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Abstract. Jaundice is one of the notable markers of liver malfunction in our body, revealing a significant rise in the concentration of an endogenous yellow pigment bilirubin. We have described a method for measuring the optical spectrum of our conjunctiva and derived pigment concentration by using diffused reflection measurement. The method uses no prior model and is expected to work across the races (skin color) encompassing a wide range of age groups. An optical fiber-based setup capable of measuring the conjunctival absorption spectrum from 400 to 800 nm is used to monitor the level of bilirubin and is calibrated with the value measured from blood serum of the same human subject. We have also developed software in the LabVIEW platform for use in online monitoring of bilirubin levels in human subjects by nonexperts. The results demonstrate that relative absorption at 460 and 600 nm has a distinct correlation with that of the bilirubin concentration measured from blood serum. Statistical analysis revealed that our proposed method is in agreement with the conventional biochemical method. The innovative noncontact, low-cost technique is expected to have importance in monitoring jaundice in developing/underdeveloped countries, where the inexpensive diagnosis of jaundice with minimally trained manpower is obligatory. [DOI: 10.1117/1.JBO.20.6.067001]

Keywords: jaundice detection; noncontact optical method; diffused reflection; diagnosis; conjunctiva; software development.

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1 Introduction

Recent World Health Organization fact sheets (updated in June 2014) on global statistics of hepatitis (A, B, C, and E) show that out of more than 400 million detected cases of potentially life-threatening liver infection, more than 1.3 million people die every year due to acute or chronic consequences of advanced liver damage. The global statistics of child mortality due to liver malfunction are also very alarming. It is stated in a United Nations Children's Fund report (2012) that 21 children die per minute, mostly from preventive causes including neonatal jaundice, in most underdeveloped/developing countries. Jaundice is a yellowish pigmentation of the skin and conjunctiva caused by high blood bilirubin levels[1,2] and is an indicator of liver disease such as hepatitis or liver cancer.[3] An early diagnosis of the neonatal and maternal (particularly due to hepatitis E) jaundice is a proven means of prevention and cure.

The current gold standard to measure the total serum bilirubin (TSB) is determined from a blood sample obtained in an invasive way. Although the method is approved for monitoring jaundice,[4,5] it has several drawbacks. Invasive blood sampling is painful and stressful for the neonates, resulting in blood loss and an increased risk of osteomyelitis[5–7] and infection at the site of sampling. In addition, a factor which is of particular concern is that in the developing world, the conventional method is expensive, laborious, time consuming, and dilatory which prevents the possibility of immediate diagnosis.[5] In the case of neonates, the possible alternative for invasive blood sampling is a transcutaneous bilirubinometer (BiliChek and JM-103 are the commercial versions of the device) that provides instantaneous cutaneous bilirubin concentration (TcB). The method is based on optical spectroscopy that relates the amount of light absorption by bilirubin (yellow skin) to the concentration of bilirubin in the skin. Since the discovery of the method in 1980,[8] several more devices have been developed in order to improve the accuracy of the device. However, even after 30 years of development,[5] no subcutaneous bilirubinometer can replace blood sampling for the following reasons. The first is the variation of accuracy in different skin colors. Most importantly, the bilirubin measured by transcutaneous bilirubinometry (TcB) is a completely different physiological parameter from TSB in blood because TcB consists of over 99% of the concentration of extravascular bilirubin. Due to largely unpredictable processes that regulate the supply and clearance of bilirubin in the extravascular space, one-to-one comparison of the TcB with TSB is impossible. Therefore, an uncertainty in the replacement of blood sampling by TcB still exists. To date, there are few other techniques described in the literature for noninvasive assessment of bilirubin level in adults, i.e., assessment of the jaundice by image acquisition of both of the eyes of the patients.[9–11] The system is not capable of making a quantitative

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estimation of bilirubin and is not portable either. It is important to note that in adults, the elevated level of bilirubin and its oxidative products causes various serious diseases including Gilbert syndrome (>6 mg/dL), Crigler-Najjar type I disease (>30 mg/dL)[12] and bilirubin-induced neurologic dysfunction.[13] Severe neurotoxicity in the case of neonates (Kernicterus) and damage in white matter of the adult brain are also the consequences of higher bilirubin levels.[14] In the case of Hepatitis E infection in pregnant women, associated hyperbilirubinemia itself is found to increase the risk of preterm delivery.[15]

In order to surmount the above mentioned limitations of a noninvasive bilirubin monitoring device, the following two strategies are viable alternatives: (1) a medical approach, requiring extensive risk analysis for the predictive value of TcB for mortality/morbidity. (2) A technological approach, where measurement volume of the device is essentially confined to intravascular space, enabling a one-to-one comparison of TcB and TSB. Our present work basically adopts the latter strategy where the spectroscopic signal essentially comes from the vascular bed of bulbar conjunctiva.[16] As the sclera, duly covered by transparent conjunctiva is white in all human subjects across variety of races, the accuracy of the proposed device is independent of skin color. The light power in the visible region (400 to 700 nm) which is required (~20 μW) for such investigation is much lower than that used in commercially available ophthalmoscope (~100 μW) for regular eye check-up, given the sensitivity of the state of the art spectrograph used in the proposed device. Thus, the features of the setup which make the device distinct from the existing noninvasive devices for jaundice detection are as follows: (1) directly monitors amount of bilirubin in blood (intensity of the absorption peak at 460 nm) with extremely high precision without any interference from other pathological conditions. (2) Noncontact device does not need any mechanical attachment to the subject, which is very important for the friendly use of the device in neonates/young infants and also virus infected (HEV) maternal subjects. (3) Signal from conjunctiva, which is white in all human subjects independent of skin color, offers uniform sensitivity across different communities in a country. (4) Very limited or almost no training would be required for the healthcare provider. Moreover, the ease of operation with precision in the detection strategy offers future development of the device for low-cost diagnosis of jaundice with minimal manual intervention.

2 Methods

2.1 *Experimental Setup*

The diffused reflectance spectroscopy-based absorbance setup (patent pending, 467/KOL/2009) for monitoring the spectral response of the conjunctiva is represented in Fig. 1(a). A white light source (Model No. LS-450) and a spectrograph (Model No. STS-VIS) with wavelength resolution of 0.47 nm (both are from Ocean Optics, Florida) were used in our study. Lab-grade optical fibers from Ocean Optics were used for the transmission and collection of light to and from the sample (conjunctiva). The light from the source is transmitted through the six surrounding fibers [Fig. 1(a), excitation fiber] and is incident on the conjunctiva while the single fiber, in the middle of the probe [Fig. 1(a), detection fiber], collects the diffused light and sends it back to the spectrograph. The corresponding spectral response as generated in the

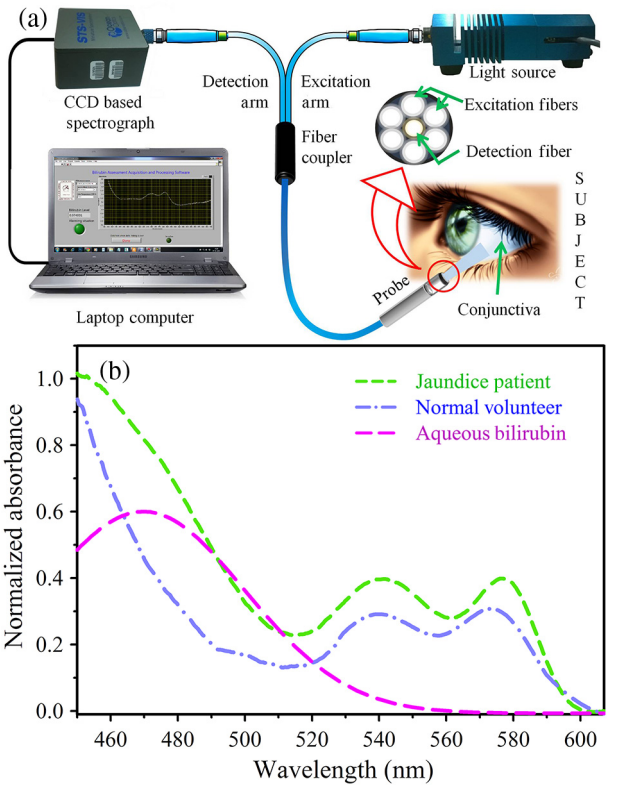

Fig. 1 (a) Schematic representation of our working device. The light from the source is transmitted through the six excitation fibers of the excitation arm and incident on the subject (conjunctiva). The diffused light is collected by the detection fiber and transmitted through detection arm to the spectrograph. The spectral response corresponding to the conjunctiva is processed and generated in the laptop computer. (b) The comparative spectral response of conjunctiva of a normal volunteer and jaundice patient has been represented. An absorption spectrum of aqueous bilirubin solution is also included as reference.

spectrograph is then transferred to a laptop computer through a USB interface where it is processed in our developed software. The wavelength calibration of our setup has been established with a He-Ne laser (632.8 nm), fluorescent lamp, and emission/absorption of a number of dyes including aqueous bilirubin solution, as shown in Fig. 1(b).[17,18] The comparative spectral response of a normal volunteer and a jaundice patient is represented in Fig. 1(b). A distinct difference in their spectral appearance is visible; the contribution of yellow pigment deposited in the conjunctiva of the jaundice patients is higher compared to the normal volunteer.

2.2 *Data Collection*

A total of 90 patients at the pathology section for liver function test in the Calcutta Medical Research Institute (CMRI) hospital, Kolkata, were recruited in our study. Data were collected in two stages: first, for calibration of the device; second, for measuring the precision of the software-driven device in contrast to the standard biochemical method. Soon after the blood sample collection, the volunteers were taken for the bilirubin assessment using our setup with a 5-min time window. Due to the noninvasive and noncontact nature of the test, there is no need for disinfecting the measuring probe. Approval of the local medical ethical committee (Ref: IEC/07/2014/APRV/23) and informed

consent from the patients' legally authorized representatives were obtained. Blood samples were taken only for clinical reasons and were obtained by professional technicians from CMRI hospital. A wide variety of age group of the recruited patients with a mean age of 45 years [standard deviation (SD) 14 years] with different skin tones were the subjects of the present study.

2.2.1 *Stage I: for calibration*

For calibration purposes, 60 patients were incorporated in this part of the study. After placing the probe close to the conjunctiva (~2 cm apart) of the patient's eye, the spectral response was generated and stored in the laptop computer for further processing. In order to avoid light interferences, minimum light was used to illuminate the place during collection of the data from the subjects.

2.2.2 *Stage II: assessment of the device*

We studied a statistically significant number of patients ($n = 30$) for the assessment of the calibrated device. After placing the probe close to the conjunctiva (~2 cm apart) of the eye, the device acquires data and displays the bilirubin value. The information is stored and a comprehensive medical report is generated for further study. In order to establish the potential of the device in terms of reproducibility, 20 patients from the total of 30 patients in this stage were repetitively examined by our device by two independent examiners.

2.3 *Software Design*

The optomechanical components have been connected to a laptop computer using a USB interface. The spectrometer (STS-VIS), which is the active detector in this setup, has been programmed on LabVIEW platform and can be modified for user defined data acquisition. The online display of the acquired data has been used to analyze the data quality and assess the medical condition of the patients. Finally, the bilirubin level of the patient is displayed with suggested medical attention on the monitor of the DAQ laptop computer. The software for automatic data acquisition has been designed in LabVIEW platform. Figure 2 shows the sequential program flow or the algorithm of the developed software. The instrument is first reinitialized to its power on status to remove any previous custom settings. The software then sets the proper integration time for data acquisition to build up the right signal-to-noise (S/N) ratio of the acquired data. This can either be set manually or automatically as decided by the software using an iterative algorithm. For a particular distance between the probe and the reference surface, the software adjusts the integration time using the mentioned iterative algorithm until the peak count reaches the maximum allowed value (here 14,000). The information is acquired through the raw socket of the USB port and the size of the array is determined, thus the wavelength array is calculated on the basis of instrument specifications. The "dark spectrum" and "reference spectrum," which can either be preacquired or can be determined *in-situ*, are then loaded for spectrum processing. The software now acquires data, produces the processed spectrum, generates an online graph, and displays the appropriate bilirubin value. The bilirubin value is calculated using the calibration equation (see Sec. 3.1). The data safety level of the patient is determined by the differential absorption values of wavelengths 460 and 600 nm. The online display also suggests the condition of the patient being within or above the safety limits. The information is stored and a comprehensive medical report is generated

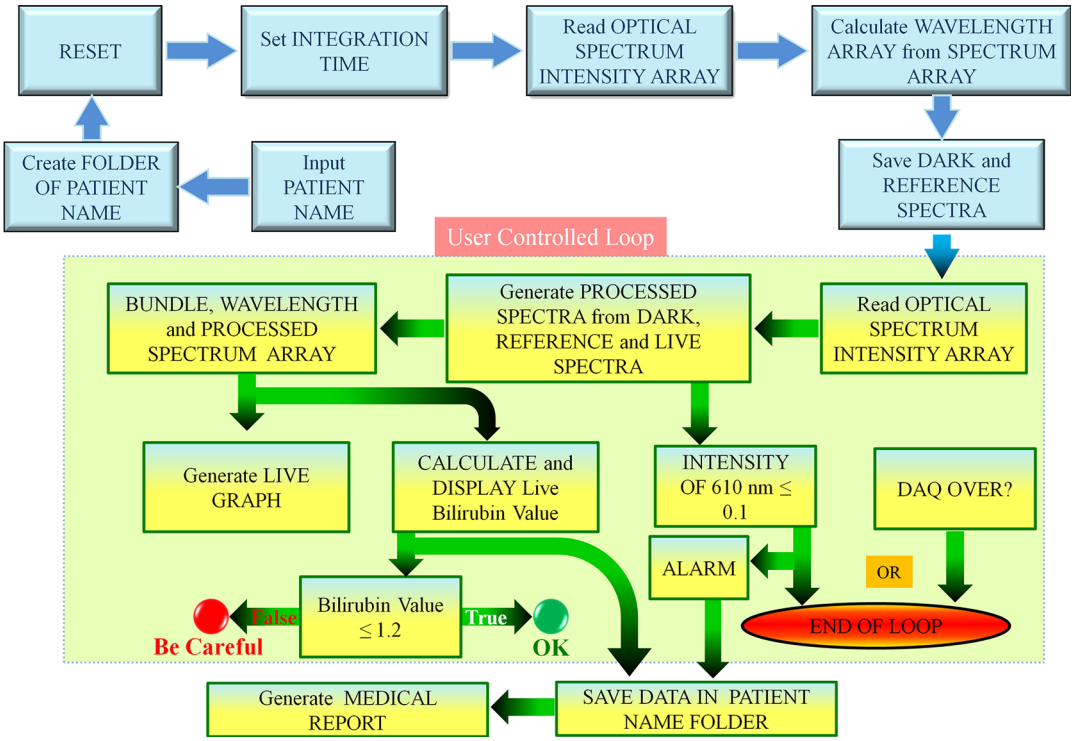

Fig. 2 The flow chart of the software designed in LABVIEW platform for noncontact online monitoring of bilirubin level in humans (see text for details).

for offline use for medical practitioners and patients. Complete care has been taken for the software to be simple on the front panel for ease of operation even with nonscientific personnel having no or minimal medical or instrumentation knowledge.

3 Results and Discussion

3.1 *Calibration and Statistical Analysis*

The stored data (stage I, $n = 60$) were then processed to find the correlation between the TSB levels of the volunteers with the spectral information obtained from the conjunctiva of the eye. It has already been reported that the spectral contribution near the 460-nm wavelength is due to bilirubin, the yellow pigment.[18–20] Different characteristic wavelengths over the conjunctival spectrum were selected for assessment, but it was found that the differential absorbance of 460 nm (a_1) to 600 nm (a_4) and ratiometric values of 470 nm (a_2) to 576 nm (a_3) were more consistent with the TSB level. The differential absorbance of 460 to 600 nm (a_1 to a_4) was chosen as the index value (x_i) to calibrate the setup with the TSB level. The dependency of the index value (x_i) with TSB level is represented in Fig. 3(a). The correlation coefficient (r) is found to be 0.84;

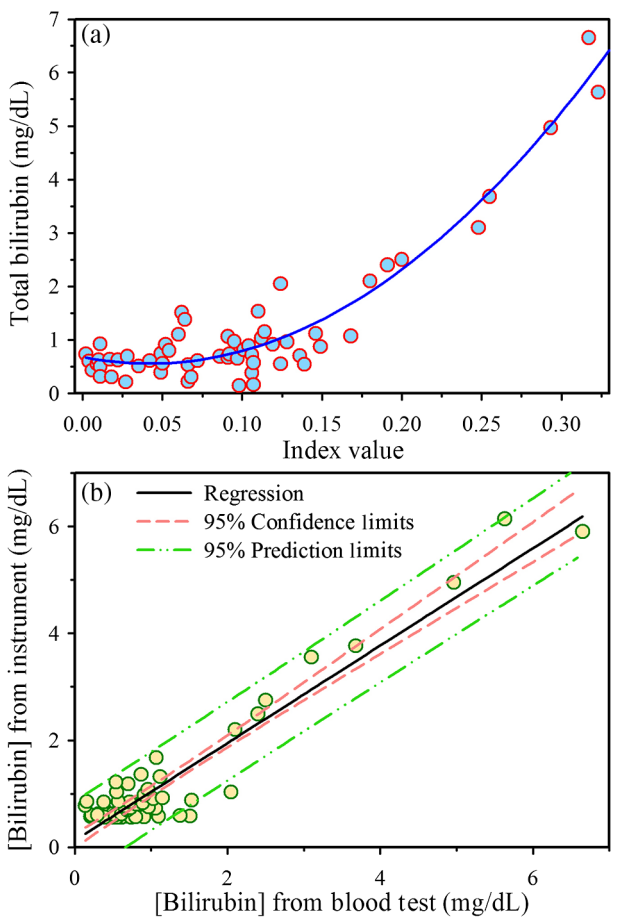

Fig. 3 Stage I, calibration: (a) The dependency of the total serum bilirubin (TSB) value from blood test with the index value from our instrument ($n = 60$) has been represented graphically. The correlation between them is found to follow a second order polynomial equation with an R^2 value of 0.89. (b) Correlation between the TSB value from blood test and from our instrument [correlation factor $(r) = 0.96$] with the 95% confidence limits and the 95% prediction interval have been represented.

$P < 0.0001$, which shows a significant relationship between the two methods (TSB and x_i). Further calibration was done in order to achieve a nearly perfect relationship. The x_i value is found to follow a second order polynomial equation $y_i = 74.67x_i^2 - 7.686x_i + 0.748$ (calibration equation), where y_i is the individual TSB level. We used this calibration equation to calculate the bilirubin level from the spectral information (x_i) obtained by our device. This modification greatly improved the correlation to almost perfect (correlation coefficient, $r = 0.96$; $P < 0.0001$). The corresponding linear regression curve is represented in Fig. 3(b) with Pearson correlation coefficient, $r = 0.96$; $P < 0.0001$ and $F = 627.1$; slope 0.932; y intercept 0.118.

In order to find the statistical significance of the noncontact optical device for online assessment of the bilirubin level, correlation and regression analyses were used.[21–23] We have also used the Bland-Altman method for assessing the agreement between the conventional biochemical technique and our noncontact optical device.[24] Two crucial factors decide whether a new method can be used interchangeably with an already established method: the amount of agreement between the methods and its clinical evaluation. We compared our proposed noninvasive bilirubin detection method to an established biochemical method using the approach described by Bland and Altman[24,25] in order to assess the statistical agreement. Thirty patients (stage II, $n = 30$) of all age groups were included in our study. Linear regression analysis and Bland-Altman plots are shown in Fig. 4. Data obtained from the linear regression

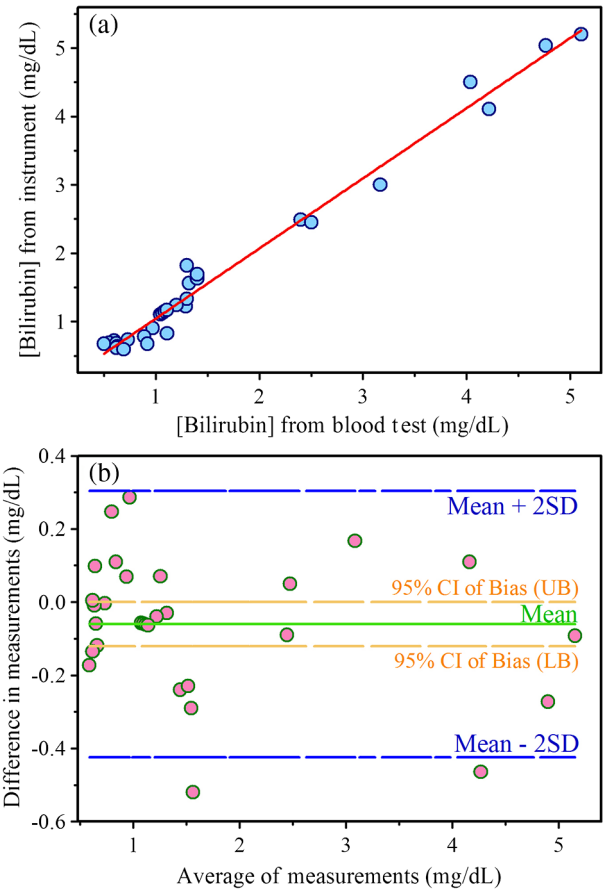

Fig. 4 Stage II, statistical significance: (a) the linear regression plot of the TSB level measured in both the ways and (b) Bland-Altman analysis: difference against mean for the TSB data (see text).

analysis [Fig. 4(a)] show that the two methods show strong correlation as the Pearson correlation coefficient, $r = 0.99$; $P < 0.0001$ and $F = 1588$; slope 1.026; y intercept 0.018.

For adequate comparison of the two methods, the difference in measurement of the two methods is plotted against their average [Fig. 4(b)]. The mean difference between the two methods is depicted as a horizontal line and is rated as bias. The other two horizontal lines (Mean $\pm$ 2SD) represent limits of agreement which explains that 95% of the differences were assumed to lie within these limits. The results exhibit reasonable agreement between our proposed method and the conventional pathological method of bilirubin detection. The difference in the two methods (conventional-proposed) has mean value of -0.06 mg/dL and SD value of 0.182. The limits of agreement are from -0.42 to 0.30 mg/dL. Hence, it can be inferred that for 95% of individuals, a measurement by our method would be between 0.42 units less and 0.30 units greater than a measurement by the conventional method. This small difference has no serious clinical significance in the diagnosis of jaundice. The mean value of the differences indicates a small bias of approximately -0.06 mg/dL. The 95% confidence interval (CI) for the bias represented in Fig. 4(b) is -0.12 to 0.00. As the CI includes 0.00, the bias is statistically nonsignificant.[26] The negative bias along with CI indicates that the predominant tendency of our instrument is to overestimate the bilirubin levels, so dangerous clinical errors are unlikely to occur. In addition, the coefficient of variation (CV) between our method and the conventional biochemical method was found to be 1.81%, which is comparable to the CV range of 0.35% to 1.96% for laboratory chemical analyzers in repeatability studies.[27] This clearly states the bias to be nonsignificant in clinical diagnosis.

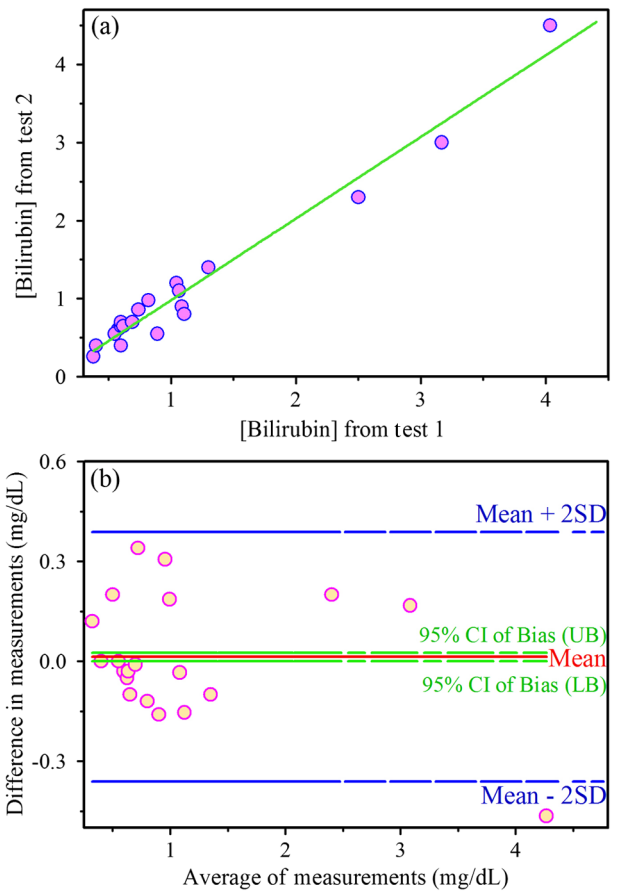

Fig. 5 Stage II, reproducibility: (a) the linear regression plot of the TSB level measured successively by two different observers and (b) Bland-Altman analysis: reproducibility in measuring the TSB level by the device (see text).

3.2 *Reproducibility*

In order to establish the potential of the device in terms of reproducibility, 20 patients were repetitively examined by our device. We found excellent precision between the bilirubin levels detected from the same subject by two independent observers. Mean and SD were almost the same in both observations and the intraclass correlation values were highly significant ($r = 0.98$; $P < 0.0001$). Linear regression analysis also illustrates the accuracy of the two measurements ($F = 557.8$; slope 1.04; y intercept -0.06) [Fig. 5(a)]. Furthermore, the Bland-Altman plot of the two successive measurements by two different observers is represented in Fig. 5(b) (mean 0.01 mg/dL and SD 0.18). The bias should be zero for an ideal instrument.[24] However, in our case, the bias is 0.01 mg/dL and the CV in between repetitive measurements is 0.79%, which have insignificant contributions for clinical diagnosis.

4 Conclusion

In conclusion, we have demonstrated that the conjunctiva could be a targeted organ to diagnose jaundice independent of race, age, and sex by using a simple diffused reflection measurement technique. Based on the aforementioned principle, we have also developed a noninvasive, easy, expeditious, reliable, and practical device for routine measurement of bilirubin levels. Although serum bilirubin measurements are still required for precise diagnosis, the proposed device has the potential to reduce frequent blood sampling. The setup would be particularly useful for the initial screening of patients for the blood test and routine examination of the prognosis of some therapeutic strategies including phototherapy in neonates. It has to be noted that evaluation of the instrument with a much larger data set with a wide range of serum bilirubin concentration, various degrees of medical severity, and a variety of age groups including neonates are our immediate future plans. We have also realized that there is an enormous scope for the development of the setup including the use of two-color light-emitting diodes (460 and 600 nm) instead of a spectrograph in a very low-cost version. Different calibration equations for different age groups of subjects would also increase the sensitivity in measurement. In the future, our study is expected to find relevance in the quick, noncontact diagnosis of jaundice in rural areas as well as in urban clinics.

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