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Signal processing system to extract serum bilirubin concentration from diffuse reflectance spectrum of human skin

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Abstract—Neonatal jaundice is a medical condition which occurs in newborns as a result of an imbalance between the production and elimination of bilirubin. Excess bilirubin in the blood stream diffuses into the surrounding tissue leading to a yellowing of the skin. The extra-vascular bilirubin act as interfering signal that limits the estimation of serum bilirubin from reflectance spectrum of human skin. This is particularly an issue for neonates who are being subjected to phototherapy (a common treatment for neonatal jaundice). Unfortunately, analytical models developed to study the light transport in human skin do not consider the effects of extra-vascular bilirubin (and other absorbing chromophores). A biomedical signal processing method that estimates serum bilirubin in presence of confounding signals such as melanin and extra-vascular bilirubin concentrations is presented. . The new system model and nonlinear solver have been successful in estimating the serum bilirubin concentration on simulated spectral databases within an average error of 15%.

INTRODUCTION

Approximately 60% of the healthy infants experience some form of hyperbilirubinemia (i.e. neonatal jaundice) arising from an increased production of bilirubin and limited ability of the underdeveloped liver to collect and excrete it. Unconjugated bilirubin is formed as a degredation byproduct during the destruction of old red blood cells. Due to an underdeveloped process for conjugation of bilirubin, unconjugated bilirubin levels often rise in newborns [1, 2]. As the unconjugated bilirubin levels rise beyond the binding capacity of albumin, diffusion processes allow the unconjugated bilirubin (sometimes referred to as free bilirubin) to diffuse out of the circulatory system and into neighboring tissues. It is this diffusion into skin tissue that causes a yellowing of the neonates skin tone.

A major concerns associated with hyperbilirubinemia is kernicterus (i.e. the diffusion of bilirubin across the under developed blood-brain barrier and into the neural tissue. While many newborns are susceptible to some level of jaundice, there is a particular concern for premature infants who have less developed liver function (leading to elevated free bilirubin levels) and reduced ability of the blood brain barrier to limit the diffusion of bilirubin into the brain (leading to an elevated risk of kernicterus) [3, 4, 5]. Phototherapy is a prominent therapeutic treatment used for hyperbilirubinemia conditions. The phototherapy process usually involves a light source in the wavelength range of 400 to 500 nm. The light interacts with the bilirubin molecules in the skin tissue. These interactions convert the bilirubin into a water soluble form which is easily excreted [6].

Reflectance spectroscopy is a non-invasive method to study the skin optical parameters and to estimate the concentration of different chromophores present in the human skin. To quantify serum bilirubin levels, a transcutaneous bilirubin index can be generated from reflectance measurement of human skin. This essentially correlates the serum bilirubin levels in the blood with a reflectance measurement of the yellowness in the skin color of jaundice patients. As described above, when bilirubin levels rise in the blood diffusion moves the free bilirubin into the skin tissue. When the phototherapy process is initiated the bilirubin kinetics are affected resulting in a reduction in free bilirubin concentration in the skin. Thus, the correlation between the transcutaneous bilirubin index and serum bilirubin levels fails.

Bilirubin deposited in the skin tissue acts as attenuating filter for the light penetrating to the bilirubin in the blood stream[7]. Thus, during the phototherapy process, the skin bilirubin is cleared at a faster rate than blood bilirubin. Since the bilirubin concentration in the blood and skin tissue are on a continuous dynamic change, there is a need for a clinical system model which could take into consideration the effect of the skin tissue bilirubin component and quantify the serum bilirubin (intravascular bilirubin) component accurately.

The objective of this paper is to develop a biomedical signal processing system to quantify the serum bilirubin concentration from reflectance spectrum of human skin. Analytical model is developed to simulate the reflectance spectrum of human skin under jaundice conditions. In a jaundiced individual skin spectrum, the serum bilirubin signal has many interfering signals such as melanin, extra vascular bilirubin etc. The signal processing system proposed is a simulation model, which would be validated with clinical experiments in the future.The has the potential to accurately quantify serum bilirubin levels

I. BIOMEDICAL OPTICAL SYSTEM

The principal components of the biomedical optical system are a white-light source optimized for the visible to near infrared region of the optical spectrum (i.e. 360-1100 nm), a reflectance probe that both directs incident light to the skin surface and collects the reflected light from the skin surface, a USB spectrometer, and a laptop computer. The spectrometer thenconverts the optical signal into a digital signal which can be processed by a signal processing

algorithm that interprets the reflected spectrum to quantify the concentrations of the different chromophores present in the skin

II. FORWARD AND INVERSE MODEL

The signal processing system to quantify the serum bilirubin from skin reflectance spectra is comprised of two parts. The first part of the system generates the reflectance spectra of human skin with varying absorption and scattering coefficients of different biological materials present in different layers of skin. The process of building a spectrum from its optical properties is defined as a forward model. In the second part of the signal processing system the serum bilirubin concentration is estimated using the forward model along with the nonlinear iterative methods till a best fit between the simulated and measured spectra is reached. Once the best fit parameters are obtained, they would be validated with clinical results.

FORWARD MODEL

The light transport through skin layers is modeled by analytically solving the radiative transfer equation or by numerically modeling with montecarlo simulations to depict the movement of photons in and out of each of the skin layers. The radiative transfer equation mathematically models the transfer of energy as photons traverse the layers of the skin. It is a differential equation based on energy conservation. Assumptions have been made to reduce the number of variables involved in RTE and the evolved model is called the diffusion approximation model. The main assumptions are that scattering is a dominant process compared to absorption and that scattering is an isotropic process. Diffusion approximation is a widely used analytical model to study light propagation in different tissues such as skin, colon etc [8]. As scattering has to be a dominant phenomena compared to absorption, it is one of the primary condition necessary to adopt the diffusion approximation model for studying diffuse reflectance spectrum of human skin. This condition goes well with wavelengths beyond 450 nm but at wavelengths below 450 nm, absorption is dominant over scattering due to high absorption from hemoglobin present in the blood vessels in the skin tissue.

The most accurate method of studying the light transport in skin is the montecarlo method. In the montecarlo method the photons are launched into the medium and the path of the photon is traced. The montecarlo method is a statistical process and consumes a lot of time to generate a result. The advantage of the analytical model compared to the montecarlo simulations of light transport are the computational time [9][10]. A Diffusion approximation of the radiative transfer equation is a widely used analytical model to for studying light propagation in different tissues such as skin, colon etc. It is also used to compute the reflectance spectra of human skin. Additionally, the model proposed by George Zonios [11] helps us to study the light transport in skin for experimental condition that go beyond the diffusion regime. The effluence of light in skin decreases exponentially as a function of the attenuation coefficient (i.e. the sum of the absorption and scattering coefficients). The reflectance phenomena observed on the skin surface is the result of the elastic scattering events. Reflectance is linearly proportional to the scattering coefficient in the absence of absorption and is defined to be a function of scattering and absorption coefficients and their ratio.

A new analytical model is derived using the existing models which solve the diffusion approximation problem and is extended to a two layered skin tissue comprising of epidermal and dermal layers [12, 13]. The Reflectance reflectance model [11] assumes that the skin as is a semi infinite turbid media and an expression for reflectance measured by a diffuse reflectance probe is given as

$$R_p = \frac{1}{k1 * \frac{1}{\mu_s^1} + k2 * \frac{\mu_a}{\mu_s^1}}$$

In a jaundiced individual the bilirubin flows in the blood stream bound to albumin but as the bilirubin levels rise beyond the binding capacity of albumin, free bilirubin concentration rise in the blood stream. This free bilirubin diffuses out of the blood stream and is deposited in the skin tissues where it binds to collagen and fat. The bilirubin that binds to the collagen and fat near the skin surface ultimately makes the skin appear yellow in color. Bilirubin that is present in the extra vascular compartment acts as an optical filter attenuating the light reaching the bilirubin present in the vascular layers [11]. Thus, the total reflectance signal is a contribution of the extra vascular bilirubin (skin tissue bilirubin) and serum bilirubin (bilirubin present in the vascular system).The free bilirubin diffuses out of the capillaries (vascular system).into the extracellular matrix. So a layer of free bilirubin (extra vascular bilirubin) is formed between the epidermal and dermal layer. Thus, photons incident on the skin surface are first filtered by the melanin layer and then pass through the extra vascular layer before they make their way to the vascular components present in the dermal layer. After a series of absorbing and scattering events, the back scattered light from the dermis traverses through the extra vascular and the melanin layers to reach the skin surface. The analytical model derived is extended to a three layered model to incorporate the optical filtering effect introduced by the presence of extra vascular bilirubin and melanin. The new model is as follows

$$Reflectance = e^{-m*\mu_m*2l_{epi}} * e^{-c_{ebilirubin}*\varepsilon_{ebilirubin}*2l_{ebilirubin}} * \left(\frac{\mu_s^{dermis}}{s_1 + s_2\mu_a^{dermis}}\right)$$

The first exponential term takes into account the effect of melanin present in the epidermal layer. As light traverses twice through the melanin layer a factor of 2 is introduced. The second exponential term takes into account the effect of extra vascular bilirubin. The third term in the expression is used to estimate the back scattered light from the dermal layer of the skin tissue. The parameters in the first exponential term: m, μ_m, l_{epi} are melanin volume fraction (skin tone), absorption coefficient of single melanosome and epidermal layer thickness. The second exponential term parameters: $c_{ebilirubin}$, $\varepsilon_{bilirubin}$, $l_{ebilirubin}$ are the extra vascular bilirubin concentration, molar extinction coefficient of bilirubin and the path length which the light travels (i.e. the thickness of the extra vascular bilirubin layer).The parameters μ_s^{dermis} and μ_a^{dermis} are the scattering and absorption coefficients of dermal layer. The parameters s1 and s2 take into account the probe geometry effects.

INVERSE MODEL

Inverse model in the field of biomedical optics is an immense research area and is continuously evolving with its application in reflectance spectroscopy, optical tomography, etc. Generating an inverse model in biomedical optics involves the process of extracting the optical properties of the tissue from the spectral response of the material studied. Various approaches like multivariate models, look up tables, spline interpolations, perturbation theory, Least squares fitting, Genetic algorithms etc have been successful in solving inverse problems in multiple fields[14,15] . In this paper based on the nature of the problem and high interdependence of the parameters on each other in shaping the reflectance spectrum, nonlinear least squares solver which implements quadratic programming is adopted. Sequential quadratic programming (SQP) is one of the most popular and robust algorithms for nonlinear continuous optimization. In this research we have adopted the NLSSOL (TOMLAB)[16].

The basic structure of the SQP method involves major and minor iterations, Major iteration is defined as

$$x = x+\alpha p$$

where α is the step length (a non negative scalar) and p is the search direction. The search directions is the solution of the quadratic problem

$$\text{Minimize } f(x) + g(x)^T p + 1/2.p^T H p$$

$$\text{Subject to } l < r < u$$

The function f(x) is the error function i.e. the difference between the measured and the simulated spectrum (using forward model).The primary goal of this solver is to minimize the error function by updating the parameters of the forward model to find a best match to measured spectrum.

III. RESULTS

The signal flow process is built by integrating the forward and inverse model. As a next step to study the performance of the signal processing system a spectral databases are built.

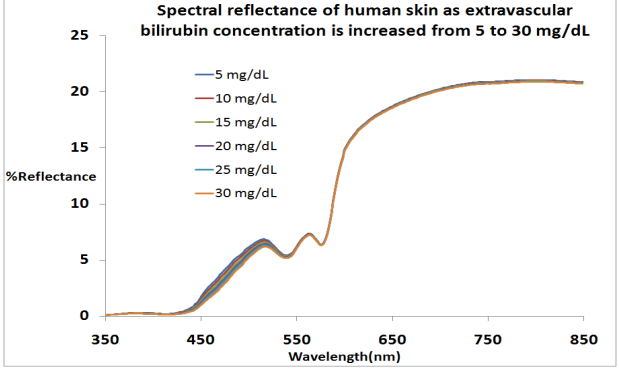

Figure 1 shows the decrease in reflectance in the wavelength range of 430-550 nm as the concentration of extra vascular bilirubin is increased in a single individual.

The first spectral database is built to simulate the in vivo conditions in a single jaundice individual. As the serum bilirubin concentration reaches its binding capacity with albumin, the unbound bilirubin starts diffusing into the skin tissue. So to simulate this condition, we have fixed the parameters like melanin concentration, hemoglobin concentration, epidermis thickness, scattering parameters and absorption properties of blood at their physiological values. As the concentration of unbound (free) bilirubin deposited in the extra vascular is increased, we see a significant decrease in the reflectance in the wavelength range of 430 to 550 nm as shown in Figure 1

The second spectral database is simulated to study the effect of melanin on the reflectance spectrum of skin. As melanin is one of the confounding factors along with the extra vascular bilirubin in masking the serum bilirubin signal. The spectra are generated for a fixed concentration of extra-vascular and serum bilirubin and all other scattering and absorption properties. The only parameter which is varied is the melanin concentration which simulates different skin tones. As the melanin volume fraction is increased in epidermal layer the spectral features are hidden as shown in Figure 2.

The next step in the process is to study the performance of the inverse model in estimating the serum bilirubin concentration as a part of the signal processing system. The forward model is validated to ensure that the spectral data

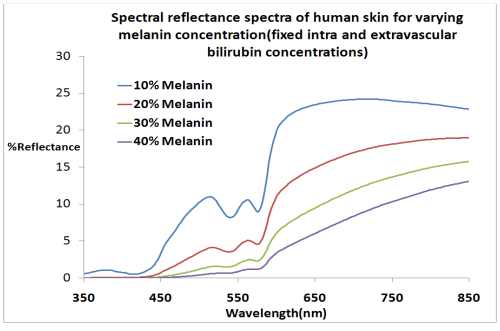

Figure 2 shows the decrease in reflectance in the wavelength range of 350-850 nm as the concentration of melanin volume fraction is increased simulating the jaundice condition in different skin tones.

generated using the simulated spectrum matched to the spectral data collected[17].The current research builds on the model developed to study the spectral variations on the reflectance spectrum as the serum bilirubin and extra-vascular bilirubin dynamics are varied[17]. The two spectral databases built earlier have a fixed serum bilirubin concentration with variability in extra vascular bilirubin concentration and melanin concentration.. The Table 1 and 2 shows the performance of the solver in estimating the serum bilirubin concentrations accurately in the presence of confounding factors.

Table 1 shows the performance of the signal processing system in estimating serum bilirubin for varying extra vascular bilirubin

TABLE I
PERFORMANCE OF SYSTEM IN ESTIMATING INTRA-VASCULAR(SERUM BILIRUBIN) FOR VARYING EXTRAVASCULAR BILIRUBIN

Extra vascular bilirubin (mg/dl)	BILIRUBIN INTRAVASCULAR CONCENTRATION IN SIMULATED SPECTRUM	Estimated bilirubin intravascular concentration
10	5	5.07
15	5	5.2
20	5	5.5
25	5	5.4
30	5	5.4

Table 2 shows the performance of the signal processing system in estimating serum bilirubin for varying melanin volume fraction

TABLE II
PERFORMANCE OF SYSTEM IN ESTIMATING INTRAVASCULAR (SERUM BILIRUBIN)

Melanin Volume fraction (%)	Bilirubin intravascular concentration in simulated spectrum (mg/dl)	Estimated bilirubin intravascular Concentration (mg/dl)
10	5	5.9
20	5	5.3
30	5	5.2
40	5	5.38

V. CONCLUSION

In this work, a biomedical signal processing system is developed to estimate the serum bilirubin concentration from simulated diffuse reflectance spectrum of human skin. The analytical model is updated to study the influence of extra vascular bilirubin component. The first spectral database simulated the reflectance spectra of in vivo conditions of a jaundice individual as the extra vascular bilirubin concentration rises beyond the binding capacity. The second spectral database simulated the jaundice condition in different individuals primarily varying their melanin (skin types). The sequential quadratic programming nonlinear least squares solver was successful is extracting serum bilirubin in presence of interfering spectral signals such as melanin and extra vascular bilirubin. The serum bilirubin concentrations estimated on the simulated spectral databases were within an average error of 15% from the nominal values. The new analytical model and the signal processing system would give us the framework to conduct the experiments on in vivo and invitro models. The system would be validated by measuring serum bilirubin levels in the skin tissue phantom model experiments planned by our team.

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