear what are the correct units for capacity [3]. The closest well-known form of communication is known as electromagnetic communication. Electromagnetic communication involves the propagation of waves at various frequencies to transmit and receive information. Applications for electromagnetic communication are wide ranging from radio to gamma radiation and have been studied since the 16th and 17th centuries. While well understood, electromagnetic communication faces its own drawbacks. For example, electromagnetic communication cannot occur in conducting fluids such as blood or seawater [1]. This is due to different forms of scattering and reflection destroying the propagating wave. Another drawback is the energy cost of electromagnetic communication might be prohibitive on a scale of this size [10]. Also, the channel the wave travels through is impossible to have a fixed model for, as the inferences a wave faces while traveling through air are impossible to predict and account for. The channel environment for molecular may offer a better opportunity of obtaining a fixed channel model. However, closed form models for these molecular environments are proving to be very challenging to obtain.

Molecular communication, compared to electromagnetic communication, enables transmission of information via chemical signaling [11]. While the difficulties in modeling air as a propagation channel are removed, a whole new world of molecular channel concerns appear. A basic model of the molecular communication is shown in Figure 1. As with most scientific breakthroughs, inspiration in nature can often be a driving force. Molecular communication has been demonstrated in quorum sensing in bacteria, where bacteria exchange messages to determine the species size of their local population [1]. Following examples in nature may offer clues to help develop these fixed models. Molecular communication also offers advantages in scalability, energy efficiency, and

Figure 1. The molecular communication system starts with the release of one or more molecules by the transmitter. After traveling through the fluid medium, the molecules are absorbed by the receiver. From [10], reprinted by permission from IEEE.
bio-compatibility [11]. This paper will offer an introduction into the field of molecular communication and provide insights into the different variables that must be accounted for.

2. Overview of Molecular Communication Environment

To begin our understanding of molecular communication, the physical environment must be first understood before an attempt at creating a mathematical model can be made. For the purpose of this paper, a rectangular propagation environment will be assumed. The subsequent sections will discuss the importance of channel shape and the means at which transportation can occur within these environments.

Within this rectangular propagation environment, there are two zones called the transmission or loading zone and the receiver or unloading zone. The loading or transmission zone is where the message bearing particles will begin their propagation and will continue until they reach the unloading or receiving zone. The propagation method for these particles are microtubule filaments, which move over molecular tracks that cover the environment. The microtubule filaments carrying the information carrying particles from zone to zone [5]. Microtubules can carry these particles due to deoxyribonucleic (DNA) acid hybridization bonds, which are used to anchor, load, and unload the information particles [7]. This environment is depicted in Figure 2 below.

![Figure 2](image)

Figure 2. An illustration showing the propagation environment. The message bearing particles are transported from the transmission or loading zone to the receiver or unloading zone through the use of microtubule filaments. From [5], reprinted by permission from IEEE

With the propagation environment defined, it is important to understand what it means to send a message over this environment. The particles moved by the microtubules are not information bearing in the sense that each particle carries a message. The transmitted message is instead represented by the number of particles that propagate across the environment and are received in the unloading zone [5] or in the time of dispersal of the molecules if the molecules are identical [10]. With this understanding of what a message is, we can begin to construct a mathematical model for molecular communication. A general molecular communication channel is shown in Figure 3 and is compared against the traditional communication channel.

![Figure 3](image)

Figure 3. Traditional communication versus Molecular Communication comparison. A traditional communication system models itself as a noisy channel, while a molecular communication system is modeled based on the random propagation of the molecules. From [5], reprinted by permission from IEEE

The last step in defining our channel model is to make some assumptions about the emission and reception processes of the molecules, which are referred to the ideal channel model assumptions [12].

1. To represent a specific message, the transmitter perfectly controls the release time and the number of molecules released.
2. The arrival time of the molecules is perfectly measured by the receiver due to the complete synchronization between the transmitter and the receiver.
3. Upon reaching the receiver, the molecule is fully absorbed and does not return to the medium.
4. While within the propagation environment, the molecule enjoys completely free propagation with no interference.
5. Inside the propagation environment, the trajectories of individual information carrying molecules can be considered independent.
Now let’s begin to define a basic mathematical model. Let $X \in \chi = \{0,1,2, \ldots, x_{max}\}$ represent the number of information particles released into the medium by the transmitter, $Y \in \chi$ represent the number that arrive at the destination after time per channel use, $T$, and $x_{max}$ be the maximum number of particles the transmitter can release per channel use. The maximum rate at which any communication system can reliably transmit information over a noisy channel is bounded by a limit called channel capacity. The channel capacity can be calculated as,

$$C = \max I(X; Y)$$

(1)

where $I(X; Y)$, is the mutual information between $X$ and $Y$. Mutual information is defined as

$$I(X; Y) = E[\log_2 \frac{f_{Y|X}(y|x)}{\sum_x f_{Y|X}(y|x)f_X(x)}]$$

(2)

where $f_{Y|X}(y|x)$ represents the probability of receiving symbol $y$ at the destination, given that symbol $x$ was transmitted by the source; $f_X(x)$ represents the probability of transmitting symbol $x$ and $E[\cdot]$ represents expectation.

Based on the model of the channel, if the PMF $f_{Y|X}(x)$ can be found, the channel capacity of the molecular communication system can be calculated fairly easily. However, finding the PMF is non-trivial because of the random motion of particles and the shape of the channel. Molecular communication, unlike traditional communication, deals with the random propagation corrupting the message [5]. The next sections will take a closer look at the motion of the particles and the shape of the channel to see how these parameters affect finding the PMF and therefore the channel capacity.

3. Molecular Transformation Methods-
Passive versus Active Transport

There are two main modes message bearing particles can use for transportation each with their own advantages and disadvantages. This section will compare and contrast these two propagation methods and provide general mathematical representations for each transportation mode. These two modes are called Passive Transport and Active Transport depicted in Figure 4.

![Figure 4. Passive and active transport are depicted in their own molecular communication systems containing the transmitters, receivers, the confined microfluidic channel (dashed lines). Top: Passive transport where the information carrying molecules diffuse in the confined microfluidic environment and follow a Brownian motion path from the transmitter to the receiver is depicted. Bottom: Active transport relies equally on stationary molecular motors attached to a glass substrate and microtubules to carry the information particles from the transmitter to the receiver. From [8], reprinted by permission from IEEE](image)

3.1 Passive Transport

The first mode to be discussed is called passive transport. In this form of transportation, information carrying particles diffuse in the confined microfluidic channel and follow a Brownian motion from the transmission zone to the receive zone [5]. Passive transport or Brownian motion can be thought of as the simplest form of transportation following a continuous time stochastic process. This particle motion is defined as a random motion of particles suspended in some fluid resulting from their collision with fast moving atoms or molecules in the fluid. The vesicles location in the loading zone are random and uniformly distributed as they are being propagated simultaneously [2]. Due to Brownian motion being a stochastic process, equations can be derived. However, due to micro-channels being confined spaces, the solutions to these equations cannot be represented in closed form. Approximations can be derived using the Monte Carlo simulations, but here only the general equation Brownian motion is presented.

Given some initial position $(x_0, y_0, z_0)$ at time $t = 0$, for any integer $k > 0$ , the motion of the microtubule is given by the sequence of coordinates $(x_i, y_i, z_i)$ for $i = 1,2, \ldots, k$. Each coordinate $(x_i, y_i, z_i)$ represents the position of the microtubule’s head at the end of the time $t = i\Delta t$, where

$$x_i = x_{i-1} + v_F \Delta t + \Delta r \cos \theta_i \cos \phi_i$$

(3)
\[ y_i = y_{i-1} + \nu_{Fz} \Delta t + \Delta rsin\theta_i \cos \phi_i \]  \hspace{1cm} (4) \\
\[ z_i = z_{i-1} + \nu_{Fz} \Delta t + \Delta rsin\phi_i \]  \hspace{1cm} (5)

where \( \nu_{Fx}, \nu_{Fy}, \) and \( \nu_{Fz} \) are the flow velocities in the \( x, y, \) and \( z \) directions [8]. A molecule’s displacement \( \Delta r \) can then be given by

\[ \Delta r = \sqrt{4D \Delta t} \]  \hspace{1cm} (6)

where \( D \) is the free diffusion coefficient and is given by

\[ D = \frac{k_B T}{6\pi \eta R_H} \]  \hspace{1cm} (7)

where \( k_B = 1.38 \times 10^{-23} \) J/K is the Boltzmann constant, \( T \) is the temperature (in K), \( \eta \) is the dynamic viscosity of the fluid, and \( R_H \) is the hydraulic radius of the molecule [2, 4].

### 3.2 Active Transport

The second mode is called active transport. Active transport assumes the vesicles are anchored to the loading zone until they are loaded onto a microtubule and the microtubule’s initial position is considered uniform and random [2]. In other words, the information particles are being actively transported through the use of molecular motors or the microtubules. The model for active transport reduces to modeling the motion of the microtubules, which only move in the \( x \)-\( y \) directions. An example of active transport is shown in Figure 5.

![Figure 5: An example of a possible trajectory of active transport. From [3], reprinted by permission from IEEE](image)

Therefore, given the same conditions as for passive transport taken for the \( x \)-\( y \) directions active transport can be modeled as,

\[ x_i = x_{i-1} + \Delta r cos \theta_i \]  \hspace{1cm} (8) \\
\[ y_i = y_{i-1} + \Delta r sin \theta_i \]  \hspace{1cm} (9)

Then the step size \( \Delta r \) at each step is an independent and identically distributed (iid) Gaussian random variable with mean and variance

\[ E[\Delta r] = \nu_{avg} \Delta t \]  \hspace{1cm} (10) \\
\[ V_{ar}[\Delta r] = 2D \Delta t \]  \hspace{1cm} (11)

where \( \nu_{avg} \) is the average velocity of the microtubule, and \( D \) is the microtubule’s diffusion coefficient. The angle \( \theta_i \) is no longer independent from step to step. Therefore, for some step to step angular change \( \Delta \theta \), we have that

\[ \theta_i = \Delta \theta + \theta_{i-1} \]  \hspace{1cm} (12)

Then \( \Delta \theta \) is an (iid) Gaussian distributed random variable, for each step, with mean and variance

\[ E[\Delta \theta] = 0 \]  \hspace{1cm} (13) \\
\[ V_{ar}[\Delta \theta] = \frac{\nu_{avg} \Delta t}{L_p} \]  \hspace{1cm} (14)

where \( L_p \) is the persistence length of the microtubule’s trajectory [6, 9].

### 3.3 Compare and Contrast

Now that we have defined what passive and active transport are, some brief comparisons can be made between the two modes of transportation. When comparing, the definition of best will be defined as having a higher information rate and therefore a higher channel capacity. Example trajectories of passive and active transport are shown in Figure 6.

![Figure 6: Simulated Trajectories of Brownian motion(top) and active transport (bottom) are shown. Dotted lines represent the boundaries of the propagation environment and dotted strips represent the loading zone (left) and the unloading zone (right). The red path indicates the unloaded motion of the microtubule for an active transport trajectory. From [2], reprinted by permission from IEEE](image)
In terms of total distance between the loading and unloading zones, passive transport (Brownian motion) is better over an infinite distance and active transport has the advantage over a small distance because active transport is limited by the number of available microtubules [4]. The channel capacity of active transport can be improved by increasing the number of microtubules and optimizing the shape of the transmission area [4]. Overall, active transport with optimal transmission and multiple microtubules will achieve the highest channel capacity [4]. These comparisons make sense as the randomness of passive transportation affects the ability to reliably communicate over a given channel.

4. Channel Shape

When one is studying molecular communication, the channel shape plays a definite role in determining the channel capacity and ultimately the information rate. In this section, the determination of ideal channel shape will be made. For our discussion of channel shape, the simulation environment has been given in Figure 7.

![Figure 7. A possible simulation environment is depicted. From [8], reprinted by permission from IEEE](image)

Up until this point in our discussion, the channel shape has been limited to a rectangular shape. The rectangular shape is defined as having the transmission zone on the left and the receiver zone on the right side [7]. The location the loading and unloading zone are typically fixed in this fashion regardless of shape. The parameters that then can be changed are the width and length of the channel, the number of sides, and the size of the unloading and loading zones [7]. The determination of which channel shape is optimal will be made with respect to the resulting channel capacity of each channel shape.

Based on the simulation environment, the changes to be made can be summarized into three parameters; constant radius, constant area, constant perimeter. For a basis of comparison, active transport will be used meaning the goal is to maximize the number of microtubule trips.

1. Assuming a constant radius, the number of microtubule trips will be maximized when $\cos \frac{\pi}{n}$ is maximized. As $n$ or the number of trips approaches infinity the function is maximized. Therefore, the optimal channel shape will be circular.

2. For constant area, the shape with the smallest perimeter would maximize the number of microtubule trips. Based on this largest ratio of area to perimeter would be considered the optimal shape. Therefore, the optimal channel shape will be circular.

3. For constant perimeter, the shape with the largest area would maximize the capacity. Therefore, similar to the constant area case, the optimal channel shape will be circular [7].

From this, the conclusion can be drawn that the optimal shape will always be circular. To further prove this, Nariman Farsad, Andrew Eckford, and Satoshi Hiyama plotted the number of sides (increasing circularity) against the number of information particles released by the transmitter and calculated the channel capacity [8]. Their results are shown in Figure 8.

![Figure 8. Number of sides increases the channel capacity, more circular then channel capacity increases. From [8], reprinted by permission from IEEE](image)

Clearly, based on the plot, as the number of channel sides increases, the channel capacity increases. Therefore, the optimal channel shape is circular. However, further study is needed to create closed forms expressions based on this circular shape.
5. Conclusion

The study of molecular communication is becoming more prevalent as devices get smaller and smaller. However, very little is currently known about how to effectively communicate on this scale. Drawing upon behavior found in nature, models have begun to be constructed based on the movement of molecules characterized by either being passive or active transport. However, the various parameters, such as channel shape, are still being explored and the closed form expressions not yet finalized.

6. References


A REVIEW ON MATHEMATICAL MODELLING OF HIV-1 INFECTION
Mounica Bandela
mbande4@uic.edu

Abstract:
Human Immunodeficiency Virus type 1, in-vivo replication can be better assessed by using mathematical modelling. Modelling studies help to determine the quantitative features of infection between Human Immunodeficiency Virus type 1, that cause Acquired Immunodeficiency Syndrome, and the cells infected by virus. The objective of this review is to analyze the models developed for eradication of Human Immunodeficiency Virus, and the significance of monotherapy and combination therapy. The review also discusses the significance of combination therapy to reduce viral population along with effect of the reverse transcriptase inhibitor and protease inhibitor on virus population.

Keywords: RT Inhibitors, Protease Inhibitors, Combination Therapy.

1. Introduction

Human immunodeficiency virus (HIV) causes Acquired Immunodeficiency Syndrome, also known as AIDS, which is one of the world’s most serious health challenges (Figure 1). The first case of AIDS was reported in 1981[7] and tens of millions of people have died of AIDS since then. Today, there are approximately 36.7 million people who are suffering with HIV, and at risk for developing AIDS. However, global efforts are being made to fight the epidemics and these efforts have been successful thus far. The number of people infected with HIV and AIDS, as well as related deaths, have declined over the years. Similarly, the number of people who receive appropriate treatment has increased to 17 million in 2016[8].

Human immunodeficiency virus (HIV) [2] belongs to a group of retroviruses also called lentiviruses. The genome of retroviruses is made of RNA (ribonucleic acid), and each virus has two single chains of RNA. The enzyme reverse transcriptase makes copies of DNA from RNA of the virus. This copy of DNA is integrated into the infected cell by an enzyme called integrase. This viral DNA is called the provirus.

The major targets of the HIV virus are CD4+ lymphocytes (T cells), but may also infect other cells like monocytes, macrophages, and dendritic cells to a lesser degree. These cells are called T-helper cells because they secrete growth and differentiation factors that are required for other immune system cells. Once an individual is infected with HIV virus, their cell count is reduced from 1000mm$^{-3}$ to 200mm$^{-3}$ or below, which is the threshold classification for having AIDS. The cells turn into HIV-replicating cells and lose their initial function in the human immune system (Figure 2).

Figure 1. Epidemics of HIV-AIDS in 2016. From [7], reprinted by permission from UNAIDS

Figure 2. Stages 1-10 of HIV replication [2]. 1. HIV virus (pink) approaches cell 2. HIV virus binds to cell via receptors on surface of cell 3. Injects capsid contents which is the HIV’s core that contains HIV RNA 4. Reverse transcription occurs to convert HIV RNA to HIV DNA 5. Integration of proviral DNA into host DNA 6. Transcription begins and directs cell to produce new HIV 7. Translation produces new viral proteins 8. Viral assembly of new viral particles 9. Budding off of host cell to produce new virus 10. Maturation Infection HIV virus. From [2], reprinted by permission from UNAIDS
Many models have been developed to determine the interaction between HIV and the decline of CD4+ T cells. Stochastic and deterministic models were designed by authors, where stochastic models determined the early events in the disease where only few infected cells were taken into consideration, whereas deterministic models were applicable for later stages of disease and for larger population sizes.

The models developed before 1995 focused only on kinetics of T cell decline. Recent advances led to development of models that also measured the number of virus particles in the blood. These models were rapid, accurate and sensitive. HIV replicates rapidly and produces $10^{10}$ viral particles per day, so treatment with a single drug would fail. In order to overcome this, a recent study focused on combination therapy instead of monotherapy where multiple drugs are used. However, combination therapy does not eradicate the virus completely. Modeling suggests that patients should be given antiretroviral drugs for longer period of time for the virus not to be detected in blood.

David Ho and George Shaw tested potent antiretroviral drugs like protease inhibitor on 20 patients to study HIV viral load and change in CD4+ cell counts after drug administration. From these changes, they estimated the rates of viral replication and elimination from the body as well as the rates at which CD4+ cells are killed and replaced by cell proliferation.

In this study, the authors have reviewed several simple and complex models, and their significance on monotherapy and combination therapy. The first objective of the study is to analyze the models developed for eradication of HIV. The other objective of this study is to examine the effect of the RT inhibitor and protease inhibitor on virus population, as well as to study the significance of combination therapy to reduce viral population.

### 2. Models to determine concentration of HIV infection

Based upon the viral population and stages of disease, two models were developed by David Ho and George Shaw to determine concentration of HIV infection.

#### 2.1 Simple HIV dynamic model

This model [3] explains that virus concentration falls exponentially with respect to time after patient is treated with potent antiretroviral drug. This is given by Eq.(1) where $P$ is an unknown function representing rate of virus production, $c$ is clearance rate constant, and $V$ is the virus concentration.

$$\frac{dV}{dT} = P - cV$$

If the drug completely blocks the viral production, (i.e. when $P=0$), then the model predicts that $V$ will fall exponentially and will be described by Eq.(2) where $V(0) = V_0$ and $t = 0$ is the time at which therapy is initiated.

$$V(t) = V_0 e^{-ct}$$

Figure 3. Plotting $ln(V)$ versus $t$ and using a linear regression analysis, it was determined that the slope estimates $c$ and half-life of virus in the plasma, $t_1/2 = ln(2)/c$. From [6], reprinted by permission from Society for Industrial and Applied Mathematics

Viral production rate before therapy (i.e, $P = cV0$) can be computed if we assume that the patient was in a quasi-steady state (Figure 3) in which $dV/dT = 0$, where $c$ and $V0$ were known parameters. Total rate of virus production in patients can be computed by measuring $V0$ for individual patient and then multiplying with the fluid volume in which virus is expected to be present [3,9].

There exist certain limitations for this model, this data would not support large viral populations. In order to overcome this drawback, a more refined model was developed.

#### 2.2 Model that incorporates viral production

A model was developed on HIV infection where a population of uninfected target cells, $T$, and infected cells $T^*$ were used.
A reasonable model for the population of cells is given by Eq. (3).

$$\frac{dT}{dt} = s + pT \left( 1 - \frac{T}{T_{\text{max}}} \right) - d_T T \quad (3)$$

Here $s$ represents rate at which new $T$ cells are formed within the body from thymus or existing $T$-cells, $p$ represents maximum proliferation rate, $T_{\text{max}}$ is the $T$ cell population density at which proliferation shuts off, and $d_T$ is the death rate per $T$ cell.

Single stable steady state is given by Eq. (4) where over bar indicates steady state value.

$$T = \frac{T_{\text{max}}}{2p} \left[ p - d_T + \sqrt{(p - d_T)^2 + \frac{4sp}{T_{\text{max}}}} \right] \quad (4)$$

The simplest and most common method for modeling infection is given by augmenting Eq. (3) with a mass action term in which the rate of infection is given by $kVT$, where $k$ is the infection rate constant.

With the simple mass action infection term, the rates of change of uninfected cells $T$, productively infected cells $T^*$ and virus $V$. The relationships are given by Eq. (5) – Eq. (7) [4].

$$\frac{dT}{dt} = s + pT \left( 1 - \frac{T}{T_{\text{max}}} \right) - d_T T - kVT \quad (5)$$

$$(dT^*)/dt = kVT - \delta T^* \quad (6)$$

$$\frac{dV}{dt} = N \delta T^* - cV \quad (7)$$

Assumptions:
The probability of infected cell death is unknown so an assumption is made where rate of death per cell is a constant $d_T$ for uninfected while $\delta$ for infected cells.
The logistic proliferation term $pT \left( 1 - \frac{T}{T_{\text{max}}} \right)$ is ignored since the proportion of infected cells is very small. The other assumption is, when each time a cell is infected, a virion enters so we can add a term $-kVT$ to equation 7. This makes the model nonlinear.

3. Results

Patients in the quasi steady state condition were given RT inhibitors, protease inhibitors, or combination of two in order to reduce the amount of virus in their bodies. The obtained results for these therapies are discussed.

3.1 RT Inhibitors

RT inhibitors [6] block the infection and reduce $k$. These inhibitors, like other drugs, are not perfect, thus an accurate model of an RT inhibitor is developed which is given by Eq. (8) – Eq. (10).

$$\frac{dT}{dt} = s + pT \left( 1 - \frac{T}{T_{\text{max}}} \right) - d_T T - (I - \eta_{\text{RT}})kVT \quad (8)$$

$$\frac{dT^*}{dt} = (I - \eta_{\text{RT}})kVT - \delta T^* \quad (9)$$

$$\frac{dV}{dt} = N \delta T^* - cV \quad (10)$$

Where $\eta_{\text{RT}}$ is the effectiveness of the RT inhibitor. If $\eta_{\text{RT}} = 1$, the inhibition is 100% effective and for $\eta_{\text{RT}} = 0$, there is no inhibition.

An assumption is made after short period of therapy where $T = \text{constant} = T_0$ and patient was in a quasi steady state before therapy began where $NkT_0 = c$. From this, the equation became linear and can be solved for eigenvalues using Eq. (11).

$$\lambda_{1,2} = -\frac{\delta c}{2} \pm \frac{1}{2} \sqrt{(\delta + c)^2 - 4\eta_{\text{RT}} \delta} \quad (11)$$

If $0 < \eta_{\text{RT}} \leq 1$, the two eigen values obtained are real, negative and distinct, and $T^*$ and $V$ are zero. But when $\eta_{\text{RT}} > 0$, this indicates that the virus is eradicated at post treatment steady state condition.

However, this model is not explained with proper illustration and it is based on an unrealistic assumption that $T$ remains constant, as virus concentration decreases CD4+ T cells should increase, where $\eta_{\text{RT}}$ should be larger than the critical value to eliminate the virus.

3.2 Protease Inhibitors

When protease inhibitors [6] are modeled, they cause infected cells to produce non-infectious virus, we have two virus populations; $V_I$ is infectious virion and $V_{NI}$ is non-infectious virion. The basic model is transformed when we consider the drug to be 100% efficient given by Eq. (12) and Eq. (13).

$$\frac{dV_I}{dt} = -cV_I \quad (12)$$

$$\frac{dV_{NI}}{dt} = N \delta T^* - cV_{NI} \quad (13)$$
The total population of viruses is given by Eq. (14).

\[ V = VI + VNI \]  

(14)

Protease dose was given to five patients in this study, and they measured viral load at regular intervals using nonlinear least squares to fit the data and estimate \( c \) and \( \delta \) for each patient. The values of the study are illustrated in Figure 4.

Figure 4. Summary of HIV-1 clearance rate, infected cell loss rate, and virion production rate for three patients. Baseline values are measured from one week prior to administration of drug. From [6], reprinted by permission from Society for Industrial and Applied Mathematics

The model was a good fit, an example for one patient is given where solid lines are model and points are data (Figure 5) [6]. The value of \( c \) ranged from 2.1 to 3.8 day\(^{-1}\) and the value of \( \delta \) ranged from 0.3 to 0.7 day\(^{-1}\).

Figure 5. Example of best fit curve based on the values listed in Figure 4. Solid line is fitted data and * is experimental data. From [6], reprinted by permission from Society for Industrial and Applied Mathematics

3.3 Combination Therapy

In combination therapy [6], both RT and protease inhibitors are used to sustain long-term response and to block the viral life cycle, because treatment with single drug often fails due to drug resistance.

A clinical trial was performed using protease inhibitor, nelfinavir and two RT inhibitors AZT and 3TC, with results indicating that the viral concentration in plasma fell dramatically below the threshold of 500 copies/ml by 8 weeks, which is considered the “first phase” of decline of HIV. Under continued therapy, it was found to be <25 copies/ml at 16-20 weeks and there was no evidence of any drug resistant virus, which constitutes the second phase of decay.

Viral concentration was plotted on logarithmic scale, where the two phases of viral decline were approximately exponential.

![Graph showing two-phase decline in plasma virus after initiation of combination therapy](image)

Figure 6. A Two-phase decline in plasma virus after initiation of combination therapy. From [6], reprinted by permission from Society for Industrial and Applied Mathematics

In the presence of both RT and protease inhibitors, the basic model is transformed to Eq. (15)-Eq. (17).

\[ \frac{dT^*}{dt} = (1 - \eta_{RT})kVT_0 - \delta T^* \]  

(15)

\[ \frac{dV_I}{dt} = (1 - \eta_{PI})N \delta T^* - cV_I \]  

(16)

\[ \frac{dV_{NI}}{dt} = \eta_{PI}N \delta T^* - cV_{NI} \]  

(17)

Where \( \eta_{RT} \) and \( \eta_{RT} \) are effectiveness of the protease and RT inhibitors respectively. If we consider quasi steady state condition and if both the inhibitors are 100% effective, then we can find total population of virus by the Eq.(18).

\[ V(t) = V_0[(1 - \frac{NsT_0}{c - \delta} - \frac{c - NsT_0}{c - \mu T})e^{-cT} + \frac{NsT_0}{c - \mu T}e^{-\mu T} + \frac{c - NsT_0}{c - \mu T}e^{-\mu T}] \]  

(18)

Data of a patient obtained by combination therapy [5] was fitted using nonlinear least squares regression where \( c \) was at a constant mean value of 3 day\(^{-1}\) and life span of long lived infected cells \( \mu_M \) was at a range 0.03 to 0.12 day\(^{-1}\) and for short lived infected cells was 0.86 to 1.92 day\(^{-1}\).
4. Discussions

Mathematical modeling of HIV pathogenesis was discussed in this paper. AIDS was considered to be a disease where the treatment was delayed until symptoms appeared and the patient was not monitored. This assumption was changed after modeling was taken as serious criteria. A study was done by AIDS cohort multicenter where they observed virus levels in blood and the rapidity of virus developing drug resistance, but these were changed when models were coupled with advances in technology [1].

A simple model was developed to estimate the HIV production and its clearance in an infected person. This model was the first quantitative interpretation involving a single linear ordinary differential equation used for estimation of HIV infection. In this model, viral clearance estimated was at lower bound which was thought to be not true rather and it was studied that the viral clearance in this model was due to the consequence of biological processes before drug was given.

In order to overcome the limitation of the simple model, a complex model was designed which incorporated both virus and infected cells. This model was successful in estimating quantitatively CD4+ T cell depletion and rate of clearance of free viral particles which was more accurate compared to simple model. HIV production can be determined using the estimated rate of clearance at steady state. This led to conclusion that on average, in an infected person approximately $10^{10}$ virus particles are produced everyday whose generation time is around 1.8 days. This indicates around 200 replication cycles per year where mutations occur at each cycle. Therefore, therapy with single drug administration would lead to resistance, and so, to overcome this, combination therapy was used and corresponding models were developed.

A more complex model was developed using the data of patients who were treated with combination therapy. Two phase decline of virus concentration in plasma was developed in this model. It was a successful model and was used to quantify the role and level of latently infected and long-lived cells in HIV infection.

5. Limitations and Future Advances.

There exist certain limitations in the article. The developed models predict the virus and infected cell concentrations to be zero under intense therapy they analyze only simplified reality and do not consider the special and compartmental aspects of the body. They also assumed that the drug is available everywhere with constant effectiveness. Additionally, some drugs do not penetrate throughout the body. For example, in the blood brain barrier, the concentration of drug in the brain and central nervous system is very low and immune system cells possess limited access to these sites; therefore, they form drug sanctuaries which generate drug resistance which leads to replication of virus until new drugs are designed and implemented.

One major drawback of this study is that only CD4+ T cells and macrophage kinetics were designed as the major targets of HIV infection, but other cells may become infected as well. These other cells possess different kinetics, which would further alter the model, but this was not discussed in the article. Also, direct cell-to-cell transmission of virus was not considered in the study, which may have an important role in long term behavior of HIV in-vivo.

The other limitation of the study was in neglecting immune response. The immune component developed due to death of viral infected cells and clearance of viral free particles make the viruses more pathogenic and drug resistant. To overcome this, the parameters in the models should be considered to vary with time and depend on the events occurring in the host.

Patients should be treated with combination therapy continuously for a period of five to seven years to eradicate the infected cells, but this remains a challenge due to the complexity of associating drug regimes, drug side effects, and cost. Alternative approaches should be developed to overcome this drawback.

The future advances in this field will be in developing mechanistic models of HIV infection, i.e; considering quantitative data on the immune response, both cellular and humoral. This will be a substantial advancement made to explain the events occurring during primary infection, and in the analysis of vaccine trial data in humans. Therefore, the models would not just describe the time evolution of the viral load, as the current models, but also the kinetics of the immune response and its effect on virus and infected cells. Another area of interest to modelers is the potential effect of cell-to-cell transmission of HIV-1.
6. Conclusion

Great contributions were given by Dr. Ho Lab; they helped to pioneer the field of quantification of HIV in infected people and revolutionized the paradigm for AIDS pathogenesis by demonstrating the highly dynamic nature of HIV replication in vivo. Their study formed the basis for combination antiretroviral therapy for which he received a Nobel prize. Such treatment has transformed the deadly disease of AIDS to a more manageable disease. Currently, his group is working on the development of vaccines for HIV as well as other innovative prevention strategies.

The models discussed in this article tend to be accurate during relatively short periods of time scale like days, months and weeks, but they do not predict long term events in infected individual accurately. The biological process of the HIV is known but developing treatment strategy and eradicating HIV from an infected person is the overall goal which has yet to be achieved. Modeling is being designed because scientists believe that it plays an important role in achieving the goal of eradicating HIV-1.

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SPECTRAL-DOMAIN OPTICAL COHERENCE TOMOGRAPHY: SYSTEM CONFIGURATION AND APPLICATIONS IN RETINAL RESEARCH
Tae-Hoon Kim
tkim219@uic.edu

Abstract
Optical Coherence Tomography is a non-invasive imaging modality used to visualize both morphological and functional changes of biological tissue. It is an extension of Michelson interferometer. Light from a low-coherence source is divided into the sample and reference arms through the optical fiber coupler (or free space) and the light backscattered or reflected from the sample and reference mirror is redirected back through the fiber coupler. The combined light is made to interfere and delivered to the surface of a spectrometer. Spectral-domain optical coherence tomography analyzes the spectrum of interference of the combined light and transforms it into the depth information of the structures according to the Fourier transformation. Spectral-domain optical coherence tomography has a fixed reference arm in a position which significantly increases axial (depth) scanning speed (up to 20 MHz) and allows having rapid 3D scanning capabilities compared to the conventional time-domain optical coherence tomography. In this paper, basic principles of spectral-domain optical coherence tomography will be introduced and the features of each major component (interferometer, light source, scanning mirror, and spectrometer) in the spectral-domain optical coherence tomography system will be demonstrated to appreciate the system configuration. Also, optical coherence tomography applications in the retinal research will be introduced.

Keywords: Optical Imaging, Spectral-domain Optical Coherence Tomography, Interferometer, Spectrometer, Retina

1. Introduction
Medical imaging technologies such as ultrasound imaging, X-ray computed tomography and magnetic resonance imaging (MRI) allow the functional and structural investigation of the human body at the organ level with tens of micrometers to millimeters resolution range [13]. However, a higher resolution is always required to detect early abnormal signatures of the microstructure of living tissues.

Optical microscopy is a higher resolution imaging modality. Although the resolution generally reaches one micrometer and is limited only by the diffraction limit of light, the penetration depth is severely restricted by scattering in biological samples, which reduces contrast as well as the signal-to-noise ratio (SNR) [10]. Thus, it is not suitable for in vivo imaging of biological samples located deeper in the body.

Optical Coherence Tomography (OCT) is a novel imaging technique that produces a high resolution for 2D and 3D images of the internal microstructure of living tissue [15]. Its applications in medicine were first reported in 1991 [4] and the constant development of OCT has significantly improved its imaging performances in terms of its resolution (up to ~1 μm), sensitivity (up to 120 dB), and imaging speed (up to 20 MHz) [15]. These promising developments provide new opportunities for researchers and physicians to investigate the internal microstructure of living tissues in vivo and could possibly replace excisional biopsy in a non-invasive manner [15].

Figure 1. The imaging range and resolution of various biomedical imaging modalities. From [3], reprinted by permission from Springer Nature

OCT falls in between ultrasound and microscopy in terms of resolution and penetration depth as shown in Figure 1, and its operation is very similar to ultrasound imaging. Ultrasound transmits acoustic waves to a sample and then measures the reflected waves. By
recording the delayed time and amplitude of reflections, an axial profile at a single transverse location in the sample is produced [13]. OCT uses light waves instead of sound waves. However, light travels at a speed much greater than sound waves and the response time of current photodetectors is much slower than the light propagation time. Therefore, it cannot be measured directly by electronic methods. The measurement is thus achieved using a technique called low-coherence interferometry and is commonly performed using a Michelson interferometer [11].

In this paper, the theoretical background of low-coherence interferometry will be first described in the following section. In addition, the system configuration of SD-OCT (section 3) in conjunction with Michelson interferometer and its applications in the retinal research (section 4) will be introduced to give more insight into OCT as a promising biomedical imaging modality.

2. Low-Coherence Interferometry

The recombined waves after reflecting from the reference and sample arms form an interference pattern on the detector. The detected signal is given by Eq. (1) where:

\[ I \propto |E_r + E_s|^2 \]  

(1)

where \( E_r \) and \( E_s \) are the reflected electrical field from the reference and sample arm, respectively. Eq. (1) can be rewritten as:

\[ I \propto |A_r e^{i(2klr - \omega t)} + A_s e^{i(2kls - \omega t)}|^2 \]  

(2)

where \( k \) represents the angular wavenumber and \( \omega \) is the angular frequency of the wave. \( l_r \) and \( l_s \) are the lengths of the sample and reference arms, respectively. Expanding the magnitude square:

\[ I \propto [A_r^2 + A_s^2 + Re\{E_r E_r^*\} + Re\{E_s E_s^*\}] \\
= [A_r^2 + A_s^2 + 2A_r A_s \cos(k\Delta l)] \]  

(3)

The third term is the cross-correlation term and it depends on the path length difference between the reference arm and sample arm (\( \Delta l \)). The intensity reflected from a real tissue sample is normally much smaller than the reflection from the reference arm. Thus, only the cross-correlation term containing the interference information remains by ignoring the very small term \( A_r^2 \) and subtracting the measurable term \( A_s^2 \) from Eq. (3). The interference has a frequency which is determined by \( \Delta l \). A larger path length difference produces a higher frequency modulation in the angular wavenumber domain that allows \( \Delta l \) to be determined, which is essential in locating reflectivity changes in a sample [11].

When a low-coherence source of a finite bandwidth is used, the detected signal can be written as a sum of all the monochromatic waves reflected from the sample [9]:

\[ I(k) = s(k) [R_r + \sum_i R_i + 2 \sqrt{R_r} \sum_j \cos(k \Delta l_j) + \\
2 \sum_i \sum_{j \neq i} \sqrt{R_i R_j} \cos(k \Delta l_{ij})] \]  

(4)
where $s(k)$ is the spectral intensity distribution of the light source, $R_i$ is the reflectivity of the reference arm mirror, $R_i$ and $R_j$ are reflectivity’s in the $i^{th}$ and $j^{th}$ layers of the sample; $\Delta l_i$ is the optical path length difference between the $i^{th}$ and $j^{th}$ sample layers. The third term in Eq. (4) contains the axial depth information in the sample which appears as interferences of light waves. $I(k)$ is the intensity as a function of the angular wavenumber $k$, which could be measured by separating the different components using a diffraction grating, which explained in section 3.3. The diffraction grating in a spectrometer redirects light of different wavelengths to different directions, allowing a line arrayed camera to detect the intensity value at particular wavelengths. The depth profile of the sample is generated from the detected signal by performing the FT from the $k$ to $z$ domain, resulting in Eq. (5) [9].

$$
|F_{k}^{-1}[I(k)]| = \Gamma(z) \otimes \\
\left\{ R_i \delta(0) + \sum_i R_i \delta(z) + 2 \sqrt{R_i} \sum_{i,j} \sqrt{R_i} R_j \delta(z \pm \Delta l_i) \right\} + 2 \sum_i \sum_{i,j} \sqrt{R_i} R_j \delta(z \pm \Delta l_{ij})$$

Here, $\Gamma(z)$, the FT of the source spectrum, represents the envelope of its coherence function. The variable $z = l_i - l_j$ represents the path length difference between the reference arm and the depth location of the reflection. The variable $\otimes$ represents convolution. The first and second term in the bracket of Eq. (5) are non-interferometric, and contribute to a DC term at $z = 0$. The third term contains the axial depth information related to the reference path and the final term corresponds to autocorrelation noise between layers within the samples, which is usually small and located near $z = 0$.

3. SD-OCT System Configuration

Figure 2(b) shows general components of a typical SD-OCT system. SD-OCT has additional system components compared to the Michaelson interferometer, such as a scanning part and a spectrometer in place of the single photodetector. To realize a high-performance SD-OCT system, all the components should be carefully selected due to their contributions to a transfer function of final system performance.

3.1 Light Source

OCT depth resolution is defined by the temporal coherence of the light source, which is inversely proportional to the spectral bandwidth [1]. Thus, broadband light sources result in better axial resolution than monochromatic laser sources. The choice of light source central wavelength is also important. According to the Beer’s law, optical penetration depth depends on the sample absorbance and this is strongly wavelength dependent [5]. Hence, different wavelengths lead to various OCT probing depths. OCT using 800 nm of wavelength is typically used to image the retina due to low absorption of the water component of the vitreous in the eye, and 1310 nm is preferred in other samples due to the reduced scattering and allowing light to penetrate deeper inside samples [6].

Popular light sources include super luminescent diode (SLD), femtosecond Titanium-sapphire laser and photonic crystal fiber based light source [1]. It is worth noting that all other optical components in SD-OCT should have a corresponding spectral range to the selected light source.

3.2 Scanning Optics

The scanning mirror allows obtaining 2D or 3D images. Incident light on a sample is a single point which corresponds to a single A-line. By scanning the light on the sample in either horizontal or vertical way, both multiple A-lines and B-scan images can be acquired to form 2D or 3D images [11]. The scanning mirror (galvanometer actuated mirror) is normally controlled by a voltage waveform input to its controller board. The controller board is a closed-loop control system using the angular orientation of the scanning mirror as feedback. The scanning range is defined based on the number of A-lines. Exporting a triangular voltage waveform to the control board with miniature steps makes the scanning mirror scan through its defined range in a linear way.

3.3 Spectrometer

The spectrometer (Figure 3) is considered as one of the most important parts of the SD-OCT system since it can affect to axial resolution, imaging range and sensitivity fall-off of system performance [6].

The spectrometer contains a dispersive element to separate the wavelength components of interference light coming back from the reference and sample arm. The incoming light detection is carried out on an arrayed line detector such as a charge-coupled device (CCD) or complementary metal oxide semiconductor (CMOS) sensor. The arrayed line detector generally has 1 x 1024 or 1 x 2048 pixels as photodetectors [6]. Hence, the separated wavelength components are detected by each pixel and the resulting spectrum is mapped out with its corresponding intensity after the FT.
The maximum line rate of the detector is directly related to the scanning speed [6]. Generally, the higher scanning speed is preferred and it can be increased by using only a small portion of the pixels (For example, 800 pixels are only used out of 1024 pixels). However, this method will result in a smaller spectral bandwidth detected, which results in worsening the axial resolution compared to the theoretical resolution [6]. On the other hand, if the spectral bandwidth is too large, this will decrease imaging range with no improvement on the axial resolution [6]. Therefore, optimizing the spectrometer design is crucial in terms of determining axial resolution and imaging range.

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4. OCT in Retinal Research

OCT has evolved as one of the most important diagnostic tools in ophthalmic practice since it is a non-invasive imaging technique and provides high-resolution for cross-sectional 2D and 3D images of retina with the optic nerve head (ONH). As shown in figure 2(b), the light from the sample arm is backscattered from the retina and interferes with the reference light, which is reflected back from the reference mirror. This interference pattern is processed in the spectrometer with the FT to construct depth profile of the retina in vivo (Figure 4). Thus, it can aid in analyzing morphological and quantifying changes in various eye disease states.

For example, the size and shape of macular holes determined by OCT correlate well with the functional outcomes following surgical intervention [2]. And the retinal thickness measurements by OCT are generally used in clinics to monitor the progress of ocular diseases such as age-related macular degeneration (AMD) and macular edema [2]. In addition, the ability of OCT to detect fluid within the retina helps clinical decisions regarding treatment. The evaluation of the vitreomacular interface is also one of the important applications of OCT [2]. Moreover, retinal nerve fiber layer (RNFL) thickness measurements using OCT helps monitor the progression in patients with glaucoma [2]. Recent commercialized OCT systems also can be used to evaluate choroidal thickness to diagnose AMD and diabetic retinopathy (DR) [2].

![Figure 3. Configuration of a spectrometer](image)

**Figure 3. Configuration of a spectrometer**

![Figure 4. Left: 1D acquisition (A-scan). A single depth profile is acquired which measures backscattered intensity vs. axial dimension (depth). Middle: 2D imaging (B-scan). The OCT beam is scanned in a transverse direction while A-scans (red arrows) are acquired. Right: 3D acquisition. Multiple B-scans are acquired such that A-scans are sampled on a 2D grid in the transverse plane. From [7], reprinted by permission from The Optical Society](image)

**Figure 4. Left: 1D acquisition (A-scan). A single depth profile is acquired which measures backscattered intensity vs. axial dimension (depth). Middle: 2D imaging (B-scan). The OCT beam is scanned in a transverse direction while A-scans (red arrows) are acquired. Right: 3D acquisition. Multiple B-scans are acquired such that A-scans are sampled on a 2D grid in the transverse plane. From [7], reprinted by permission from The Optical Society**

Besides structure analysis, recent research has put more efforts on developing functional OCT systems since the early sign of the diseases normally first appears as functional abnormalities before structural changes.

One of the promising techniques is OCT angiography (OCTA), which aims to visualize and quantify blood flow [8,15]. OCTA can measure retinal blood circulation and this allows OCTA to evaluate the microcirculation of specific regions in the retina [14]. Several techniques for OCTA have been developed such as eigen-decomposition (ED) analysis, Doppler (Figure 5), speckle variance (SV), phase variance (PV), optical microangiography (OMAG) and correlation mapping (CM).
Another promising OCT technique is intrinsic optical signal (IOS) imaging in the retina (Figure 6). The IOS refers to stimulus-evoked changes of all types of intrinsic optical properties, such as transient light scattering, absorption fluctuations and birefringence changes in excitable cells [16]. Therefore, physiological malfunctions at cellular levels can be recognized by observing scattering and birefringence response through OCT B-scan image after light stimulation. By analyzing the variation of each pixel intensity in B-scans before and after light stimulation, we can construct retinal IOS images [16]. While reliable mapping of fast IOS signal in a human subject is still challenging due to potential contamination of stimulus-associated metabolic changes and eye movements, recent pilot studies have shown promising results [16]. Thus, it is expected that better instrument and software improvements of OCT in the near future may help to realize the functional IOS mapping of human retinal photoreceptors in clinics, which can aid in early detection of many eye diseases.

5. Conclusion

In this paper, we concisely reviewed SD-OCT including the fundamental principles of low-coherence interferometry, system configuration, and medical applications in retinal research. SD-OCT still has a lot of aspects to be improved in their performance by developing both hardware components and software algorithms, which can allow much faster scanning and correcting noises. As like other imaging modalities, SD-OCT can also provide in vivo structural and functional images of human tissues at the cellular level. These capabilities make SD-OCT a promising imaging modality, which fills the gap between microscopy and ultrasound imaging. Although OCT using light as an imaging source has inherent limitations of imaging range, its presence in ophthalmology, where small imaging range (less than a few mm) with high resolution (a few μm) is mainly required, will become indispensable as time goes by.

6. References


3. Drexler, W. and Fujimoto, J. G. Optical coherence tomography: technology and applications (Biological and Medical Physics, Biomedical Engineering). Springer, Boston


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.

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

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

Author Name

Abstract

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

Keywords: Template, UIC, Bioengineering, Student, Journal

1. Introduction

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

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

2. Example of Numbered Heading

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

Figure 6. Figure captions are to be below the figure in 9pt Times New Roman, Justified

2.1 Example of Subheading and Table

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

| Table 1. This table descriptor is 9pt Times New Roman, Justified |
|-------------------|----------------|--------------|--------------|
| Column 1 | Column 2 | Column 3 | Column 4 |
| Row 1 | This | is | Times |
| Row 2 | New | Roman | 10pt |

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.

\[ E_{(t)} = m^2 a(s-h) + P_o + A(t) * \Sigma(s) \]  (1)

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)


