Novel Bilirubin Quantification Method: Computational and *In Vitro* Validation

Using Technological Politics to Examine Racial Healthcare Disparities in Neonatal Jaundice Assessment

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

Neonatal jaundice is a prevalent condition resulting from an accumulation of bilirubin in the bloodstream and affects approximately 50% of term and 80% of preterm infants (Woodgate & Jardine, 2011). If left untreated or undetected, jaundice can lead to severe complications such as encephalopathy (brain disease), hearing loss, and kernicterus—a debilitating and long-lasting neurological disorder (Kemper et al., 2022). Presently, non-invasive transcutaneous bilirubinometers (TcB) often overestimate bilirubin levels in neonates with darker skin tones (higher cutaneous melanin concentrations), reducing the effectiveness of TcB screening in this racial group (Varughese et al., 2018). I propose the development of a novel computational model that distinguishes between the absorbance spectra of melanin and bilirubin, coupled with an *in vitro* model mimicking bilirubin transport into the skin, enabling realistic testing. By developing a more accurate method for bilirubin assessment, this project aims to enhance the value of neonatal jaundice monitoring for both healthcare providers and the neonatal population, particularly those with darker skin tones.

As the accuracy of bilirubin measurements has profound technical and social implications, adopting an interdisciplinary approach that considers both the social and technical aspects of neonatal jaundice monitoring is crucial to the success of this project. I will draw on Langdon Winner's Technological Politics (TP) framework to investigate how bilirubinometers unintentionally exhibit implicit bias in their design, favoring neonates with lighter skin tones while unintentionally disadvantaging those with higher levels of melanin. By analyzing these social factors, I aim to shed light on the implications of racial bias in healthcare, emphasizing its consequences and contributing to a broader understanding of this pressing issue.

Attending to both the technical and social aspects of the sociotechnical challenge provides a more comprehensive and holistic, and thus more effective, approach to addressing the challenge. By acknowledging the social aspects, technical solutions can be designed that are not only accurate but also equitable, ensuring that all neonates, regardless of their skin tone, receive appropriate care. Because improving neonatal bilirubin assessment is sociotechnical in nature, it necessitates addressing both its technical and social aspects. In what follows, I elaborate on two related research proposals: first, a technical project that describes an enhanced approach to neonatal bilirubin assessment, and an STS project that examines the technological politics surrounding non-invasive transcutaneous bilirubinometers. STS project insights will help inform algorithm development in the computational model to mitigate overestimation of TcB and shape the *in vitro* model to accurately replicate diverse neonatal melanin concentrations. This integration aims to develop a solution that not only advances the state of the art in bilirubin assessment but also mitigates racial bias in healthcare.

Technical Project Proposal

To manage neonatal jaundice, up to 10% of full-term and 25% of premature neonates need phototherapy, a treatment that employs blue light to reduce bilirubin levels in the blood (TSB) by photoisomerizing the bilirubin in the skin (TcB) into the easily-excretable lumirubin (Queensland Clinical Guidelines, 2022). Monitoring and diagnosing neonatal jaundice currently rely on two methods: the invasive measurement of total serum bilirubin (TSB) through venous or heel stick blood samples and non-invasive transcutaneous bilirubinometry (TcB) using a handheld bilirubinometer. While the former is accurate, it comes with notable health risks and neonatal discomfort, whereas the latter offers a non-invasive and efficient alternative (Onesimo et al., 2011; Onks et al., 1993). However, TcB screening presents a significant challenge,

particularly for neonates with darker skin tones, due to the substantial overlap in absorption spectra between bilirubin and melanin (Varughese et al., 2018). This overlap can lead to TcB overestimation, potentially resulting in unnecessary phototherapy prescriptions with side effects such as imbalances in the neonatal thermal environment, reduction of early-stage maternal-infant interactions, and melanocytic nevi and skin cancer that disproportionately affect darker skinned neonates (Xiong et al., 2012).

Last year's Capstone group developed a proof-of-concept measurement method involving continuous photoconversion of bilirubin, akin to phototherapy. Transmittance of 460 nm light through the skin is measured at specific intervals. By analyzing the decay curve and identifying the point where the transmittance curve reaches a horizontal asymptote as bilirubin fully converts to lumirubin, the initial cutaneous concentration of bilirubin (TcB) can be determined. This year's goal is to refine the computational model for more accurate bilirubin assessment from absorbance measurements and establish an *in vitro* model that replicates bilirubin flow and diffusion into the skin, facilitating realistic testing.

Currently, there is no way to computationally account for the overlap of absorbance spectra between bilirubin and melanin, thereby making non-invasive transcutaneous bilirubinometers inaccurate for patients with higher concentrations of melanin. To remedy this, we will integrate existing absorbance data to differentiate between melanin and bilirubin absorbance spectra through an Exponential Moving Average (EMA) computational model that will approximate the photoconversion decay asymptote. We will then employ mass balance equations to develop a time-dependent mathematical model for neonatal bilirubin concentration. Finally, we will optimize parameters within the computational model, validated by an *in vitro* model and the mass-balance model, to enable realistic testing.

Additionally, the mechanism behind the movement of bilirubin from the bloodstream into tissues remains poorly understood. This creates a limited knowledge base for constructing a multi-compartmental computational model to simulate bilirubin flow and photoconversion, potentially leading to inaccuracies in bilirubin quantification. To address this knowledge gap, an *in vitro* flow dialysis model will be created that includes a bilirubin solution dialyzing into a hydrophobic gel. Initially, stable solutions mimicking blood will be created by incorporating varying physiological concentrations of bilirubin, albumin, and oxyhemoglobin. Additionally, a hydrophobic material will be created that replicates *in vivo* skin properties, including the skin chromophore melanin. *In vitro* continuous flow dialysis will then be used to assess the diffusive properties of bilirubin as it moves from the solution into the tissue replica. Using the *in vitro* model, spectrophotometry will be employed to measure the photoconversion of bilirubin under 460 nm light, providing a more robust proof of concept for this method of quantifying bilirubin levels. This model will not only validate the computational model but also assist in refining computational model parameters and enhancing our understanding of bilirubin movement and photoconversion.

The combination of the computational model, enriched by insights from the *in vitro* model, will enable accurate prediction of bilirubin levels in skin with varying melanin concentrations and deepen our understanding of the mechanisms of bilirubin transport within the body. This integrated approach ensures a holistic understanding that neither model can achieve in isolation and strengthens the proof-of-concept for the innovative method developed by last year's Capstone group, potentially paving the way for the future development of a prototype medical device.

STS Project Proposal

To reduce the health risks associated with the invasive measurement of TSB, transcutaneous bilirubin screening presents a non-invasive alternative. This method employs a handheld bilirubinometer, which emits specific light wavelengths into the skin and analyzes the reflected light's spectrum. The variations in this spectrum are dependent on the wavelengths of light absorbed by various skin components, including bilirubin, hemoglobin, and melanin. The degree of light absorption by the skin serves as an indicator of bilirubin concentration (Onks et al., 1993). These non-invasive measurements offer a quantitative assessment of the risk for infants who may develop severe jaundice or bilirubin encephalopathy, facilitating timely clinical decisions, especially in regions with limited access to traditional laboratory tests (Sarici et al., 2004).

While non-invasive transcutaneous bilirubin screening is considered an effective and safe alternative, it also performs significant social and political work. Currently, neonates with darker skin tones, characterized by higher levels of cutaneous melanin, often encounter challenges with the accuracy of TcB screening. This issue arises from a significant overlap in the absorption spectra of bilirubin and melanin, as illustrated in Figure 1. Notably, melanin's absorption is particularly prominent near the peak absorbance of bilirubin, which is the optimal wavelength for detecting or monitoring bilirubin concentration. Moreover, melanin's absorption is consistently higher than bilirubin's at various points across the spectra. Consequently, higher cutaneous melanin levels can effectively obscure variations in bilirubin absorption, making it more difficult to

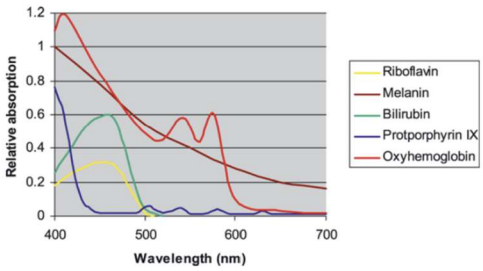

Figure 1: Comparative absorption profiles of typical skin pigments in the spectral range of 400 to 700 nm (Mahmoud et al., 2008).

accurately assess bilirubin concentrations in the skin (Mahmoud et al., 2008; Lamola & Russo, 2014). This overlap commonly leads to an overestimation of TcB, as most bilirubinometers misinterpret the increased absorption as indicative of higher bilirubin levels (Onks et al., 1993).

The overestimation of bilirubin levels poses several risks, primarily increasing the chances of neonates receiving phototherapeutic treatment for jaundice. Although this therapy has historically been deemed safe, recent research has brought to light potential side effects that were previously not fully understood. These adverse effects encompass short-term consequences, including disturbances in the neonatal thermal environment, water loss, electrolyte imbalances, disruptions in liver function, alterations in the newborn's circadian rhythm, and interference with early-stage maternal-infant interactions. Moreover, specific studies have hinted at the possibility of long-term consequences, such as the development of melanocytic nevi, skin cancer, allergic diseases, and retinal damage (Xiong et al., 2012). Therefore, if we continue to think that TcB screening only performs technical/functional work, we will miss how it also performs political work by affecting power relations among neonates with varying skin tones, particularly those with higher levels of melanin. Given the issue of TcB overestimation in neonates with darker skin tones, their heightened likelihood of receiving phototherapeutic treatment points to an unintentional introduction of racial bias into bilirubinometers. The racial bias inherent in the current approach for obtaining accurate transcutaneous bilirubin readings disproportionately affects these individuals, restricts their access to equitable healthcare, and contributes to larger issues of racial health disparities on a global scale.

Drawing on Langdon Winner’s Technological Politics (TP) framework, I argue that bilirubinometers perform political work by privileging neonates with lighter skin tones and marginalizing neonates with higher levels of melanin through an unintentional effect of design

choices that express implicit bias. Winner's framework claims that technological artifacts have "politics" through intentional or unintentional design choices which lead to the arrangements of power and authority in human associations. Therefore, technological designs can affect relations of power and privilege among groups of people by empowering some while marginalizing, excluding, or harming others (Winner, 1980). To support my argument, I will analyze evidence from primary research articles detailing the overestimation of TCB levels in neonates with higher melanin content, with a particular focus on studies conducted in African hospitals.

Conclusion

In summary, the technical project proposes an innovative computational model and *in vitro model* for neonatal jaundice monitoring, aiming to enhance accuracy and reduce the risk of overestimation of TcB, thus increasing its value to both healthcare providers and neonatal patients. Meanwhile, the STS project focuses on the social factors surrounding non-invasive transcutaneous bilirubinometry, particularly in the context of racial bias in healthcare. By drawing on Langdon Winner's framework, I aspire to gain a deeper understanding of how technological politics influences medical decisions and disparities in neonatal care, with the goal of contributing to a broader understanding of racial health disparities.

Insights from the STS project will directly inform the technical project by helping refine algorithms in the computational model to reduce TcB overestimation and optimize the *in vitro* model to accurately mimic different neonatal melanin concentrations. By examining both technical and social aspects, these projects work together to provide a more comprehensive and effective solution for neonatal jaundice monitoring. They strive to bridge the gap in racial healthcare disparities, ultimately aiming to make healthcare more equitable for all neonates, regardless of their skin tone.

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