VALIDATING A NOVEL BILIRUBIN QUANTIFICATION METHOD: A COUPLED COMPUTATIONAL AND IN VITRO MODELING APPROACH

ETHICAL CONSIDERATIONS OF LIFE-PROLONGING TECHNOLOGY POLICY

A Thesis Prospectus
In STS 4500
Presented to
The Faculty of the
School of Engineering and Applied Science
University of Virginia
In Partial Fulfillment of the Requirements for the Degree
Bachelor of Science in Biomedical Engineering

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October 27, 2023

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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 Thesis-Related Assignments.

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Introduction

With the development of new diagnostic and life-extending technology, life expectancy has been steadily increasing since the 1960s by approximately 10 years as of 2020 (Medina et al., 2020). Improvements in speed of diagnosis and the expansion of treatment options have improved the prognosis of many severe illnesses, including neonatal jaundice, which is a relatively common condition characterized by yellow-tinged skin. Jaundice in newborns is usually indicator of underdeveloped liver function and insufficient clearance of red blood cell breakdown products, especially the protein bilirubin. Over 80% of newborn infants are born with some degree of jaundice and one of the severe risks of untreated jaundice is kernicterus (Kemper et al., 2022; Woodgate et al., 2011). Kernicterus is brain damage resulting from accumulation of bilirubin, called hyperbilirubinemia, in a high enough concentration to cross the blood-brain barrier. Although this condition is rare due to early diagnosis, it can be devastating when untreated, with significant mortality (10%) and long-term morbidity (70%) (Ip et al., 2004).

Measurement of bilirubin accumulation has classically been done with a blood test; however, this requires a painful heel prick and increases infection risk (Meites, 1988). A non-invasive screening method, Transcutaneous Bilirubinometry (TcB), has been developed using optical spectrometry to measure the absorbance of bilirubin and quantify its concentration. Optical spectrometry measures the absorbance of light over a specific section of the electromagnetic spectrum, in these devices it is measured in the visible light range. Measuring absorbance specifically in the visible light range is also called spectrophotometry. However, because the skin chromophore melanin has a heavily overlapping absorbance spectra with bilirubin (Figure 1), TcB devices can overestimate the amount of bilirubin in infants with greater amounts of melanin (Olusanya et al., 2017). Incorrect measurement of jaundice leads to unnecessary or prolonged treatment for neonates with higher melanin concentrations. One common treatment for hyperbilirubinemia is phototherapy, which takes advantage of bilirubin's photoconversion property. Phototherapy uses blue, 460 nm light to convert insoluble bilirubin into soluble lumirubin, allowing it to be easily excreted (Figure 2). However, excessive phototherapy can potentially lead to disruption of neonates' thermochemical environment, separation of infant and mother, melanocytic nevi, and skin cancer (Xiong et al., 2012). Thus, new bilirubin quantification technology must be developed to address this healthcare inequality and ensure accurate diagnostic ability regardless of skin tone to improve quality-of-life and prevent early mortality. One skin tone inclusive method that shows great promise for accurate bilirubin quantification takes advantage of the known photoconversion of bilirubin. As bilirubin is converted into lumirubin under 460 nm light, the decreasing absorbance measurements over time will be used to calculate initial bilirubin concentration. Prior capstone research showed proof of concept for this method in cuvettes with varying bilirubin and melanin concentrations, representing an oversimplified model of bilirubin accumulation (Yurish, 2023). This project will focus on further development and validation of a non-invasive, skin tone inclusive method of bilirubin quantification, and the second part of this report will discuss ethical questions presented by mechanical circulatory and respiratory support devices.

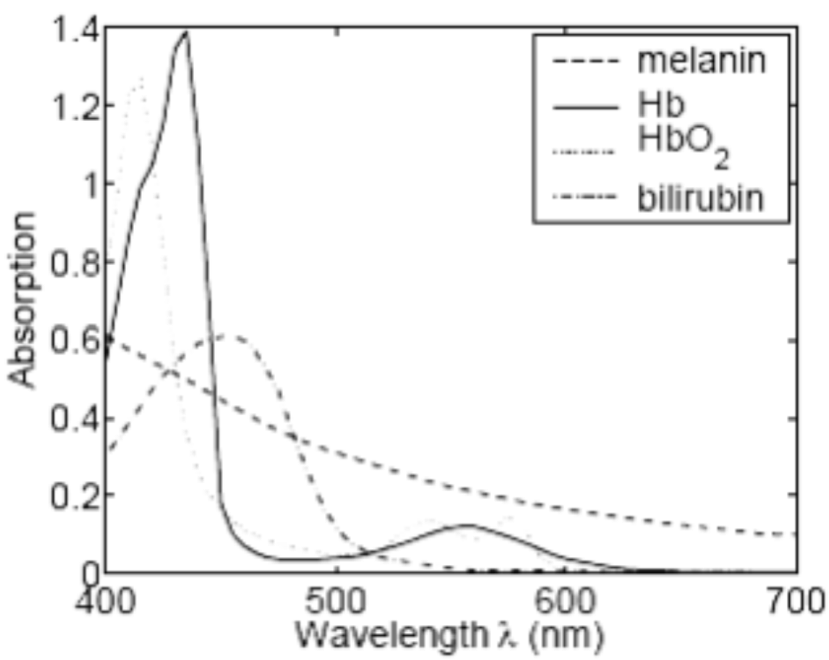

Figure 1. Absorption Spectra for Bilirubin and Melanin (Anderson & Parrish, 1981)

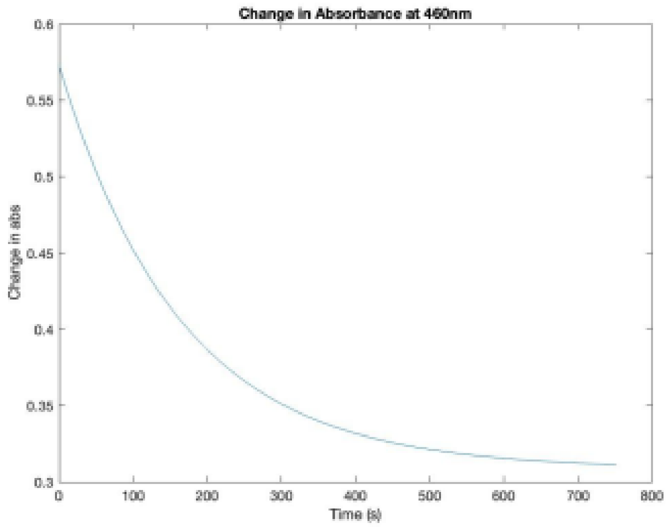

Figure 2: Simulated photo decay of bilirubin under blue light, illustrating the photoconversion of bilirubin into lumirubin during phototherapy (Yurish, 2023). The change in absorbance measurements at 460 nm are plotted over time.

Designing a Skin Tone Inclusive TcB Measurement Method

Bilirubin is the final product of Heme degradation, produced as red blood cells breakdown. As a hydrophobic molecule it often travels through the blood bound to the protein albumin and is excreted by the liver (Wang et al., 2006). In the first few days of life there is more than twice the bilirubin production rate compared to adults due to increased red blood cell turnover (Porter & Dennis, 2002). Additionally, for a large portion of infants the liver is not fully developed, leading to an accumulation of cytotoxic bilirubin that occurs when the concentration of bilirubin exceeds that of albumin (Wang et al., 2006).

Before the advent of noninvasive screening devices, clinicians would have to wait for clinical presentations of hyperbilirubinemia to identify candidates for TSB testing. The development of TcB devices have allowed infants to be screened for hyperbilirubinemia before the presentation of symptoms, allowing for more accurate identification than visual inspection and reducing the amount of painful heel pricks for blood collection (Keren et al., 2009; van den Esker-Jonker et al., 2016). The direct relationship between increasingly yellow-colored skin and the amount of unbound bilirubin in the blood is the basis for non-invasive bilirubin measurement. The first TcB devices were developed in 1980, but were quickly found to have inconsistencies in measurement with age and skin tone. Newer generations were developed, such as the JM-103 bilirubinometer, which uses spectrophotometry to measure the scattering of blue relative to green light in the skin. Bilirubin's absorbance spectra peaks in the blue light wavelength, so hyperbilirubinemia would cause less blue relative to green light to be measured (Lyon et al., 2009). While these devices improved certain aspects of original bilirubinometers, such as calibration requirements and age-dependent measurements, they still overestimate the TcB levels in neonates with increased melanin concentrations (Maya-Enero et al., 2021; Olusanya et al., 2017).

To address this healthcare disparity, a detailed computational and *in vitro* physical model will be created to determine the viability of using photoconvertible properties of bilirubin to quantify its initial concentration. To computationally account for the absorbance spectra overlap of bilirubin and melanin, existing absorbance data will be incorporated to differentiate between melanin and bilirubin absorbance spectra through an Exponential Moving Average computational model. Then, mass balance equations will be used to develop a time-dependent analytical model for neonatal bilirubin concentration. Finally, computational model parameters will be optimized and validated by an *in vitro* model and the mass-balance model to enable realistic testing. An *in vitro* flow dialysis model will also be created that contains bilirubin-albumin solutions dialyzing into a hydrophobic gel, mimicking bilirubin diffusion into tissue. This model will be used to assess the diffusive properties of bilirubin from solution into the tissue replica. Using the *in vitro* and computational models, spectrophotometry will be used to measure the visible light absorption as bilirubin photoconverts under 460 nm light, allowing initial bilirubin concentration to be computed and providing a more robust proof of concept for this method of quantifying bilirubin levels. Validating this skin tone-independent method of bilirubin measurement could pave the way for a prototype device to be developed that could eventually be found in clinical settings to address healthcare disparities stemming from overestimation of bilirubin levels.

Ethical Considerations of the Use of Extracorporeal Membrane Oxygenation Devices

When patients experience significant trauma or the end-stages of severe illness, they can be left in a coma and reliant on life-support for breathing and blood circulation. Families are faced with heartbreaking decisions about treatment, quality-of-life concerns, personal beliefs, and hopes for recovery. Life-extending technologies, particularly mechanical ventilation and circulatory devices, have made it possible to maintain someone who is near death past the point of meaningful interaction with their surroundings. Mechanical ventilation and circulatory devices have even changed the definition of death, causing the addition of a brain death criteria because pulse and respiratory cessation could no longer solely define death (Parent & Turi, 2020). These devices, called Extracorporeal Membrane Oxygenation (ECMO) devices, aerate and pump blood through the body, acting as both heart and lungs (Featherstone & Ball, 2018).

ECMO has transformed end-of-life and intensive care by extending life past natural capabilities. However, along with the ability to live for a greater quantity of time, the quality of that time must also be considered. To analyze the legal, ethical, and economic facets of ECMO in compassionate end-of-life care, multiple ethical frameworks will be used, each to analyze a unique dimension of the technology’s impact. Duty ethics will be used to understand legal complications arising from the development of ECMO. Duty ethics says that people have specific duties and one of the most important is to protect the rights of others (Fleddermann, 2004). Legal constructs governing the use of life extending technology, including Advanced Directives and Durable Power of Attorney, have been created, exemplifying the key idea in duty ethics that individuals must be respected. These legally protect a patient’s autonomy through written instructions concerning end-of-life care or another person to advocate for their best interests even if the patient is no longer competent (Meisel, 2016). Care ethics will be used to understand ethical implications that have shaped clinical practice guidelines. Care ethics emphasizes the importance of relationships, stating that morals are learned from the responsibility resulting from connections with others and care felt towards them (van der Poel, & Royakkers, 2011). Due to the inherent doctor-patient power imbalance, ethics and morals are the cornerstone of clinical practice. This is echoed in the results of a study finding an overwhelming majority of clinicians supported withdrawing life-sustaining care in certain contexts, with chief justifications including having no possibility for improvement and prevention of suffering (Fauriel et al., 2005). Finally, utilitarianism will be used to analyze the use of ECMO from an economic and resource-optimization perspective. Utilitarianism is an ethical decision-making framework that says actions are good that maximize human well-being (Fleddermann, 2004). Utilitarianism prioritizes the good of the collective over the individual. Decisions to use life-sustaining technology can be based on the cost-benefit analysis of balancing financial concerns of high end-of-life care costs with the meaningful interactions and comfort gained. Additionally, hospitals must consider how to triage resources most effectively to provide the most good to the most people, which could influence their ECMO use policies. Overall, end-of-life care decisions are multi-faceted and policies have been built to allow for the most ethical action within the unique context.

Research Question and Methods

The expanded capabilities and resulting ethical quandaries afforded by ECMO beg the question: What does compassionate end-of-life care look like when ECMO is used and how have legal, ethical, and economic perspectives shaped regulations and guidelines surrounding its use? This question is important in understanding the values that have been codified as a result of the development of this technology and to what extent those values exemplify widely held societal views. Laws and judicial decisions often embed general societal agreements and beliefs of the time and have immense power in shaping societal behaviors and attitudes. For end-of-life care there have been key legislative and judicial policies governing the use of advanced life-sustaining technologies. Clinical practice guidelines are also important in specifically guiding physician’s actions and ethical views. These regulations and guidelines will be used to understand how society has come to define compassionate end-of-life care through various ethical frameworks. Landmark judicial decisions of In re Quinlan 1976 and Cruzan v. Director 1990, legislation including the 1981 Uniform Determination of Death Act and the Health Care Decisions Act, and clinical practice guidelines published by the American Thoracic Society will be thematically coded to analyze implicit values pertaining to the care and duty ethical frameworks. Additionally, sources describing the economic impacts of life-sustaining care will be analyzed from a utilitarian perspective. Integrating these sources will help illustrate the societal impact of life-sustaining technologies.

Conclusion

To conclude, the technical report will detail an accurate, non-invasive, and skin tone inclusive method of quantifying neonatal jaundice tested in a physiologically representative system. Computational and *in vitro* models will be created to better understand bilirubin transport and how its photoconvertible characteristics can be leveraged in diagnostics, which will determine the feasibility of creating a TcB prototype device using this method. This project will help reduce healthcare disparities by validating a non-invasive method to accurately quantify bilirubin, allowing clinical decisions concerning further testing and treatment to be unbiased. Additionally, I will illustrate how the development of life-sustaining technology has caused the development of regulations regarding its use. Through the analysis of economic factors, legal regulations, and clinical guidelines surrounding end-of-life care and concurrent ECMO technological development, its impact on societal views of compassionate care will be better understood.

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