AN IMAGE PROCESSING-BASED TOOL FOR NONINVASIVE MEASUREMENT OF BILIRUBIN LEVEL

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ABSTRACT

Jaundice is a yellowish pigmentation of the skin, the conjunctiva, and other mucous membranes caused by increased levels of bilirubin in blood beyond normal levels (hyperbilirubinemia). Jaundice occurs in neonates in 2 forms: Pathological and Physiological Jaundice. In Pathological Jaundice, high bilirubin levels can result in severe neurotoxicity, brain damage, hearing loss, muscular disorders and physical abnormalities. So measuring the exact level of bilirubin in blood in neonates is very crucial. In the past, serum bilirubin has been the preferred method of detecting hyperbilirubinemia in newborns. The ordering of serum bilirubin in neonates is based on visual evaluation by either physicians or nursing staff. Skin puncture collection of blood exposes the neonate to trauma and risk of infection. A noninvasive device for predicting serum bilirubin levels in newborns diminishes the need to do skin punctures. There are numerous studies demonstrating the transcutaneous bilirubin measurements reasonably close to serum bilirubin performed by clinical laboratories. These devices use spectrophotometry (light absorption measurements at standardized wavelengths of light) to calculate measurements. All existing methods involve transcutaneous detection of bilirubin, which is not error free, as there are various factors affecting its accuracy, like presence of hemoglobin and melanin, and maturity of skin tissue and fibres. So this gave an urge for us to develop a new technique of quantitating bilirubin level noninvasively. This study was done by analyzing conjunctival images that would imitate the blood level of bilirubin by calculating the intensity of yellow color. Machine learning techniques were applied in order to develop a system capable of predicting the bilirubin level.

KEY WORDS

Hyperbilirubinemia, image processing, machine learning, neonatal jaundice, transcutaneous bilirubinometry.

1. Introduction

The incidence of neonatal hyperbilirubinemia has been reported to be between 30-60% in full-term newborns and nearly 100% in premature infants [1]. Toxic levels of unconjugated bilirubin can lead to neurotoxicity resulting in neurodevelopmental abnormalities and may cause death.

The main causes of pathological jaundice are prenatal factors such as birth trauma or infection, maternal factors such as Rh incompatibility or ABO incompatibility and neonatal factors such as prematurity, sepsis, birth asphyxia, genetic syndrome such as Crigler-Najjars and Gilbert's syndrome, breast milk jaundice, hemolytic disease like glucose-6-phosphate dehydrogenase deficiency [2].

High levels of bilirubin in blood cause yellowish staining of the skin and the eyes. A bilirubin level of more than 85 umol/L (5 mg/dL) manifests clinical jaundice in neonates and in natural daylight, one can perceive levels of 4 mg/dL in the conjunctiva.

Although flawed by some imprecision, the gold standard remains the "heel pricking" or sometimes "application of cannula" for subsequent extraction of blood samples. These methods are difficult and indeed very painful to the neonates. So this gives an urge for researchers to develop new tools to detect the bilirubin levels in newborns which is easier and safer than the existing invasive methods. One tissue in the body is transparent and stains soon following increase levels of bilirubin is the conjunctiva.

In the present study, the yellow color in conjunctiva was measured quantitatively and later compared with the bilirubin level in blood. Based on correlation between the two value, efforts was made to formulate a mathematical equation that may anticipate the blood levels of bilirubin by measuring the quantity of yellow color in conjunctiva only.

The present study is based on image processing and machine learning. The principle is as follows:

- Capture images of the conjunctiva of eyes using high-resolution digital camera and analyze them to get the amount of yellow color in the area of interest.

- Correlate the laboratory values of bilirubin in blood with the amount of yellow color obtained by the camera using a mathematical equation.

- Apply machine learning techniques on a high number of samples (images) before measuring new samples.

2. Methodology

2.1 Data acquisition

In accordance with institutional guidelines and after obtaining consent from 25 participants in the study, eye images were taken and blood samples were analyzed. For images we used a Samsung S4 Zoom Digital Camera of 16 Megapixel resolution to capture left and right eyes. During the acquisition procedure, a special care was given to the ambient conditions so as to guarantee a good quality of the final result. The collection of samples was made in Institute of Liver and Biliary Science (ILBS), New Delhi, India. The present study was approved by the Institutional Ethical Committee of the university.

2.2 Preprocessing

The captured images were preprocessed in order to remove all irrelevant areas. We preserved only the region of interest (ROI) (the conjunctiva) from which relevant information were extracted in the subsequent stages of the system. The preprocessing comprises elementary operations: isolation of the conjunctiva by masking outer pixels and equalization operation in order to adjust the brightness and the contrast. As for the segmentation, we decided to perform it manually after getting unsatisfactory results from automatic detection of the ROI. We used Photoshop software to isolate the white part of the eye. For the equalization, we used Matlab software Image Processing Toolbox to improve the contrast of the value channel in the HSV color representation of the image.
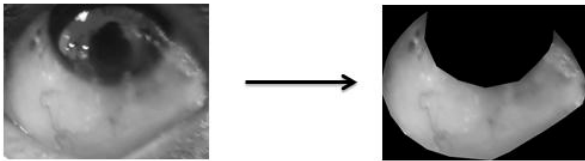

Figure 1. Result of the preprocessing stage

2.3 Feature extraction

In the present study, the main feature that represents the level of bilirubin is the "quantity" of yellow color in the conjunctiva. Image processing techniques implemented in Matlab were used to extract this feature. Pixel information in the preprocessed images were transformed into a value representing the yellow to white ratio. First, the RGB image is converted to the equivalent HSV image. Then, for each channel (hue, saturation and value) we identify all the pixels that lies in a predefined interval (specific to that channel) to get a mask. Once the 3 masks were determined, we combine them to obtain the final mask representing the targeted yellow color (defined by the value intervals of the 3 HSV channels). At this level we count the number of yellow pixels from the obtained mask. As for the white pixels, we count them after

converting the original image (RGB) to a binary image (black and white). Finally, we can compute the yellow to white ratio. Due to the variability of the shade of yellow color, the feature extraction was applied on a spectrum of yellow between 50º to 70º of hue is the HSV color system. Both eyes were used to calculate the mean of yellow to white ratio. Figure 2 shows an example of extracted yellow pixels in the predefined range of hue. The density of yellow in this example is around 25 %.
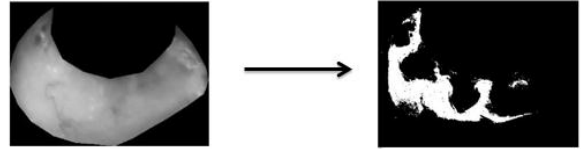

Figure 2. Result of the feature extraction stage

2.4 Training

The training stage is considered as the main component of the system which aims to detect the level of bilirubin based on the pixels information from the image samples. In order to achieve this objective, we performed the training of the system on a 25-observation dataset in which the input variable is the ratio obtained from feature extraction and the output variable is the laboratory bilirubin level. In order to determine the "right yellow" to be analysed, we decided to do the training for different values of hue ranging from 50º to 70º. Thus, for each hue value, we obtained a model (a linear function) and we chose the one that maximizes the coefficient of determination ($R2$).

Each training iteration was carried out as follows: first, feature extraction is done using as a target hue one of the values defined earlier. Secondly, we perform a linear regression on the dataset to obtain the regression line which is then stored. Finally, we determine the R2 value of that fit and we store it in an array. After completing all the iterations, we search in the obtained array for the maximum R2 and adopt the corresponding model as the best one in representing the relation between bilirubin blood levels and yellow to white ratios in the eye.

It is noteworthy to mention that the present study deals only with the training stage as the number of samples is too low to divide it into training set and test set. Nevertheless, we could measure the "goodness" of the training based on a formal measure, the R2.

2.5 Bilirubin level measurement

After the training, new eye images can be analyzed and the corresponding bilirubin level evaluated using a predictor built on the previously obtained model. The procedure is as follows: the sample image should be preprocessed with the same parameters as in the training stage. After that, feature extraction is applied and the resulting value is fed into the predictor which determines a predicted value for the bilirubin level.

2.6 Bloc diagram of the system

The complete bloc diagram of the system is presented on Figure 3. It is composed of two major stages: A training stage that generates a model for the bilirubin expression as yellow color in the eyes; a test stage where "unknown" eye images are used to estimate the blood bilirubin level. In the present study, we focused only on the first stage.

(a)

Eye images → Preprocessing → Feature Extraction → Training → Model

Blood samples → Lab bilirubin analysis → Training

(b)

Left / Right Test Eye images → Preprocessing & Feature Extraction → Prediction → Bilirubin Level
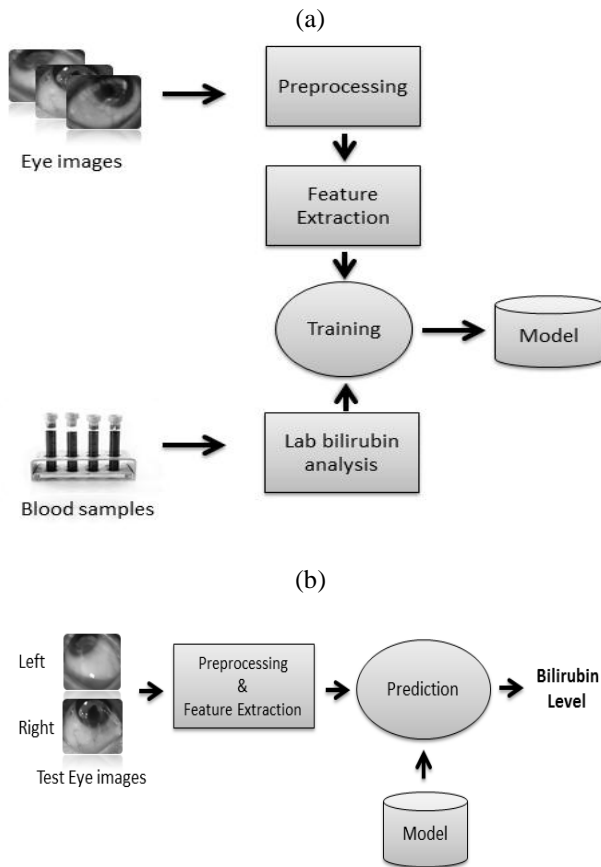
Model → Prediction

Figure 3. Complete bloc diagram of the system
(a) Training stage, (b) Test stage

3. Results

After performing many experiments, we obtained some encouraging preliminary results that show a correlation between blood total bilirubin values and the measured density of yellow in the conjunctiva. Table 1 presents the blood levels of total bilirubin and the measured density of yellow color in the conjunctiva. Based on the collected eye images, we performed linear regression resulting in a linear fit (Figure 4) of the samples which represents the model upon which the system is built.

Figure 5 depicts the variation of the R^2 value of the linear fit when the hue varies from 50º to 70º. For each of these values of hue, we performed the linear fit on all the samples and measured the R^2 value.

In order to confirm the "correct" yellow color, we determined the proportion of pixels with a hue value between 55 º and 65 º in the hue channel histograms of the image samples (Figure 6) for 2 cases:

- Images of patient with low bilirubin level (< 10):5 %

- Images of patient with high bilirubin level (> 25):25 %

Table 1. Bilirubin level and measured yellow/white ratio

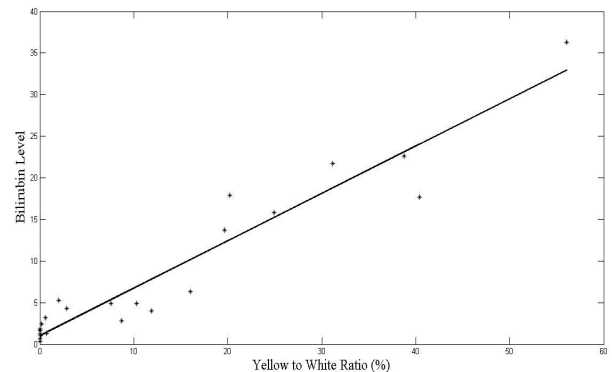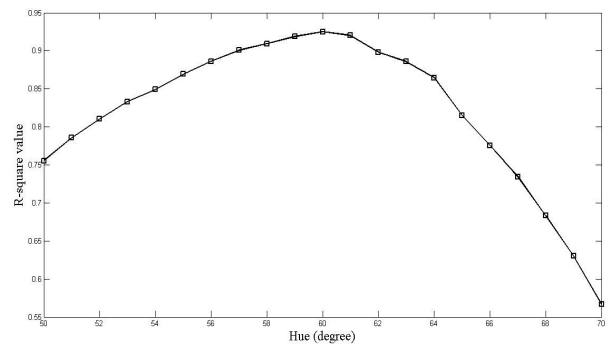| #Patient	Bilirubin level	Yellow/White ratio (%)
1	13.7	21.2
2	17.9	28.5
3	3.2	0.009
4	36.3	69
5	22.6	40.7
6	0.3	0.005
7	0.6	0.009
8	6.3	25.3
9	1.6	0.008
10	1.2	0.008
11	17.7	44
12	21.7	31.8
13	0.6	0.034
14	1	0.004
15	0.6	0
16	4	5.5
17	4.3	1
18	15.8	21.8
19	2.8	5.3
20	1.3	0.07
21	4.9	3.6
22	5.3	0.06
23	2.4	0.22
24	1.8	0.004
25	4.9	6.3

Figure 4. Linear fit of the samples
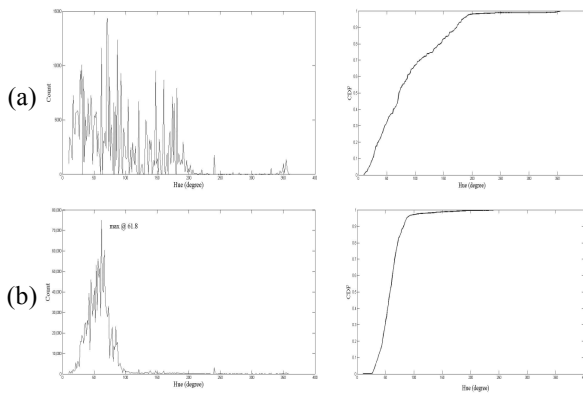
Figure 5. R^2 value as a function of hue

Figure 6. Histograms and cumulative density function of
hue channel of (a) high bilirubin level
(b) low bilirubin level image samples

4. Discussion

The problem of non-reliable estimation of the bilirubin level by visual inspection of the skin was addressed by Rowntree and Brown, in 1925 when they proposed a tintometer for the evaluation of skin color [3]. Later, Knudsen and Brodersen stated that the mechanism by which bilirubin is deposited in the skin is similar to the mechanism by which it traverses the blood brain barrier [1] which has given an initiation in the line of research of detection of bilirubin on skin.

The first sophisticated device for non-invasive bilirubin measurement was the Minolta/Air Shields Jaundice Meter [4], which measures the optical densities of blue and green light, thus providing a measure of intensity of the yellow color developed by Schumacher, Thombery , and Gutcher in 1985. According to Cashore visual recognition of jaundice and its relationship to serum bilirubin is often inaccurate and unreliable for the prediction of severity of subsequent hyperbilirubinemia [5]. In 1998 a different device called Chromatics Colormate 111 was developed by Chromatics Color Sciences International Inc., New York, NY which used skin color (Chromatics Colormate 111, Chromatics Color Sciences International Inc., New York, NY) but employs a sophisticated computer algorithm for assessing the underlying skin color [6]. By mathematically isolating the light absorption of certain interfering factors (hemoglobin, melanin, and dermal thickness), the absorption of light due to the presence of bilirubin in the capillary beds and subcutaneous tissue can be isolated by spectra subtraction. In theory, this allows for an unbiased measurement that is independent of the race, age and weight of the newborn.

In a multi-centre study performed with this device, the close correlation between BiliChecK and HPLC was shown to be equivalent to that of HPLC and laboratory tests [7]. In 2002 Giovanna Bertini and Firmino Rubaltelli invented the newer TcB devices which could be used not only as screening tools but also as reliable substitutes for serum bilirubin measurements. The Chromatics Colormate III is still based on the colour of the skin,

estimating serum bilirubin from skin-reflectance (skin color) whereas BiliCheck measures transcutaneous entire spectrum of visible light (380 to 760 nm) reflected by the skin [3]. For the bilirubin assessment a system was implemented by Penhaker, Kasik et al. in 2013, as a photometric method utilizing measurement system with two specific wavelengths for the non-invasive bilirubin value assessment. The electronic device was implemented and connected to an analogue digital unit for computer visualization and recording the values and their time trends in a database [8].

The above mentioned literature presents a multitude of methods of non-invasive measurement of bilirubin. We can see that many of these methods and tools are complicated and need special equipment. In spite of this complexity, the results are not always as accurate as it is required. In the present study, the designed system is easy to implement and has a low cost.

The obtained results show that it is possible to measure bilirubin level based on captured images of the eyes. As depicted in Figure 4, there is a linear relationship between bilirubin level and yellow density of the conjunctiva. Although the extracted "model" is not very representative of the dataset, it could be improved by increasing the number of samples and improving the image acquisition procedure which in our case produced many low quality images.

We can conclude from Figure 5 that the best model that describes the relationship between bilirubin level and yellow density corresponds to a hue value of 60º. This value represents the "pure" yellow in the HSV color system.

Furthermore, the analysis of the histograms of the hue channel (Figure 6) shows that for high bilirubin levels, the corresponding images manifest a "narrow" distribution of pixel values centered around 61.8º and that for low bilirubin levels, the distribution is more "spread". This demonstrates that the concentration of yellow color is directly correlated with the level of total bilirubin in the blood which is compatible with the above mentioned results.

5. Limits of the proposed solution

The following issues represent some of the limits of the proposed solution:

- The quality of the acquired images could be a source of error since the pixel values may not represent the real color structure of the eye. This may be due to artificial light reflection (white spots), camera focus issues and non-uniformity of ambient light conditions across the sample images.

- The proposed system relies on the manual definition of the region of interest (ROI). The automatic detection of ROI is complex due to the variability of eye morphology from one patient to the other.

- For very low levels of bilirubin in blood, the proposed system manifests more imprecision than in the case of high bilirubin levels.

6. Conclusion

The present study aims to design a simple tool for non-invasive measurement of bilirubin level. This technique could be used for screening both patients suffering with hepatic disorders and also the neonates with hyperbilirubinemia.

The system is based on image processing and machine learning techniques including linear regression for the prediction of bilirubin level from eye images.

The main objective of the present study is to model the relationship between bilirubin level and yellow density of the conjunctiva. The obtained results prove that such a relation can be established using a dataset of collected samples represented by the laboratory value of bilirubin and the captured image of the eyes. The model that we generated could be enhanced by increasing the number of samples and improving the quality of captured images.

For the future work, as the dataset size will be increased, we plan to test the model via new test sample images and compare the results with actual lab analysis data to assess the validity of the proposed solution. We also need to handle the limits of the current solution by improving the acquisition and processing stages and also by experimenting with more advanced algorithms for training.

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