NON-INVASIVE MEASUREMENT OF BILIRUBIN TO BE INCLUSIVE FOR ALL SKIN-TONES

OPTICAL IMAGING: EXPLAINING RACIAL DISPARITIES SEEN IN COVID DEATHS AND TREATMENT

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On my honor as a University student, I have neither given nor received unauthorized aid on this assignment as defined by the Honor Guidelines for STS papers

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Optical imaging is a clinical technology used by a broad range of mechanical devices to measure blood oxygen saturation, heart rate, and jaundice progression (Pirovano, 2020). Neonatal jaundice is very common and is caused by a buildup of bilirubin in the blood. Bilirubin is a yellow chemical that is produced when the red blood cells get broken down. This chromophore is normally taken care of by the liver, which processes bilirubin and sends it to the intestines so it can be removed from the body, but the combination of underdeveloped livers and high red blood cell concentration in infants leads to neonatal jaundice. Monitors tend to overestimate bilirubin concentration in infants with high melanin content due to an overlap in the frequency of absorption of bilirubin and melanin (Lamola and Russo, 2015). Because melanin governs skin-tone and is a potent light absorber, this chromophore decreases the amount of light that can be used diagnostically, preventing deeper penetration of image devices (Mantri and Jokerst, 2022). Overestimation of bilirubin levels leads to the infant undergoing phototherapy to treat jaundice for longer than necessary durations which has many negative side effects (Okwundu, 2017).

In practice, these longer phototherapy prognoses are influenced by skin-tone, shedding light on a dissonance in the quality of healthcare received by different ethnic groups. In order to remedy this issue, and over the course of two semesters, the technical team will investigate alternate methods for detecting TSB in neonates with high melanin content. This involves designing a transcutaneous, non-invasive bilirubinometer that provides accurate values regardless of an individual's skin tone. Using literature and experimental analysis, the group will develop a computational and physical model that will coalesce to provide a proof concept of measuring serum bilirubin non-invasively while being skin-tone inclusive.

Common medical parameters used to guide clinical decision making include blood oxygen saturation; blood oximeters report significantly higher blood oxygen saturation levels in darker-skinned individuals; biases results in a 3.2-fold increased likelihood that dark-skinned patients are not diagnosed for hypoxia and thus do not receive supplemental oxygen that they would otherwise need (Sjoding et al., 2020). These disparities in medical treatment illustrate the importance of creating skin-tone inclusive designs and investigating how different political and medical groups respond to racial biases surfacing from technical research. Tightly coupled, the STS component will examine how skin melanin content can change medical outcomes pertaining to pulse oximeter administration. The report will look into different optical imaging methods through the context of Pacey's Triangle and assess racial disparities in COVID-19 deaths and treatment.

JAUNDICE IN NEWBORNS

Neonatal jaundice occurs in approximately 50% of term and 80% of preterm infants within the first week of life (Queensland, 2019). Jaundice causes the skin to turn yellow due to hyperbilirubinemia which is a buildup of bilirubin in the blood. Careful monitoring of all newborn infants and the application of appropriate treatments is essential since high bilirubin concentrations can cause acute bilirubin encephalopathy and kernicterus (Kemper et al. 2022). Kernicterus is a permanent disabling neurologic condition characterized by the following: choreoathetoid cerebral palsy, upward gaze paresis, enamel dysplasia of deciduous teeth, sensorineural hearing loss, and dyssynchrony spectrum disorder (Perlman, 2018). Phototherapy is completed in 10% of term and 25% of preterm neonates to treat severe hyperbilirubinemia by photoisomerization bilirubin to an easily excretable form (Quensland, 2019).

Glucose-6-phosphate dehydrogenase (G6PD) deficiency, an X-linked recessive disorder that decreases protection against oxidative stress, is now recognized as one of the most important causes of hazardous hyperbilirubinemia leading to kernicterus in the United States and across the globe (Kuzniewicz, 2014). Knowing information about genetic ancestry can help inform the assessment of G6PD risk. Overall, 13% of African American males and about 7% of African American females have G6PD deficiency (Nkhoma, 2009). This data emphasizes the importance of developing skin-tone inclusive designs for the evaluation of hyperbilirubinemia; this greater susceptibility exacerbates the consequences of inaccurate measurement of TSB (Kuzniewicz, 2014).

TAKING AN UNBIASED APPROACH TO BILIRUBIN MEASUREMENT

The current gold standard method used to determine blood bilirubin levels is using serum samples involving Total Serum Bilirubin (TSB), which requires obtaining venous or heel stick blood samples (Shaw and Ohlsson, 2011). This procedure, while accurate, is painful and invasive, and poses a danger to the infant as it is associated with significant increased risk of infection (Pediatrics, 2022). Other risks of heel pricks include puncturing the heel bone or joint disease, which causes damage to cartilage and bone; in order to continuously monitor TSB, nurses must prick the newborns numerous times, a procedure that is often carried out in the previous heel stick site (Shah and Ohlsson, 2011).

Transcutaneous bilirubinometry (TcB) has emerged as an easy, safe, and convenient method for the evaluation of the severity of jaundice, since no invasive procedure is involved (Ebbesen, 2021). However, while there is no debate regarding the efficacy of this method on

White babies, monitors tend to overestimate bilirubin concentration in infants with darker pigment due to an overlap in the frequency of absorption of bilirubin and melanin as shown in Figure 1 below (Lamola and Russo, 2015).

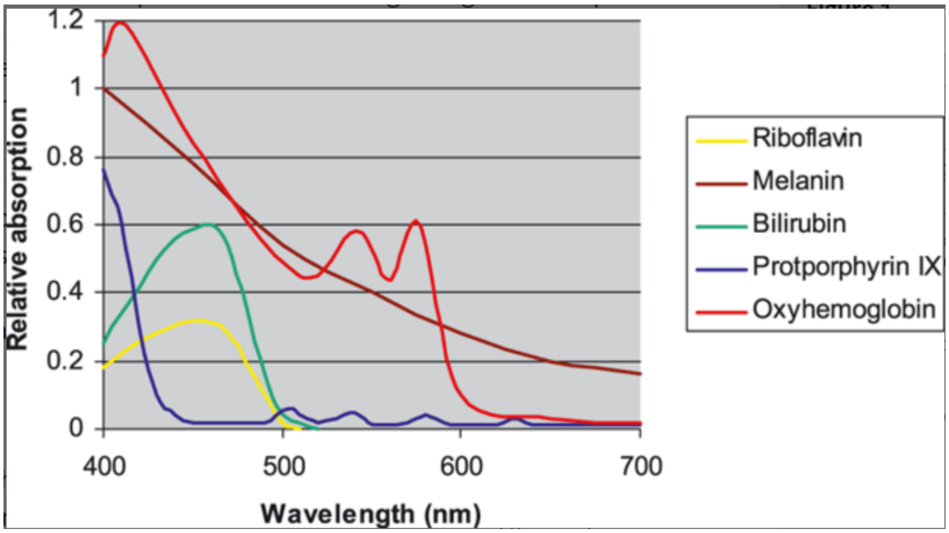

Figure 1: Skin chromophore absorption spectra: Shows the relative absorption of different light energy wavelengths for cutaneous chromophores (Mahmoud et al., 2008).

Light wavelengths used via phototherapy in a clinical setting fall somewhere in the range of 450 to 500 nm; Figure 1 shows biliribun's peak relative absorbance wavelength at 470 nm respectively. The absorbance line for melanin is greater than bilirubin at all points on the graph. There is literature to support that the absorbances of these chromophores are additive such that melanin will absorb photons meant for conversion of bilirubin into lumirubin which the body can readily break down and excrete (Ennever, 2010). For darker-skinned infants, the line for melanin has a significantly larger absorbance spectrum due to the darker pigment. Monitors will thus overestimate the amount of bilirubin due to the significant increase in melanin chromophore content (Onks, 2007).

This overestimation of TSB leads to the infant undergoing unnecessary phototherapy for long durations which has many negative side effects, including depleting essential nutrients, disrupting the thermochemical environment, and needlessly separating the infant from its mother (Okwundu, 2017). The criteria for success of this project is based on the overarching improvements it aims to achieve over current technologies. Most importantly, this involves designing a transcutaneous, non-invasive bilirubinometer that provides accurate values regardless of an individual's skin tone.

The needs regarding the light intensity and wavelength employed are based on their impact on the rate and percentage of photoisomerization of bilirubin in the skin. The wavelength of light used has been shown to significantly impact the proportion of lumirubin formed relative to other byproducts that are more difficult to excrete (Pediatrics, 2022). The light intensity is important because if too low, bilirubin photoisomerization would occur too slowly for the device to work in a timescale similar to existing devices. If the light intensity is too strong, the patient may experience notable damaging side effects (Ebbesen, 2021 & Pediatrics, 2022). Considering the absorption spectra of the myriad of components in the skin is essential, as their absorbance spectra overlap with that of bilirubin and impact the quantitative values attained via transcutaneous methods (Mahmoud et al., 2008).

The technical team, including Sam Thapaliya, Cooper Yurish, Eddy Trujilo, and myself, all fourth year Biomedical Engineering undergraduate students, plan to tackle this problem throughout the course of two semesters with guidance from William H. Guilford, associate professor in the department of Biomedical Engineering. Timed photobleaching will be utilized in order to create a decay curve for individual patients. To complete this, we will create a computational framework in MATLAB that will allow for the determination of the optimal photoisomerization wavelength using extinction coefficients and quantum yield of bilirubin and melanin from existing literature. Then, we will adapt this framework to model the decay of bilirubin at different concentrations of melanin and bilirubin during phototherapy.

To validate the computational model, we will create a physical model using a visible light laser diode from ThorLabs centered at 470 nm that will photisomerize bilirubin in a cuvette at different concentrations of melanin. Building a physical model that only accounts for melanin and bilirubin is an important step; melanin is found in particularly high concentrations in the skin and the peaks of its reflectance spectrum overlap significantly with that of bilirubin (Lamola and Russo, 2015). This likely makes melanin the cutaneous component that may impede the progression of our concept. As such, it is imperative that the computational and physical model coalesce in order to successfully utilize efficacy ratios for light with different peak wavelengths.

Our research could improve the quality of neonatal care, allow for the monitoring of discharged newborns, and reduce the number of newborns readmitted to the hospital for phototherapy or exchange transfusion. In addressing the dissonance in healthcare received by infants with higher melanin levels, the future applicability of work provides an avenue for better tackling the mathematical and experimental intricacies of a bigger racial problem in healthcare.

HOW HARD IS IT TO CHANGE TECHNOLOGY?

Pulse oximeters are widely used in clinical and nonclinical settings to measure blood oxygenation levels of critically ill, perioperative, and chronically ill patients (Pirovano, 2020).. They work by shining light at two wavelengths: 660nm and 940nm through the skin, which correspond to deoxygenated and oxygenated hemoglobin absorption (Jurban, 2015). The increase in absorption during a heartbeat is measured at each wavelength, then ratio of light absorption at the deoxygenated to oxygenated hemoglobin wavelengths is used to estimate blood saturation level with a calibration curve. Blood oxygenation is used as a threshold for determining the use of supplemental oxygenation as treatment (Jurban, 2015).

However, these absorption values are also affected by the relative concentration of other cutaneous contents such as melanin, the chromophore responsible for skin-tone. Melanin has a greater absorption at 660 nm than 940 nm wavelengths meaning greater melanin concentration increases the deoxygenated wavelength absorption baseline (Bicler, 2005). This value gets read by the computer, interprets the smaller increase of absorption, and reports an overestimate of blood saturation level.

The increased estimation of blood oxygen in darker-skinned patients has been observed clinically since the 1990's: Juran and Tobin found that the target pulse oximeter saturation level of patients receiving supplemental oxygen was 3% higher in darker-skinned patients than lighter-skinned patients because of the overreporting of actual saturation levels in Black subjects (Juran and Toblin, 1990). This bias prevents darker-skinned patients from access to supplemental oxygen or insurance reimbursement if those decisions are based on blood saturation levels read from oximeters. But if this literature has existed for over 30 years, why has it taken more than 10 studies and numerous op-ed's for the FDA to finally acknowledge this device bias? (FDA, 2021, Sojoding, 2020).

This discovery raises many questions regarding the larger network of which this technology is a part. In Arnold Pacey's book on the culture of technology, he defines technology as the application of scientific knowledge to practical tasks by ordered systems that involve people and organizations. In doing so, Pacey examines people and machines to identify the cultural aspects of technology practices which would otherwise be neglected (Pacey, 1983).

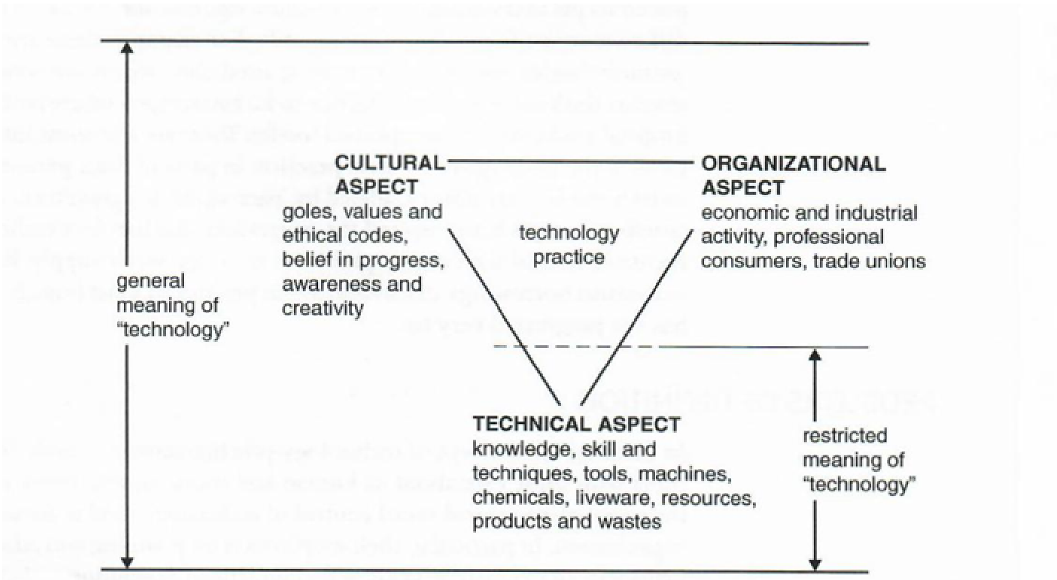

Figure 2: Pacey's Triangle of Technology Practice: identifies the larger network which a particular technology is a part. (The MIT Press., 1983).

As shown in Figure 2 above, Pacey neatly diagrams this concept as a triad of aspects that work together to comprise technology-practice. The technical aspect is the aspect that is most often associated with knowledge, skill and technique, tools, chemicals, and the products themselves. The organizational aspect is primarily institutional, with concerns in social and political groups and businesses designed to get things done. The third, and arguably most important aspect, is the culture, which Pacey identifies deals with the ideological aspects of technology, perceptions, and values (Baum, 1994).

Applying Pacey's triangle to optical imaging, the socio-technical intricacies of this healthcare practice start becoming significantly important. If cultural values about progress and beliefs have a major impact on the nature of optical imaging, and if these values are the ones that stand behind discourse that drives technological advancement, why do we continue to see racial disparities in medical devices?

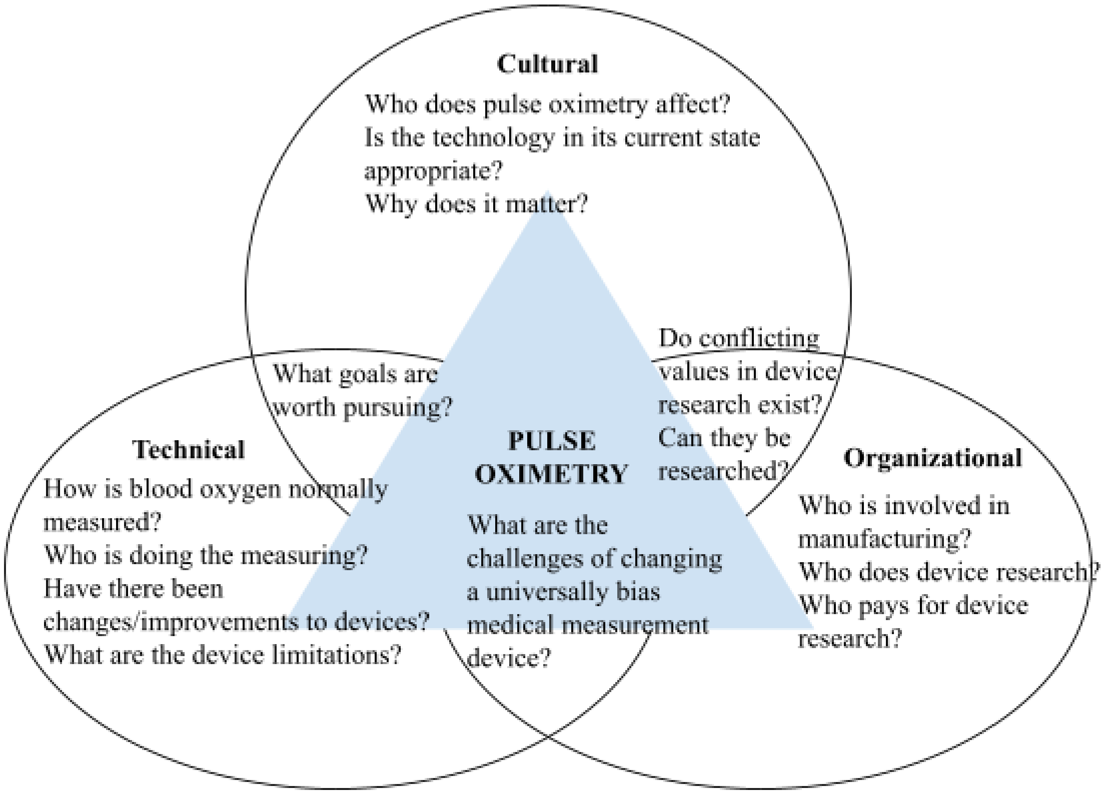

Figure 3: Pacey's Triangle of Technology Practice as a venn diagram: highlights research questions to achieve a fundamental understanding of optical imaging intricacies (Adopted by Van Spinelli from P. Macmillian., 2022).

Questions with regard to the otherwise invisible factors that influence optical imaging as a medical technology are shown in Figure 3 above. In the regions of overlap, questions concerning the values of medical device researchers and the technological goals that would be appropriate to pursue are surfaced. These are key to understanding the power dynamics and political commitment to the technocentric narrative of optical imaging technology. The STS component will provoke and encourage engineers to take a step back and examine the technical apparatus of a technology they aim to improve. While some distinction exists between pulse oximetry and bilirubin measurement, one could argue that both pose many of the same issues viewed through the lens of Pacey's Triangle. In this light, the STS component aims to answer the question: what are the challenges in addressing a universally biased clinical measurement device? This question, while focused, is complex and very rich in depth. The hope is that by acknowledging all three aspects of Pacey's triangle, a foundation to the question posed will surface. The plan is to evaluate pulse oximetry data and shed light onto manufactures, shareholders, and research funders. Importantly, laying down the foundation for the big players involved in optical imaging will involve thinking deeply about the literature that is available to the public. In spite of this, the Technical group will be exposed to many of the challenges associated with ground work and researching methods in attempting to establish an unbiased alternative to bilirubin measurement; the hope is that our experience and relevant anecdotes will transfer over smoothly to the STS analysis. This substantive approach to dismantling the technical apparatus is simple in concept, but has rich applications for tracing power, politics, and mythos in these technologies.

CHANGING THE SOCIO-TECHNICAL FUTURE

In order to form more robust understandings of the nature of technology controversy, the causes of scientific and technological change, and the limits of rational analytic methods in characterizing complex problems, it is necessary to identify human and non-human actors influencing a technology's progress. Optical imaging devices have existed long enough for STS frameworks to establish motivations for production; Pacey's Triangle can offer an avenue for answering questions regarding challenges involved in technological change. The mission of the STS and Technical components of this prospectus is to empower and motivate the next generation of engineering professionals so that they are capable of making creative, ethical, and inspired contributions to the design of our socio-technical future.

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