

A photothermal optical sensor enables measurement of hemoglobin concentration in unprocessed, nanoliter blood sample

Examining blood sample is like looking over the index of a book on the health of humans. For example, measuring cholesterol concentration in blood enables detection of hyperlipidemia, which is related to pancreatitis and cardiovascular disease, and glucose contents in blood serves as a criterion for diagnosis of diabetic disease. In addition, quantification of various blood components such as leukocytes, thrombocytes and inorganic ions make it possible to screen inflammation, pancreatic and renal diseases. Here, our research group turned our eyes on hemoglobin (Hb). Hb binds and transports oxygen to the organs while circulating human body. Therefore, concentration of hemoglobin ([Hb]) serves as a crucial indicator of the oxygen-carrying capacity of the blood. Since disorders of oxygen supply are a serious problem for vital activity, significant [Hb] alterations can lead to hepatobiliary disease, neurological disorders, cardiovascular disorders, and endocrinological disorders.

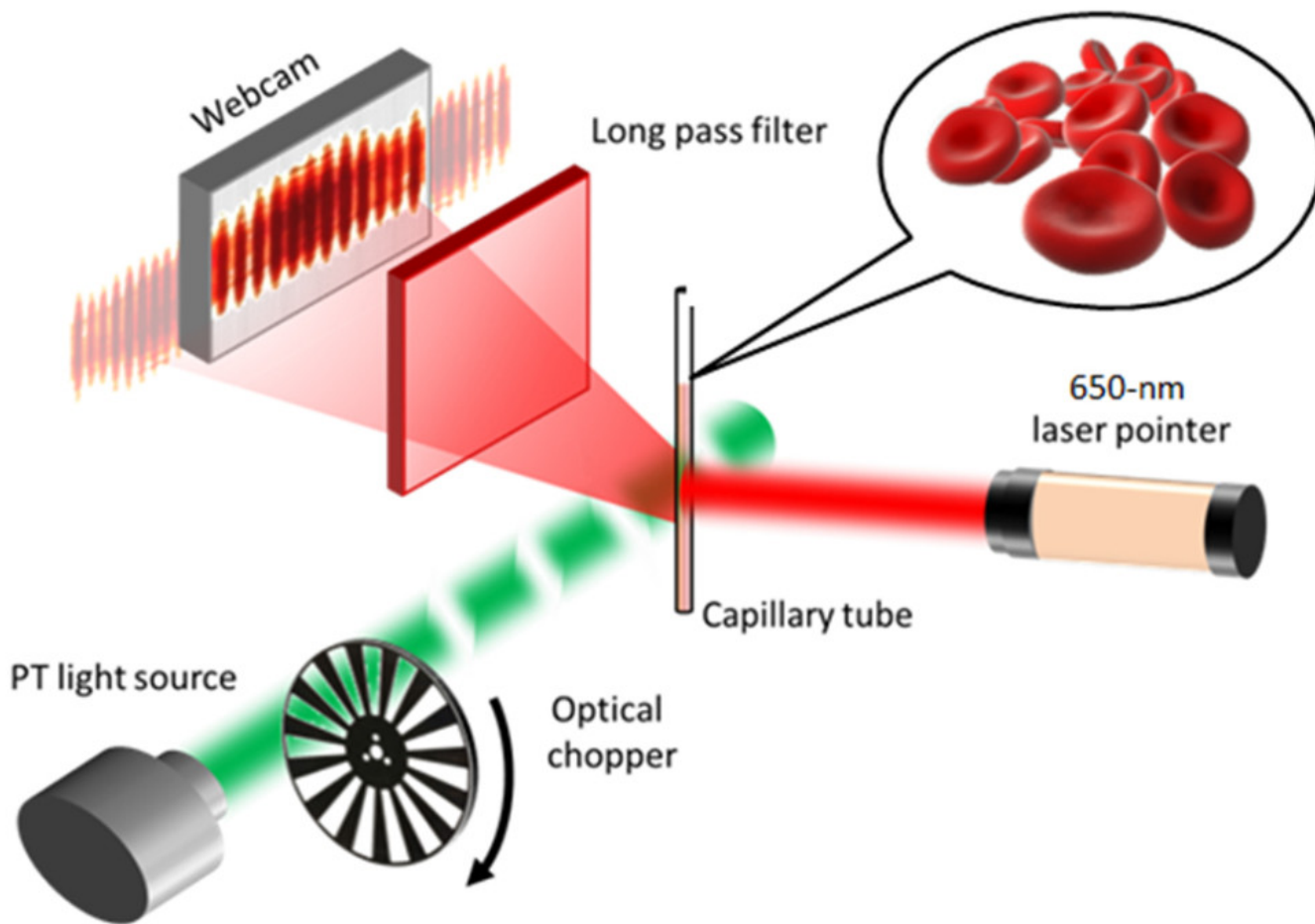


Fig. 1. Schematic of the PT-AS sensor for rapid and direct [Hb] measurement. 650-nm probe light from a commercial laser pointer is directed to a blood-containing capillary tube. The interference of the scattered light from the tube produces a distinct pattern on a webcam. Under the illumination of 532nm light, where Hb exhibits high absorption, Hb absorbs the light energy and converts it into heat, leading to a change in the refractive index of blood. This photothermal change in refractive index results in a shift in the scattering pattern. Quantification of this shift in the scattering pattern enables high-accuracy [Hb] measurement in unprocessed blood sample.

Because of its importance, measuring [Hb] is a significant and common task in blood test. Representative and widely employed methods for [Hb] detection are hematocrit analyzer and HemoCue® device. Hematocrit analyzer is the standard technique for measuring [Hb] and is used to precisely analyze the patient's blood in hospitals. Unfortunately, the equipment is bulky and costly, and involves a cumbersome procedure. On the other hand, the HemoCue® device is a relatively inexpensive, portable and simple method based on hemolysis and colorimetric analysis. Yet, its operation requires toxic chemicals such as potassium cyanide, which may pose potential hazard to the users and involves high operating expense.

We developed a novel and simple method, termed photo-thermal angular light scattering (PT-AS sensor), to measure [Hb] without any processing of blood and chemicals for operation. Figure1 shows a schematic of the PT-AS sensor. 650-nm probe light from a cheap laser pointer is directed to a blood-containing microcapillary tube. The light is then scattered to form a distinct pattern on a webcam. This scattering pattern varies with the refractive index and diameter of the tube. Under the illumination of 532nm light, where Hb exhibits high absorption, Hb absorbs the light energy and converts it into heat, leading to a change in the refractive index of blood. This photothermal change in refractive index of blood results in a shift in the scattering pattern. Monitoring the shift of scattering pattern enables quantification of [Hb]. Employing micro-capillary tube as a blood container to form the scattering pattern, amount of blood volume required for measurement can be reduced down to 22nL. The accuracy of our sensor was evaluated by comparing its measurements with those examined by a conventional hematology analyzer (Figure2), and it exhibited a high correlation ($r=0.96$) with the hematology analyzer.

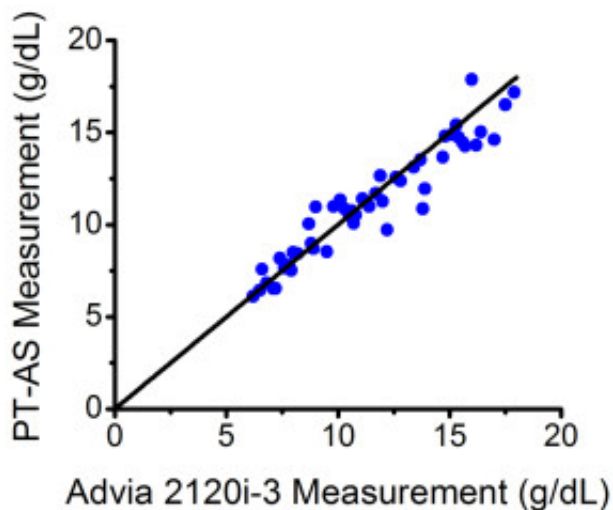


Fig. 2. Comparison of PT-AS measurements against those from a hematology analyzer, ADVIA® 2120i.

The PT-AS sensor is ready to be applied in the field settings and is characterized by distinct advantages compared to conventional sensors. Any preconditioning of blood sample or toxic chemicals is not needed. It can be implemented as a portable and inexpensive device because it is composed of low-cost components such as a laser pointer and webcam. No chemicals are required, eliminating potential harm to the user and reducing the operating cost. Use of a micro-capillary tube for detection also contributes to low operating cost of less than 0.20\$, and significantly reduces the amount of blood to nanoliter-scale. The total measurement time of our current implementation is only 5 seconds, being appropriate to rapid and point-of-care testing. Besides hemoglobin, the same detection scheme can be applied to measure disease biomarkers such as hemozoin crystals for malaria. We are continuing to improve the sensitivity of PT-AS sensor and to package it in small form factor, so that it can be widely deployed to use in the field-settings.

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