On the Assisted Assessment of Anemia and Bilirubinemia Conditions

Ankita Dey, Gladimir V.G. Baranoski and Tenn F. Chen
Natural Phenomena Simulation Group, School of Computer Science, University of Waterloo

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1 Introduction

In this report, we review a number of procedures and devices that are used to diagnose and quantify the severity levels of two ubiquitous medical conditions, anemia and bilirubinemia (jaundice). Both conditions are associated with changes in the contents of specific chromophores present in the blood, more specifically hemoglobin present in the red blood cells (RBCs) and biliribin found in the plasma. In general terms, anemia results from a decrease in the hemoglobin content, while jaundice results from an increase in the bilirubin content. The lower the hemoglobin content, the more severe the anemia condition becomes [1]. Conversely, bilirubinemia becomes more severe with a higher bilirubin content [2]. While both intravenous and extravenous (transcutaneous) methods are being used to measure bilirubin, direct procedures based on the collection of blood samples are normally used to measure hemoglobin content.

The remainder of this report is organized as follows. In Section 2, we examine issues related to the assessment of anemia, and in Section 3 issues related to jaundice. This report closes with a summary and an indication of directions for future research in this area.

2 Anemia

Anemia is generally diagnosed through a complete blood count (CBC) test and/or a physical examination by a medical practitioner. Besides the volume fractions of red blood cells, a CBC test would also report on their size, which can further help in distinguishing between the distinct types of anemia [3]. Other laboratory tests include [1]:

- stool hemoglobin test - to detect bleeding from stomach or intestines,
- bilirubin level test - to determine if excess RBCs are being destroyed,
- iron and transferring level test - to determine if there is iron deficiency in the body,
- folate and vitamin B_{12} test - to assess the contents of vitamins needed to produce RBCs,

- hemoglobin electrophoresis - in the case of a family history of anemia, this test can provide an indication of sickle cell anemia[1] or thalassemia[2],
- liver function and kidney function tests,
- bone marrow biopsy - to evaluate the production of RBCs in the bone marrow, and
- reticulocyte count - it gives a count of the new red blood cells produced by the bone marrow.

Mahadevan *et al.* [6] have developed a device to analyze the red blood cells of a patient suffering from sickle cell anemia. This device was developed to determine whether sickle cell patients are at high risk for complications. There are also other devices employed in the measurement of hemoglobin content in whole blood samples. For example, automated hematology analysers are used to measure the average volume of the RBCs in a sample, also known as MCV (mean cell volume) [7]. Laser technology is also utilised to determine the cell volume [8]. All of these devices require a blood sample (using a finger prick technology) to provide results.

Strohm *et al.* [9] have found that when RBCs are hit with laser light, the resulting high frequency sound waves can be used to determine the size and shape of red blood cells, and thus assist in the identification of potential blood related diseases. This is based on the reasoning that RBCs have a specific shape to enable efficient transport of oxygen to other body cells, and that in the presence of any disease or disorder, the shape of the blood cells may change. This method has been used to detect the deformation of RBCs in patients with malaria and sickle cell anemia patients whose RBCs are swollen and crescent-shaped, respectively. A photoacoustic microscope is used to sense sound and differentiate between healthy and irregularly shaped cells.

3 Bilirubinemia

The diagnosis of bilirubinemmia, or jaundice, by a medical practitioner begins with an examination of a patients medical history in order to determine its possible cause. However, this is just a preliminary step, and the process usually involves additional testing. In this section, we outline procedures and devices commonly employed in the assessment of this condition with respect to two groups: adults and neonates.

3.1 Assessment in Adults

3.1.1 Blood Tests

A blood test conducted for a patient suffering from jaundice will usually give a good indication of a raised level of "liver enzymes" as well as a high bilirubin content. Further testing may be conducted depending on which enzymes show abnormal levels. For example, a CBC test is useful in order to detect blood infections or blood cell abnormality [3]. The doctor can also recommend an electrolyte[3] panel test, which provides the contents of sodium, potassium, chloride and carbon dioxide within the blood sample [11]. A

[1] Medical condition in which red blood cells of a patient are sickle-shaped or crescent-shaped by birth [4].

[2] An inherited disorder where the body does not produce enough hemoglobin due to the weakening and premature destruction of the RBCs [5].

[3] Electrolytes are minerals that maintain the balance of bodily fluids [10].

blood test for analysing hepatitis risk factors can also be done. It is worth noting that long periods of fasting or caffeine intake can have a confounding effect on results for the blood test [12].

3.1.2 Urinalysis

Chloride levels can be an effective indication of the pH value in urine. This information can assist in the determination of the level of unconjugated bilirubin in the body [13]. An analysis of the urine for obvious abnormalities in color, clarity and cloudiness may also suggest the presence of a liver disease that may be associated with the onset of bilirubinemia [14]. The physical interpretation of urinalysis is done using a dipstick [15].

3.1.3 Imaging Methods

Bilirubinemia can also be a consequence of obstructive cholestasis [16], a condition where the liver cannot successfully secrete bile into the tube-like structures called the bile ducts. Hence, in some cases, a scan of the abdomen is required to assist the diagnosis of bilirubinemia. The following imaging techniques are most generally used:

- ultrasound - uses sound waves to examine the abdomen as well as to detect stones in gallbladder, dilated bile ducts and any other abnormalities in the liver, gallbladder and pancreas [17],
- computerized tomography (CT) scan - although not as effective as ultrasound, it can, however, identify other abnormalities in the abdomen such as pancreatic lesions [18],
- cholescintigraphy (also known as hepatobiliary iminodiacetic acid (HIDA) scan) - uses radioactivity to evaluate the gallbladder and bile ducts[4],
- magnetic resonance imaging (MRI) scan - uses magnetic field technology to obtain a detailed examination of abdominal organs and bile ducts [20],
- endoscopic retrograde cholangiopancreatography (ERCP) - uses an endoscope to identify stones, tumours or blockages in the bile duct through a procedure involving an endoscope [21], and
- laparoscopy - consists in a direct inspection of liver and gallbladder[5].

3.1.4 Liver Biopsy

The liver biopsy procedure uses ultrasound technology to guide the placement of a needle in order to extract a sample from the liver. Biopsies can assist in the identification of abnormalities in liver enzymes or inflammation of the liver, cirrhosis (a condition than be caused by hepatitis or fatty liver disease) and cancer [17, 18].

[4] A radioisotopic HIDA scan is expensive and beyond most hospital patients [19].
[5] Jaundice caused by cholestasis may occasionaly require laparoscopy to be performed on the patient [22]

3.1.5 Intravenous Techniques

The serum concentration of unconjugated bilirubin in the body is a good indication of jaundice [23]. Intravenous techniques to extract serum bilirubin samples are most commonly employed. Normally, a bilirubin test is requested every 2 days in order to examine the changes. In some cases, adequate pain control injections are also required to supplement intravenous procedure. Intravenous techniques are painful especially when periodic tests are required to monitor a patient [19]. This has led to the search for other transcutaneous and noninvasive procedures.

3.1.6 Transcutaneous Procedures

While intravenous techniques draw samples directly from the intravascular space, transcutaneous measurements rely on light propagated through multiple layers of the skin. Hence, these measurements do not required frequent blood sampling and can provide faster results than intravenous techniques.

Transcutaneous bilirubinometry employs principles of optical spectroscopy to estimate the amount of bilirubin present in the skin tissues [24]. For example, Bilichek [25, 26] is a transcutaneous bilirubinometer that uses fiberoptic sensors and reflectance spectrophotometry to estimate bilirubin. Reflectance measurements are performed at multiple wavelengths in the 400-760 nm range [25].

It has been demonstrated [27] that bilirubin content may vary depending on the skin melanin pigmentation level, with darkly pigmented individuals having lower bilirubin conten than moderately and lightly pigmented individuals. Accordingly, several improvements have been incorporated to the bilirubinometers in order to take into account the presence and absorption effects of other skin chromophores like melanin and hemoglobin. For example, in a study making use of Bilichek [20], the patients were subjected to both blood sampling and transcutaneous bilirubin (TcB) assessment procedures. The interval between both was approximately 2 to 6 hours. The fiber-optic tip was placed in contact with the skin at 3 sites in order to get readings. Due to varying dermal thickness and melanin content, the sites chosen for analysis were forehead, sternum, deltoid and forearm since all these have different degrees of thickness. Upon comparison with the intravenous techniques for serum bilirubin, it was found that the forehead was the most appropriate location and consequently, readings were taken from two different areas of the forehead. It should be noted that the employed transcutaneous bilirubinometer was not calibrated for use in an adult, whose skin thickness and melanin content can vary significantly from that of a neonate.

3.2 Assessment in Neonates

The bilirubin measurement devices for neonates can be broadly divided into the following types [28]:

- handheld devices or transcutaneous bilirubinometers for noninvasive reading,
- devices for non-chemical photometric measurement of blood samples, and
- devices for chemical photometric measurement of bilirubin content.

The available transcutaneous bilirubin (TcB) measurement devices (*e.g.*, Bilichek [20], Bilimed [27] and Biliblitz [28]) differ on the basis of the probing mechanism, number of wavelengths and the underlying model to extract the bilirubin concentration reading [24]. Skin absorption coefficients are usually measured in the 450-600 nm range. The concentration of bilirubin is then evaluated by discarding the contributions of other skin chromophores such as melanin and hemoglobin. Since the specific absorption coefficients of

the other chromophores are known, the bilirubin levels at different wavelengths can be estimated. It is important to note that such operation requires a computer model that can correctly account for the light interaction with human skin. However, information about such models is usually not provided along with the devices' overall description, preventing a direct quantitative evaluation of their predictive capabilities. In fact, these devices tend to underestimate TSB (transcutaneous serum bilirubin) contents [29], notably when their values are high [30]. For example, in the case of Bilichek, 6% of false negatives were observed for measured TcB readings [25].

Devices such as blood gas analysers are designed to measure bilirubin in plasma. For example, bilirubin levels are measured by the ABM 735 analyzer at reading points between 478-672 nm. Other blood gas measure bilirubin concentrations at different wavelengths. For example, the Roche OMNIS and Twin Beam analysers perform these measurements in the 460-660 nm and 455-755 nm ranges, respectively [28].

Hitachi 912, Dimension RxL and Vitros 250 are clinical chemical analysers used in laboratories for measuring the bilirubin content in serum or plasma [28]. The most common procedure used to obtain a blood sample from a neonate is the heel stick [31]. In a standard heel stick sample collection procedure, blood is collected from the neonate's heel. This method is painful and may cause osteomyelitis[6] [30]. Hospitals generally employ a two-stage testing approach. In the first stage, a noninvasive test is performed using a transcutaneous bilirubinometer. In the second stage, a blood test may be performed if the result of the first stage indicates that the neonate's bilirubin level is high [25].

4 Summary

In this report, we briefly discussed different techniques and devices used to estimate hemoglobin and bilirubin contents in order to assist the diagnosis of anemia and bilirubinemia, respectively. For anemia, hematology analysers are usually employed. However, to the best of our knowledge, all the current analysers in the market are based on a finger-prick technique that involves collection of blood sample to measure the hemoglobin level [33]. Further research can be done in this field to investigate noninvasive methods that do not involve blood collection. For jaundice, both intravenous and transcutaneous procedures/devices are usually employed. While the latter are less painful and provide faster results, the former are more accurate for determining rising bilirubin contents. Even though transcutaneous bilirubinometers take the presence of bilirubin, hemoglobin and melanin into consideration, they do not account for possible changes in the distribution of these pigments within the different skin layers as well as their impact across different wavelengths. We believe that future progress in this area will depend on the development of more accurate and reliable devices. This, in turn, will require the use of accurate models of light and skin interaction whose predictive capabilities can be evaluated and reproduced in a transparent manner [34].

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